Measurement, Incidence and Risk Factors of Maternal Peripartum Infection

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I Susannah Louise Woodd, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

Abstract

Introduction

Pregnancy-related infection causes an estimated 11% of maternal deaths and increases the risk of stillbirth and neonatal mortality. However, definitions vary, measurement methods are inconsistent, and the incidence remains poorly described. This thesis aims to improve understanding of the measurement, incidence and risk factors of maternal peripartum infection.

Methods

I conducted a systematic literature review of global incidence of maternal peripartum infection; I explored infection definitions and data collection methods. I conducted a literature review of postnatal follow-up methods.

Applying learning from the reviews, I designed a telephone-surveillance cohort study to measure incidence and risk factors of postnatal infection in Tanzania.

Results

No existing study met the full WHO criteria for maternal peripartum infection. In high-quality studies, pooled infection incidence per 1000 women was 39 for chorioamnionitis, 16 for endometritis, 12 for wound infection and 0.5 for sepsis. Only 19% of studies met all quality criteria and 41% used a standard definition for infection. Less than half of studies followed women after hospital discharge. In the literature review of postnatal follow-up, telephone surveillance studies reached 63-91% of women.

We recruited 879 women and interviewed 791 (90%) by telephone in Tanzania. Age, delivery mode and hospital did not affect the chance of reaching women, but 29% of interviews required over one call attempt. At day-28 postnatal, infection incidence per 1000 was 49 for maternal peripartum infection; 27 for endometritis, 28 for wound infection and with no cases of chorioamnionitis. The infection rate was higher in women with caesarean childbirth.

Conclusion

Maternal peripartum infection remains an important complication of pregnancy and prevention strategies need increased attention. Improved measurement requires validated, standard definitions for constituent infections, applicable to low-resource settings, plus active postnatal follow-up. Telephone surveillance should be considered for follow-up; in Tanzania it achieved good coverage, and infection estimates were consistent with other studies.

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List of Acronyms

aHR	Adjusted Hazard Ratio
AMR	Antimicrobial Resistance
App	Mobile Telephone/Tablet Application
BP	Blood Pressure
BMI	Body Mass Index
CDC	Centre for Disease Control and Prevention
CI	Confidence Interval
cRCT	Cluster Randomised Controlled Trial
CS	Caesarean Section
DALY	Disability Adjusted Life Year
EPDS	Edinburgh Postnatal Depression Scale
GAS	Group A haemolytic *Streptococcus*
GBD	Global Burden of Disease
GBS	Group B *Streptococcus*
GEE	Generalised Estimating Equation
GLOSS	Global Maternal Sepsis Study
GP	General Practitioner
HIC	High-income country
HIV	Human Immunodeficiency Virus
ICD-9/10	International Statistical Classification of Diseases and Related Health Problems 9^{th}/10^{th} Revision
ICD-MM	ICD Maternal Mortality (WHO application of ICD-10 to deaths during pregnancy, childbirth and the puerperium)
ICU	Intensive Care Unit
ID	Identification (number)
IHI	Ifakara Health Institute
IQR	Inter-quartile range
KPMP	Kaiser Permanente Medical Program
LIC	Low-income Country
LILACS	Latin American and Caribbean Health Science Information
LMI	Lower Middle Income
LMIC	Low and Middle-Income Countries
LSHTM	London School of Hygiene and Tropical Medicine
MMR	Maternal Mortality Ratio
MPI	Maternal Peripartum Infection
NHDS	US National Hospital Discharge Survey
NIS	US National Inpatient Sample
NOIS	Norwegian National Surveillance System for Healthcare Associated Infections
ODK	Open Data Kit
OR	Odds Ratio
$PaCO_2$	Partial pressure of Carbon Dioxide

PI	Prediction Interval
PPH	Postpartum Haemorrhage
PRAMS	US Pregnancy Risk Assessment Monitoring System
PROM	Premature/prelabour Rupture of Membranes
pSBI	Possible Severe Bacterial Infection (in the newborn)
pSOFA	Paediatric SOFA
qSOFA	Quick SOFA
RCT	Randomised Controlled Trial
SDG	Sustainable Development Goal
SDI	Socio-demographic index
SES	Socio-economic scale
SIGN	Scottish Intercollegiate Guidelines Network
SIRS	Severe Inflammatory Response Syndrome
SOFA	Sepsis Organ Failure Assessment
SSA	Sub-Saharan Africa
SSI	Surgical Site Infection
UK	United Kingdom
UMI	Upper Middle Income
US	United States
UTI	Urinary Tract Infection
WCC	White Cell Count
WHO	World Health Organisation
YICSS	Young Infant Clinical Signs Study

Chapter 1: Introduction and Aims

1.1 Importance of maternal infections

Preventing maternal and newborn infections was identified in 2015 as a high priority for the World Health Organization (WHO) as part of their vision of good quality care for mothers and newborns[1]. Since then, maternal sepsis has received growing international interest, leading to the launch of the Maternal and Neonatal Sepsis Initiative by WHO and Jhpiego in early 2017[2]. The potential seriousness of the condition is hard to ignore. Case-fatality is high; in one study in the Netherlands 8% of women with severe obstetric sepsis died[3], and a study in California found case-fatality rates of 2% among women with severe sepsis and 25% for those with septic shock[4]. The WHO Global Maternal Sepsis Study (GLOSS) conducted in hospitals in 52 countries reported a case-fatality of 7% among women with severe infection-related maternal outcomes[5]. Case-fatality was highest (15%) in study hospitals in low-income countries, and zero during the survey week in high-income countries (HICs). A review in low- and middle-income countries (LMICs) in 2001 reported case-fatalities across four African studies ranging from 4% to 50%[6].

This high case-fatality leads to a large proportion of all maternal deaths being attributed to sepsis. A systematic analysis by WHO in 2014 estimated pregnancy-related sepsis accounted for approximately 11% (6-19%) of maternal deaths[7]. Similarly, sepsis and pregnancy-related infection accounted for 11% of all maternal deaths (21,200/193,600 maternal deaths) in the Global Burden of Disease (GBD) study in 2017[8]. While the vast majority of deaths, and therefore infection-related deaths, occur in LMICs[9], infection continues to cause a high proportion of maternal mortality in HICs. A study of United States (US) hospital discharge data from 2013-16 found 23% of maternal deaths were sepsis-related[10] and the United Kingdom (UK) confidential enquiry into maternal deaths in 2016-18 found 11% of direct and indirect deaths were caused by sepsis[11].

The cause-specific maternal mortality ratio (MMR) for sepsis varies widely between regions and countries in line with the large variation in overall MMR. This is illustrated in Table 1.1 which applies data from the 2015 GBD study to describe the sepsis-specific MMR globally, for countries with high and low socio-demographic indices, and a selection of countries within sub-Saharan Africa (SSA)[12].

Table 1.1: Comparison of cause-specific sepsis MMR in different regions and countries

Region	Cause-specific sepsis MMR per 100,000 live births[1]
World	12.4
High SDI[2]	1.0
Low SDI[2]	25.2
Sub-Saharan Africa	21.0
Namibia	4.2
Tanzania	24.6
Central African Republic	36.6

1) Using data on deaths and livebirths from the 2015 GBD study

2) Sociodemographic Index

Even when not fatal, sepsis can have serious long-term consequences, with studies showing prolonged physical and cognitive dysfunction[13]. Genital tract infection can lead to chronic pelvic inflammatory disease, future ectopic pregnancies and infertility[14]. In addition, maternal infection has been shown to be associated with poor newborn health. Intrapartum fever of >38°C carries a large increased risk of perinatal death in population-based studies[15] and maternal infection in labour is associated with neonatal infection[16].

1.2 Estimates of incidence

Given the importance of maternal infection, surprisingly little was known about the overall incidence when I began this PhD. It was the only major direct cause of maternal mortality without a systematic literature review of the burden of disease. Instead, the incidence of maternal sepsis was commonly quoted as 40 per 1000: a figure modelled by Dolea and Stein for the 2000 GBD study[6], using observed data from a single-centre US study[17], the difference in infection incidence between home and hospital births found in two African studies, and the protective effect of prophylactic antibiotics for caesarean delivery from a Cochrane review[18]. More recently, the 2017 GBD study estimated the number of cases of maternal sepsis and other maternal infections (including urinary tract and breast infections) at 11.9 million women, using a model built from US claims data, hospital inpatient data, survey data and literature, applying several correction factors and matching to mortality rates[19]. They do not present an incidence risk, but using an estimated 140 million births per year[20], this number translates to approximately 85 per 1000 births.

Primary global data is available from two key WHO studies. GLOSS collected data on pregnant and postpartum women with infection from 713 facilities in 52 countries of all income levels over the course of one week in 2017[5]. A total of 2850 women had suspected or confirmed infection from any source, giving a ratio of 70.4 women per 1000 livebirths (95% Confidence

Interval (CI) 67.7-73.1), of whom 57% (40.1 per 1000) were diagnosed during labour or postpartum. Endometritis, chorioamnionitis and skin or soft tissue infections (including wound infections) were each diagnosed in 15% of the women with infection, corresponding to incidences of 10.6 per 1000 livebirths. An earlier WHO multi-country study, reported on various outcomes for 314,623 women delivering in hospital in 29 countries across Africa, Asia, Latin America and the Middle East in 2010-11[21]. Puerperal endometritis was diagnosed in 321 (1 per 1000) women, and sepsis or other systemic infections in 1,216 (4 per 1000). Both studies benefited from extensive geographic coverage but were limited to women hospitalised at secondary and tertiary facilities.

A review of puerperal infectious morbidity in SSA in 2009 found limited data, primarily from facility-based studies, and concluded that a single, reliable estimate of incidence could not be made.[22] The largest of the three population-based studies included in the review is a prospective study of 20,326 women across six West African countries. Active post-partum follow-up identified severe maternal morbidity from puerperal sepsis, leading to hospitalisation, hysterectomy or death, in 18 (1 per 1000) women. The high case-fatality rate of 33% meant that these few infections contributed to 15% of the total deaths.[23] Among the facility-based studies, incidence ranged from 2-190 per 1000 women, with the highest risk occurring among women with human immunodeficiency virus (HIV) in a South African trial.[22]

1.3 Defining maternal infection

One of the barriers to measuring, managing, and preventing maternal infection is the heterogeneity in definitions used. This lack of consensus limits the comparability of studies in regard to burden, risk factors, and effective interventions. Terms and definitions found in the literature vary according to timing, site and severity of infection. They reflect differences in diagnostic capacity, the intentions of the research, and developments in scientific thinking.

Below, I consider three over-lapping groups of maternal infection and the different ways they have been defined: a. maternal infection occurring throughout pregnancy and postpartum b. maternal sepsis and c. peripartum infection.

1.3.1 Maternal infection throughout pregnancy and postpartum

Table 1.2 illustrates four definitions of maternal infection used in large-scale estimates of maternal morbidity and mortality throughout pregnancy and postpartum. The first three definitions measure direct infectious causes of maternal morbidity and mortality, including genital tract, urinary tract, obstetric wound and breast infections. The definitions are very similar, but none are identical. Only the WHO analysis specifically includes obstetric tetanus,

and appears to leave out genitourinary tract infections during pregnancy[7] and breast infections. The GBD study does not list infection in labour[12, 19] but is otherwise similar to ICD-Maternal Mortality (ICD-MM)[24]. The more recent GLOSS study takes a different approach, including all causes of infection, irrespective of whether they are related to or aggravated by pregnancy[5].

Table 1.2: Classification of infection throughout pregnancy and postpartum

Description of infections included:	ICD-10	Study			
		GBD 2015[12] and 2017[19]	ICD-MM[24]	WHO systematic analysis of maternal death[7]	GLOSS[5]
Infections of genitourinary tract in pregnancy	O23	X	X		
Obstetric tetanus	A34			X	
Infections of the amniotic sac and membranes	O41.1		X	X	
Sepsis during labour	O75.3		X	X	
Puerperal sepsis	O85	X	X	X	
Other puerperal infections	O86	X	X	X	
Infections of the breast associated with childbirth	O91		X		
Suspected or confirmed infection (direct and indirect)					X

1.3.2 Sepsis

Some studies focus specifically on maternal sepsis – a severe consequence of infection with high case fatality. Understanding and usage of the term sepsis has developed over the last decades. In 1992 a Consensus Conference defined sepsis in adults as infection plus a systemic inflammatory response syndrome (SIRS) based on abnormal values of: temperature, heart rate, respiratory rate or $PaCO_2$, or white cell count[25]. This was updated in 2016 to the current definition of 'life-threatening organ dysfunction caused by a dysregulated host-response to infection', designated Sepsis-3[26]. Alongside this, the Sepsis Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) were developed to assess severity of organ dysfunction. Subsequently, the WHO and Jhpiego underwent a process of re-defining maternal sepsis,

publishing a new definition in 2017, defined as "organ dysfunction resulting from infection in pregnancy, childbirth, post-abortion, and postpartum"[27].

However, applying sepsis definitions is not without its challenges. A US study comparing ICD-9 codes with clinical and laboratory findings in patient hospital records found only 11/64 (17%) women with a code for severe maternal sepsis or septic shock (a diagnosis similar to the 2017 definition) met the existing consensus definition[28]. In addition, the criteria for sepsis diagnosis in pregnancy are still in doubt. A systematic review has demonstrated that SIRS criteria overlap with normal physiologic parameters during pregnancy making them unspecific to disease[29], and similar concerns have been raised about using SOFA and qSOFA criteria for an obstetric population[30]. Bespoke obstetric scoring systems have been developed but perform worse at predicting mortality compared to those used for the general adult population[31]. SOFA has shown good predictive value for severe maternal outcomes and death[32, 33] but the ability of qSOFA to predict severe disease or intensive care unit (ICU) admission is mixed[34, 35].

A primary aim of the new definition of maternal sepsis is to improve earlier identification and treatment, and so reduce mortality. However, the focus on women with organ dysfunction carries the danger of resources being transferred to expensive critical care, and away from primary and secondary prevention where there may be more opportunity to reduce the overall burden of infections.

1.3.3 Peripartum infection

The period around birth and postpartum is of particular interest in relation to maternal infection due to the high burden of disease, the shared risk factors and opportunities for intervention. A commonly used term for infection during this period is puerperal sepsis, widely defined as bacterial infection of the genital tract related to childbirth. Confusingly, despite the name 'sepsis', signs of severe disease are not a requisite, and the precise timing varies between definitions. ICD-10 defines it as occurring postpartum[36], some medical dictionaries specify up to 10 days postpartum[37], whereas the WHO technical working group also includes intrapartum infection and continue until 42 days[38] (Table 1.3).

In 2014 WHO created a new term, 'maternal peripartum infection', in relation to guidelines for prevention and treatment of childbirth-related infections. Defined as "bacterial infection of the genital tract or its surrounding tissues occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum" it expands on their earlier definition of puerperal sepsis to include infections related to the process of childbirth, such

as caesarean section and perineal tears, and clarifies the inclusion of intra- as well as post-partum infection[39]. It overlaps with ICD-10 O85 and part of O86, 'Other puerperal infections'[36].

Table 1.3: Classification of peripartum infection

Source	Term	Definition	Time period	Site
ICD-10 O85[36]	Puerperal sepsis	Fever, Puerperal endometritis, Peritonitis or Sepsis. (excludes septicaemia during labour)	Postpartum	Genital tract
ICD-10 O86[36]	Other Puerperal infections	Infection of obstetric surgical wound, Other infection of genital tract (cervicitis, endometritis, vaginitis), Urinary Tract infection, Pyrexia of unknown origin, Other specified puerperal infections	Postpartum	Genital tract, urinary tract, obstetric wounds, other
WHO technical working group[38]	Puerperal sepsis	Genital tract infection with 2 or more of: Fever, Pelvic pain, Abnormal vaginal discharge, Abnormal smell of discharge, Delay in uterine involution	Rupture of membranes/ labour to day 42 postpartum	Genital tract
WHO recommendations for prevention and treatment[39]	Maternal peripartum infection	Bacterial infections related to childbirth. Similar clinical diagnosis to WHO puerperal sepsis.	Rupture of membranes/ labour to day 42 postpartum	Genital tract or surrounding tissues (including delivery-related wound infection)

The WHO definition provides clinical criteria for diagnosis of maternal peripartum infection, identical to those previously used for puerperal sepsis, and easily applied in LMICs and in community settings, without access to laboratory diagnostics. This group of infections comprises intrapartum clinical chorioamnionitis (bacterial infection of the genital tract in labour), endometritis (bacterial infection of the genital tract postpartum) and infection at the site of a caesarean section wound or perineal trauma (infection of surrounding tissues). Separate definitions exist for these constituent infections which provide criteria specific to each of them.

In this PhD I will focus on maternal peripartum infections. The WHO guidelines had been recently published when I began, therefore this particular group of infections were of current interest. These infections carry a significant burden, for example they are responsible for

more than half the cases of severe maternal sepsis in the UK. In addition, as global facility delivery rates increase, they present a key opportunity for prevention.

1.4 Measuring Peripartum Infection

Good epidemiological measurement of disease frequency requires not only a standard definition and consistent time period, but also a specified population, a clear denominator and a defined measure of disease frequency. The aim should be to measure an incidence rate or risk over a specified time. This requires an identified population, free of disease at the beginning of study, with follow-up measures in place to identify all cases over the time-period of interest[40].

There are several challenges in applying these principles to maternal peripartum infection. Firstly, the population of interest is usually all women giving birth. However, in countries with low facility birth rates, low attendance at birth by a registered practitioner and low birth registration, this population can be hard to identify completely. Efforts needed to detect new pregnancies and births at community level are intensive, including regular home visits by lay workers, and reports from village health workers. A common substitute is to study a cohort of women giving birth in a health facility, who can be easily identified and recruited during their admission. In these cases, it is important to recognise that this population studied may carry a different risk of infection to women giving birth outside a facility, related to the level of hygiene, the skill of the birth attendant, but also their additional risk of intervention during labour, particularly if they intended to deliver at home but sought facility care for complications in labour.

Another common practice, particularly in near-miss studies, is to identify cases, usually from admissions to one or more health facilities, and either present them as a percentage of all near-miss cases, or as a rate per number of facility (live) births as the denominator[41]. Neither of these options results in an incidence risk or rate because the denominator does not include the whole population of women at risk. The relationship between the population contributing to the number of births, and the population producing the cases, will inevitably affect the outcome, limiting comparability between studies. Studies conducted in tertiary facilities, or in settings with low facility birth attendance, are particularly prone to selection bias by including women as cases who do not contribute to the denominator because they gave birth elsewhere (another facility or at home).

Ensuring that women in the cohort are free of the infection at the beginning of follow-up is straightforward for some peripartum infections. Postnatal endometritis and birth-related

wound infections are, by definition, only present after childbirth. However, if a woman presents with chorioamnionitis in labour it can be difficult to determine whether the infection started after labour, or before, and therefore whether to include her as a case, or exclude her from the population at risk. Similarly, urinary tract infections (UTI) can occur throughout pregnancy, as well as postnatally, and their onset in relation to labour may be unclear.

The final challenge is to identify all cases occurring throughout the postnatal period. Most infections will start in the community after hospital discharge[42], and milder cases will be managed solely by primary healthcare providers or are self-managed, so are consequently missed by hospital-based studies. Collating all the relevant sources of health data, or following women throughout the postnatal period, is difficult even in HICs. The challenges are multiplied in low-resource settings where healthcare delivery involves a multitude of informal and private providers, computerisation of records is infrequent, women may live far from their place of birth, or from any health facility, and methods of remote communication (telephone or post) are more limited.

1.5 Aetiology

1.5.1 Microbiology

The classic, historical cause of puerperal sepsis, Group A haemolytic S*treptococcus* (GAS), remains an important cause of severe disease today. In a study of all maternal sepsis cases in 2011-12 in the UK, GAS was the single largest cause of genital tract infection and was associated with progression to septic shock[43]. Outbreaks of GAS have been traced to single healthcare practitioners and new cases have stopped after improved hand hygiene, or treatment of the individual[44, 45]. However, a recent 13-year retrospective cohort study in Israel only identified a healthcare source in 1/124 cases, leading to the conclusion that most transmission occurs in the community, particularly from other family members[46]. The authors suggest further studies into screening during pregnancy, while other groups are keen to develop a GAS vaccine to protect against disease[47, 48]. Despite the continued significance of GAS, endogenous pathogens are now of equal, if not greater, importance in HICs. In 2011-12 in the UK, *Escherichia coli* and Group B *Streptococcus* (GBS) were almost equally common causes of genital tract sepsis and *E. coli* caused the majority of sepsis from urinary tract infections, making it the most common organism causing sepsis overall[43]. Likewise, *E. coli* was the most frequently identified organism in studies of maternal sepsis in Canada and the US[28, 49, 50].

Studies in LMICs show a different pattern, most frequently identifying *Klebsiella pneumoniae*, *E. coli* and *Staphylococcus aureus* as causes of puerperal sepsis and infection, including organisms cultured from blood, endocervical swabs and occasionally urine[51-55]. The data tend to come from small, single-facility studies, reflecting the limited laboratory capacity in these contexts, and may not represent of whole countries or regions. In addition, the relative rarity of cases of *Streptococcus* and anaerobes described may be partially explained by the greater challenges in identifying them[14, 22].

The value of performing blood cultures to identify a bacterial aetiology in cases of maternal sepsis is well-recognised, although many LMICs lack that capacity. However, confirming pathogenesis of genital tract infection is not straightforward, even in well-resourced settings. Endometrial sampling from the postpartum uterus is risky[56], and swabs are frequently contaminated by cervical and vaginal flora, making it difficult to interpret results[57]. The more easily performed cervical samples are usually a poor predictor of endometrial organisms and of limited value[57]. In addition, the significance of bacterial growth is not always clear: one study comparing samples from afebrile patients and those with clinical endometritis found no difference in endometrial flora[58] although others have shown associations between bacterial isolates and clinical infection[22, 59].

As evidenced from the studies cited above, research into maternal sepsis and genital tract infection has primarily focussed on bacterial aetiology. While the WHO definition of maternal peripartum infection stipulates a bacterial cause, the new definition of maternal sepsis does not specify the aetiology, and future sepsis research will need to give more consideration to identifying viral, fungal and parasitic pathogens.

1.5.2 Antimicrobial resistance

There is a small recent literature that raises the alarming possibility of growing antimicrobial resistance (AMR) of peripartum infections[60-62]. The increasing rates of facility delivery[63] and caesarean section globally[64] will expose more women to resistant organisms present in health facilities, and to broad-spectrum antibiotics that can drive resistance further. This has the potential to limit treatment options, worsen outcomes and increase the cost of care. Studies of obstetric infection and sepsis in Spain[62] and the US[50] both found high levels of resistance to ampicillin (65% and 81% respectively) among *E. coli* isolates, with some resistance to gentamicin and cefotaxime. In addition, almost half the US cases were resistant to extended spectrum beta-lactamases. However, *Bacteroides*, *Enterococcus*, GBS and GAS were sensitive to ampicillin[50]. In a study of postpartum women in Uganda, multidrug-

resistance was high (80%) among gram-negative organisms isolated from blood and urine cultures[60] and resistance to third-generation cephalosporins was frequent in *Enterobacteriaceae* causing postnatal infection in Bangladesh[61].

A Cochrane review of antibiotic treatment failure for postpartum endometritis found that clindamycin and gentamicin (or an alternative aminoglycoside) performed better than cephalosporins or penicillins[65], reflecting both the common infective organisms (e.g *E. coli*) and their resistance patterns.

1.5.3 Risk Factors

Given the potential severity of infection, and growing resistance to treatment, it is important to understand and address risk factors for becoming infected or progressing to severe disease. These include maternal factors that predispose a woman to infection, and complications at the time of birth and healthcare interventions that increase the risk of introducing pathogenic agents. Maternal socio-demographics and behaviours, including alcohol intake, tobacco use, poor nutrition and obesity, anaemia, low socio-economic status and coming from an ethnic minority group have shown associations with infections[4, 43, 49, 66]. In addition, sepsis is increased in women with pre-existing medical conditions including diabetes and hypertensive disorders[4].

Complications around the time of birth such as pre-labour or prolonged rupture of membranes and prolonged labour increase the chance of vaginal colonising organisms ascending to the upper genital tract and causing infection[56, 66]. Postpartum complications, including retained products of conception, or haemorrhage also increase the risk of infection[4, 49, 66].

Interventions during birth may similarly increase the risk of ascending infection, and provide a route of entry for infectious organisms. Caesarean section appears to be the single most important risk factor for developing puerperal infection, particularly emergency operations following prolonged rupture of membranes or labour[4, 43, 49, 56, 66, 67]. Multiple vaginal examinations have been shown to increase vaginal colonisation in labour[68], and together with instrumental delivery, and episiotomy are also cited as risk factors[17, 66]. Poor hygiene behaviours by birth attendants is also considered a risk[66, 69].

Again, data from LMICs are more limited, but, in addition to the factors already mentioned, there is also evidence of increased risk of direct peripartum infections among women infected with HIV and malaria[22].

1.6 Newborn Infection

Early-onset neonatal sepsis is understood to be transmitted vertically from the mother's genital tract around the time of birth, and is related to maternal intrapartum fever and chorioamnionitis[16]. Alongside features of neonatal vulnerability such as low birth weight, prematurity and the need for resuscitation, certain risk factors for maternal infection also increase the risk of neonatal sepsis, including premature rupture of membranes, prolonged labour, and increasing vaginal examinations during labour[70, 71]. Due to this related aetiology, it is important to consider the health of the newborn when studying maternal peripartum infection.

1.6.1 Estimates of incidence among neonates

There are more deaths from neonatal infection and sepsis than deaths from maternal infection. In 2013, sepsis accounted for an estimated 430,000 neonatal deaths globally (15.6% of all neonatal mortality), with other infections including pneumonia and tetanus contributing a further burden[72]. As with maternal infection, definitions vary between studies. A 2021 systematic review of studies meeting a standard definition for neonatal sepsis estimated an overall incidence of 28.2 per 1000 live births with a 17.6% case fatality rate. Most of the studies were conducted in middle-income countries and those measuring only culture-positive sepsis or possible severe bacterial infection (pSBI) were excluded. However, there remained substantial heterogeneity between studies and a moderate to high risk of bias[73]. Incidence varied considerably between world regions. An analysis of hospital-based reports in South Asia measured the more restrictive outcome of culture-positive sepsis. As expected, the pooled incidence was lower than that of the systematic review at 15.8 per 1000 live births, but case fatality was higher, at 34.4%[74]. An earlier systematic review of SSA, south Asia and Latin America used the broader definition of pSBI to estimate incidence of 76 per 1000 births[75].

This burden of disease has significant consequences. The economic burden of neonatal sepsis in SSA in the year 2014 is estimated at $10 billion to $469 billion, based on the annual loss of 5.29-8.73 million disability-adjusted life years (DALYs)[76]. Moderate to severe neurodevelopmental impairment is estimated to affect almost one quarter of survivors of neonatal meningitis, and 16% of survivors of neonatal tetanus[77]. Data is lacking for impairment following neonatal sepsis, but an effect on the developing brain is biologically plausible and very likely[78].

1.6.2 Defining newborn infection

Defining sepsis in newborns is even more challenging than in pregnant/postnatal women and, as mentioned above, there is considerable variation in the definitions used. The current adult definition of sepsis as life-threatening organ dysfunction has not yet been adapted to neonates. An adapted paediatric SOFA score (pSOFA) has shown promise as a diagnostic and prognostic tool and a neonatal-specific SOFA has been proposed, but requires further work and testing[79]. Isolation of an infective organism is a common diagnostic criteria in HICs[79], but in LMICs, where microbiological capacity is limited, there is greater reliance on clinical signs. The WHO Young Infants Clinical Signs Study (YICSS) identified seven clinical signs and symptoms detected by primary care health workers that predicted severe disease requiring hospital admission in the first week of life[80]. Their algorithm is now used to define what is termed 'possible severe bacterial infection' (pSBI). However, as their aim was to identify sick neonates requiring further management to reduce mortality, the criteria favour sensitivity over specificity, and the diagnosis includes severe non-infective conditions[75].

1.6.3 Aetiology of newborn infection

In HICs the most common infective organism for early-onset newborn sepsis is GBS, followed by *E. coli*[70]. In contrast, a systematic review of the pathogenesis of neonatal sepsis in LMICs identified *Klebsiella*, *Staph aureus*, Coagulase-negative *Staphylococcus* and *E. coli* as the leading organisms[81]. *Klebsiella* was predominant in Africa compared to Asia and Latin America, Coagulase-negative *Staph* was higher in Latin America and E. coli was more dominant in Asia. Findings were similar in a systematic review confined to SSA with *Staph aureus* (25%), *Klebsiella* (21%) and *E. coli* (10%) the most common isolates[82]. Resistance was reported to β-lactams (68%) and aminoglycosides (27%). The BARNARDS study provides recent data on resistance across seven African and south Asian countries[83]. Reporting on gram-negative bacteria causing sepsis, they found the majority (67%) were resistant to at least one β-lactam and one aminoglycoside, and many were also resistant to third-generation cephalosporins.

1.7 Background to Tanzania and Dar es Salaam

The fieldwork conducted in this PhD was done in Dar es Salaam, Tanzania. The population of Tanzania is approximately 60 million, of whom 30% live in urban areas including Dar es Salaam[84]. The population of Dar es Salaam is on average wealthier and better educated than the rest of Tanzania, with 84% of households falling into the highest wealth quintile. Among women of childbearing age (15-49 years), 44% have completed secondary school and 66%

are employed; 63% in unskilled labour or domestic service. Across all urban areas of Tanzania, 56% of households access mains electricity and 92% own a mobile telephone.

The maternal mortality ratio in Tanzania in 2015-16 was 556 per 100,000 live births and perinatal mortality in urban areas was 47 per 1000 pregnancies lasting over 7 months. In Dar es Salaam, 94% of women deliver in a health facility and 17% deliver by caesarean section, almost half of which are elective operations. Despite this high facility delivery rate, only 58% of women and 69% of newborns have a postnatal check in the first 2 days after giving birth and 38% of women have no postnatal check in the first 6 weeks. Many women (61%) describe at least one problem with accessing health care; money problems (40%) and distance to health facility (37%) being the most common[84].

1.8 Aims and objectives

In response to the knowledge gaps and measurement challenges described above, this PhD aims to improve understanding of the measurement and incidence of, and risk factors for maternal peripartum infection, with a particular focus on LMICs. A comparison of measurement methods should help to explain the heterogeneity of results, highlight challenges and limitations, and lead to improved methods in future research. Estimates of incidence and assessment of risk factors will draw attention to the scale of the problem and potential preventive activities. This information can be used to advocate for improved policy and practice, and ultimately enhance efforts to prevent disease, while protecting the efficacy of antibiotics.[38]

To meet this aim, I conducted a systematic literature review of infection incidence, narrative reviews of measurement methods, and primary data collection in Tanzania. In doing so, I sought to address the following questions:

1. What is the global and regional incidence of maternal peripartum infection in existing literature?
2. How is incidence of maternal peripartum infection measured in existing literature and what are the strengths and limitations of these methods? With particular reference to:
    - Data collection methods to identify cases
    - Infection definitions
3. Considering the importance of identifying infection in a cohort of postpartum women, what are the strengths and limitations of methods used in the literature to conduct postpartum follow-up of mothers and newborns?
4. Applying lessons learnt on infection measurement, is telephone surveillance of postpartum infection feasible in urban Tanzania? What are the factors associated with coverage and efficiency
5. What is the incidence of postpartum infection in urban Tanzania, measured by telephone surveillance?
6. What are the risk factors and consequences of postpartum infection in urban Tanzania?

1.9 Structure of thesis

This thesis is presented as a combination of three papers, two published and one unpublished, with additional chapters of methods and results. An introduction to each of the three papers details the role of the candidate, while a cover sheet provides publication details and the role of co-authors. The published papers have been formatted and edited to bring them in line with the style of the thesis overall. The published versions are provided in the appendix.

Chapter 1 provides the background to maternal peripartum infection incidence, measurement and risk factors, and presents the aims and structure of this thesis.

Chapter 2 presents a published systematic review, meta-analysis and meta-regression to answer question 1.

Chapter 3 presents the methods and results of an additional analysis of the studies included in the published systematic review, to answer question 2.

Chapter 4 presents the methods and results of a literature review, to answer question 3.

Chapter 5 presents the methods for a postpartum telephone surveillance study conducted in Tanzania, to address questions 4-6.

Chapter 6 presents a paper (unpublished) on the feasibility of the surveillance study conducted in Tanzania, to answer question 4.

Chapters 7 presents a published paper of the incidence, risk factors and consequences of infection in the Tanzanian study, to answer questions 5 and 6.

Chapter 8 discusses the key findings and their implications for future research and practice

Chapter 2. Incidence of maternal peripartum infection: A systematic review and meta-analysis

2.1 Introduction

The first question asked by this PhD is 'what is the global and regional incidence of maternal peripartum infection in existing literature?' To address this question, I conducted a systematic review of published literature from the preceding 10 years that reported the frequency of maternal peripartum infections. I conducted meta-analyses of the results to produce pooled incidences of infection, and meta-regressions to investigate heterogeneity between studies.

I conceived the methods within the framework for systematic reviews provided by the Maternal Morbidity Working Group of the WHO. I developed the specific research question, search strategy, extraction forms and analysis. I received some advice on the search strategy from a librarian at London School of Hygiene and Tropical Medicine (LSHTM) and colleagues who had conducted maternal morbidities reviews within LSTHM. I conducted the database search, title and abstract screening, full-text screening, and data extraction, together with the second author, Ana Montoya. Two other co-authors contributed to the screening and extraction process. With statistical support from Clara Calvert and Andrea Rehman, I developed the analysis plan and conducted the meta-analyses and meta-regressions. I produced the tables of results and Forest Plots, wrote the first draft of the paper, and led on all revisions.

2.2 Cover Sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	310061	**Title**	Dr
First Name(s)	Susannah		
Surname/Family Name	Woodd		
Thesis Title	Measurement, incidence and risk factors of Maternal Peripartum Infection		
Primary Supervisor	Professor Oona Campbell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Medicine		
When was the work published?	December 10th 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the methods within the framework for systematic reviews provided by the Maternal Morbidity Working Group of the WHO. I developed the specific research question, search strategy, extraction forms and analysis plan. I conducted the database search, title and abstract screening, full-text screening, and data extraction, together with other authors. With statistical support from other authors I conducted the meta-analyses and meta-regressions. I produced the tables and figures, wrote the first draft of the paper and led on all revisions.

SECTION E

Student Signature	[redacted]
Date	18/11/21

Supervisor Signature	[redacted]
Date	10/11/22

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The published article[85] is reproduced as Appendix A

2.3 Manuscript 1. Incidence of maternal peripartum infection: A systematic review and meta-analysis

Short title: Incidence of maternal peripartum infection

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2.3.1 Abstract

Background

Infection is an important, preventable cause of maternal morbidity and pregnancy-related sepsis accounts for 11% of maternal deaths. However, frequency of maternal infection is poorly described and to our knowledge it remains the one major cause of maternal mortality without a systematic review of incidence. Our objective was to estimate the global incidence of maternal peripartum infection.

Methods and Findings

We searched Medline, EMBASE, Global Health and five other databases from January 2005 to June 2016 (PROSPERO: CRD42017074591). Specific outcomes comprised chorioamnionitis in labour, puerperal endometritis, wound infection following caesarean section or perineal trauma, and sepsis occurring from onset of labour until 42 days postpartum. We assessed studies irrespective of language or study design. We excluded conference abstracts, studies of high-risk women and data collected before 1990. Three reviewers independently selected studies, extracted data, and appraised quality. Quality criteria for incidence/prevalence studies were adapted from the Joanna Briggs institute. We used random-effects models to obtain weighted pooled estimates of incidence risk for each outcome, and meta-regression to identify study-level characteristics affecting incidence.

From 31,528 potentially relevant articles, we included 111 studies of women in labour or postpartum from 46 countries. Four studies were randomised controlled trials, two were before-after intervention studies and the remainder were observational cohort or cross-sectional studies. The pooled incidence in high-quality studies was 39 per 1000 (95% Confidence Interval (CI) 18-68 per 1000) for chorioamnionitis, 16 per 1000 (95% CI 9-25 per 1000) for endometritis, 12 per 1000 (95% CI 10-15 per 1000) for wound infection, 0.5 per 1000 (95% CI 0.3-0.7 per 1000) for sepsis and 11 per 1000 (95% CI 3-24 per 1000) for maternal peripartum infection. 19% of studies met all quality-criteria. There was little data from developing countries and marked heterogeneity (I^2>99%) in study designs and infection definitions, limiting the interpretation of these estimates as measures of global infection incidence. Interpretation is further limited by the inclusion of studies that were not conducted at population-level and of those restricted to low-risk groups of women. In addition, studies published after June 2016 have not contributed to our findings.

Conclusions

In this study we observed pooled infection estimates of almost 4 per 1000 in labour and between 1-2 per 1000 postpartum indicating that maternal peripartum infection remains an important complication of childbirth. Incidence risk appears lower than modelled global estimates, although differences in definitions limit comparability. Better quality research, using standard definitions, is required to improve comparability between study settings and to demonstrate the influence of risk factors and protective interventions.

2.3.2 Introduction

Infection is an important preventable cause of maternal morbidity and mortality, with pregnancy-related sepsis accounting for approximately 11% (95% uncertainty interval 5.9%-18.6%) of maternal deaths globally[7]. Infection also contributes significantly to deaths from other causes[27] and leads to serious consequences, including chronic pelvic inflammatory disease, ectopic pregnancy and infertility[14]. Intrapartum fever also increases the risk of perinatal death[15]. Improved understanding of maternal infection is key to achieving the sustainable development goals (SDGs) and executing the strategies toward ending preventable maternal and neonatal mortality. However, the frequency of infection in pregnancy is poorly understood; review of maternal morbidity identified no published systematic literature review of infection incidence, making it the one major direct cause of maternal morbidity without such a review to our knowledge[86]. A commonly cited estimate of 40 per 1000 for puerperal sepsis, modelled for the 2000 Global Burden of Disease (GBD), is based on a single-centre United States (US) study, two African studies comparing home and hospital, and a Cochrane review on antibiotic prophylaxis for caesarean section comprising 66 studies[6]. Recent 2017 GBD data estimate 12.1 million incident cases of maternal sepsis and other maternal infections, including mastitis[19].

A challenge in quantifying the incidence of pregnancy-related infection is the variety of terms, definitions, time-periods, sites and severity of infections used, partly reflecting the breadth of infectious disease in this period. A commonly used term such as puerperal sepsis can range from localised symptoms and signs of genital tract infection[38] to more disseminated disease, including peritonitis, pyemia and sepsis[36], and with time-periods that can vary from the first 10 days[37] to 42-days postpartum[36] and sometimes include sepsis in labour[38]. In partial response to this quantification challenge, a new definition for maternal sepsis was published in early 2018[27]. However, the challenges remain in relation to less severe disease.

This review focusses on recent epidemiological evidence for the incidence of 'maternal peripartum infection', defined by the World Health Organization (WHO) in 2015 to encompass infections of the genital tract and surrounding tissues from onset of labour or rupture of membranes until 42 days postpartum[39]. At a time of increased global attention on maternal sepsis, this group of infections was chosen as being notable for causing over half the cases of severe maternal sepsis in the UK. In addition, the direct association of maternal peripartum infection with the process of giving birth presents key opportunities for prevention and for protecting the efficacy of antibiotics, amidst growing concerns about

antimicrobial resistance[39]. To aid prioritisation by decision makers and guide future research, we set out to estimate the average global incidence of maternal peripartum infection.

2.3.3 Methods

The review was registered with PROSPERO [CRD42017074591] and conducted according to PRISMA guidelines (Appendix B).

Search strategy

We searched Medline, EMBASE, Global Health, Popline, CINAHL, the Latin American and Caribbean Health Science Information (LILACS) database, Africa-Wide Information, and regional WHO on-line databases using Global Index Medicus from January 2005 to June 2016. Search strategies were customised to each electronic database's individual subject headings and searching structure (Appendix C). The approach was to include articles if their abstract, title, or keywords contained a maternal term, an infection term, and a term for incidence/prevalence.

Exclusion Criteria

All identified studies were systematically assessed, irrespective of language or study design. For clinical trials where the infection risk differed between study arms ($p<0.05$), we used the control arm or the arm most similar to usual care. There were no case-control studies in which incidence/prevalence could be estimated.

Studies were excluded if their titles or abstracts indicated they had any of the following:

- No data on maternal peripartum infection
- A composite outcome from which it was not possible to extract data on maternal peripartum infection alone
- Only a subgroup of women at higher risk of infection than the general population of peripartum women (e.g. only caesarean section deliveries or only women with diabetes)
- No quantitative data
- No numerator
- No denominator for the total population of women
- Fewer than 30 participants
- Data collected before 1990, because of potential decreases in incidence over time. If a study spanned 1990 but disaggregated by year, data from 1990 onwards were used
- Conference and poster abstracts

- No primary data, except for reviews, which were hand-searched for additional primary studies.

We sought the full text for all remaining studies, including those where the abstract had insufficient information to decide. The same exclusion criteria applied to full texts.

Outcome definitions

WHO defines maternal peripartum infection as 'a bacterial infection of the genital tract or surrounding tissues occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum'[39]. We considered this to encompass specific constituent infections, namely chorioamnionitis in labour, puerperal endometritis, and wound infection following caesarean section, perineal tear or episiotomy. We included sepsis occurring within the defined time-period, restricted to sepsis of genital tract or wound origin when possible. We included a fifth category, 'maternal peripartum infection', for studies with a composite outcome of two or more of the above infection types or those that used a broader or unspecified definition of infection within the peripartum period.

Measures of Frequency

We aimed to estimate the incidence risk of infection in the peripartum period, defined as cases of infection emerging until 42 days postpartum among women who were infection-free at the start of labour. As the starting point is clear (labour) and the follow-up period is short (42 days), we considered most studies to have approximated a measure of incidence risk (rather than a rate or period prevalence), and report the results as such.

Screening and data extraction

We used the Institute of Education software, Eppi-Reviewer 4, to store citations and full-text articles, to detect duplicates, and to code screening and data extraction. SW and AM double-screened 300 (approximately 1%) title and abstracts to ensure consistency; the rest were single-screened. Full-text screening and extraction was conducted by SW, AM and MB, with approximately 8% of articles double-screened and extracted to ensure consistency. AM extracted Spanish papers, and MB extracted Portuguese papers. LP screened over 40 Chinese-language papers and extracted from the included studies. Queries were resolved through discussion and, when necessary, with input from a third reviewer (OMRC). Nine authors were contacted to clarify study eligibility.

Data extracted included language, location and dates of study, study population, study design, sampling, outcome definition, denominator, time-period for observing infection, data source, diagnosis, and incidence of infection (Appendix D).

Critical appraisal of studies

We appraised the quality of each study outcome according to criteria in Table 2.1, adapted from Joanna Briggs Institute criteria for assessing incidence/prevalence studies[87]. For each criterion, estimates were classified as having met the criteria or not or of providing insufficient information to judge. Estimates meeting all five criteria were considered high-quality.

To determine if a standard definition was used (criterion 3), we compared the study definition to internationally recognised definitions for each infection (Table 2.2). The most recent definition of sepsis (Sepsis-3) agreed upon in early 2016[88] and the related definition for maternal sepsis[27] proposed by WHO and JHPIEGO in 2017 were not used as these supersede our included studies, however, these revised definitions are similar to the definition for severe sepsis.

If all study cases fell within these definitions, the criterion was met, even if the study definition was more restrictive and may have consequently underestimated infection incidence. Reference to national guidelines or obstetric textbooks met the criteria, as did clearly specified and appropriate ICD-9/10 codes (Table 2.3). No codes exactly match the WHO definition of maternal peripartum infection, but we classified studies using ICD-9 670 (Major puerperal infection, including endometritis and puerperal sepsis)[89] and ICD-10 O86 (other puerperal infection including endometritis and wound infection)[90] as having measured maternal peripartum infection.

Table 2.1: Quality Assessment Criteria

	Quality assessment criteria	
1	Were study participants representative of the study target population? (appropriate recruitment strategy and sampling)	Selection bias
2	Was data analysis conducted with sufficient coverage of the identified sample? (refusals and loss are small (<15%) and unlikely to be related to the outcome)	Attrition/missing data
3	Was a clear, standard definition used for maternal infection?	Measurement bias
4	Was infection measured reliably using trained/educated data collectors, appropriate/reliable diagnostic procedures, or reliable forms of retrospective data (clinical records meeting standard definitions)	Measurement bias
5	Were study subjects and setting described in sufficient detail to determine whether results are comparable with other studies?	Poor characterisation of study population

Table 2.2: Standard Definitions for Infection outcomes

Infection	**Subgroup**	**Definition**	**Additional comments**
Chorioamnionitis[91]		Fever (>38°C), plus one of: maternal tachycardia, fetal tachycardia, uterine tenderness, or foul-smelling vaginal discharge during labour.	Studies of histological chorioamnionitis and microbial invasion of the amniotic fluid were excluded from the review
Endometritis[92]		At least two of the following: fever (>38°C), abdominal pain with no other recognised cause, uterine tenderness with no other recognised cause, or purulent drainage from uterus.	
Wound Infection[92]	Superficial	One of: a) purulent drainage, b) organisms cultured, c) incision deliberately opened AND at least one of pain, tenderness, swelling, erythema or heat, or d) diagnosis by attending doctor.	
	Deep	Involves fascia and muscle and one of a) purulent drainage, b) spontaneous dehiscence or reopening AND organisms identified AND symptoms similar to superficial infection, or c) abscess.	

	Organ/space	Deeper than fascia and meets criterion for a specific organ/space infection e.g. endometritis, and one of a) purulent drainage from a drain, b) organisms, or c) abscess	
Sepsis[25]	Infection plus SIRS[a]	At least 2 of a) temperature >38°C or <36°C, b) heart rate >90/minute, c) respiratory rate >20/minute or $PaCO_2$[b] <32 mm Hg, and/or d) WCC[c] >12,000/mm^3 or <4000/mm^3 or >10% immature bands	We also accepted slightly different ranges (e.g. heart rate >100/minute, WCC[c] >17,000/mm^3) because of uncertainty regarding appropriate values for pregnant and postpartum women
	Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Abnormalities included, but were not limited to, lactic acidosis, oliguria, or an acute alteration in mental status	Studies that used management indicators of severe disease such as ICU admission or prolonged hospital stay were also accepted.
	Blood stream infection	Positive blood culture	
Maternal Peripartum Infection		Two or more of the above definitions, presented as a composite outcome	

[a]SIRS – Systemic inflammatory response syndrome. [b]$PaCO_2$ – Partial pressure of Carbon Dioxide. [c]WCC – White Cell Count.

Table 2.3: ICD 9/10 codes for infection definitions

Outcome		**ICD-9**	**ICD-10**
Chorioamnionitis		658.4, 659.2, 762.7	O41.12
Endometritis		670.1	O86.12
Wound infection		674.3 – But no studies specified ICD codes	
Sepsis:	SIRS* (including puerperal sepsis)	670.2, 995.91	O85
	Severe Sepsis	995.92, 785.52	R65.20, R65.21
	Bacteraemia/Septicaemia	038, 659.3, 790.7	R78.81, A40, A41
Peripartum infection		670	O86
		Plus a combination of the codes above	

*SIRS – Systemic inflammatory response syndrome

Data Management and Analysis

We analysed infection incidence estimates separately for chorioamnionitis, endometritis, wound infection, sepsis, and maternal peripartum infection.

We exported and managed data in Microsoft Excel and STATA 15.1. We extracted information on study characteristics with potential to influence the risk of infection for use in meta-regression. We categorised geographical location using SDG world regions[93]. We created a variable named 'study extent' to reflect how nationally representative the study population might be: national level (total population or representative sample), state/regional level, health facility network (e.g. surveillance network or insurance scheme), two or more facilities or field sites, single facility or field site. Data collection was coded as routine or specific to the study. We coded diagnostic method as clinical or based on reported symptoms, except for chorioamnionitis, for which we compared the use of ICD codes with specified clinical signs. We grouped total follow-up time as being until hospital discharge, 7 days, 30 days or 42 days postpartum. We grouped studies as only being of low-risk women (e.g., low obstetric/medical risk, live birth, vaginal delivery, singleton pregnancy or term birth) versus including all women who delivered.

We conducted meta-analyses in R version 3.5.0 using the meta[94] and metaphor[95] packages to obtain a weighted pooled estimate of incidence of each infection outcome 1) all studies, 2) for high quality studies, and 3) stratified by world region. The pooled estimate of sepsis was also stratified by three levels of severity. When studies using nationally representative databases measured the same infection outcome over the same dates, we kept the study with the longest time-period.

Infection incidence risk (as a proportion) was transformed using the Freeman-Tukey transformation to approximate a normal distribution and stabilise the variance[96, 97]. Because study designs and outcome definitions varied, we used random effects to combine study estimates[87]. The tau^2 measure of between-study heterogeneity was estimated using restricted maximum likelihood[98]. The pooled estimates were back-transformed, and results were presented as proportions. We generated prediction intervals to provide a predicted range for the true incidence in any individual study[99]. As sensitivity analyses, we calculated standardised residuals, removed outliers with $p>0.05$ (based on the t distribution), and noted changes in heterogeneity and precision intervals.

We used meta-regression and reported odds ratios (OR), 95% Confidence Intervals (CIs), and p-values from Wald-type tests to explore whether world region or study characteristics influenced infection incidence. Infection risk was log-transformed, and univariate random-effects models were used to explore associations between each variable and odds of

infection. World region and variables with evidence of association ($p<0.1$) were included in multivariable models unless data were sparse or closely correlated.

2.3.4 Results

Figure 2.1 shows the 31,528 potentially relevant articles identified, of which 1543 were eligible for full-text review after title and abstract screening. We could not find two full texts. Of the remaining 1541 full texts screened, 111 were included. Common reasons for exclusions were ineligible types of publication (N=493) or for which the study involved only a subgroup of high-risk women (N=405), e.g. caesarean deliveries only. Most included papers were in English, with six in Chinese[100-105], four in Spanish[106-109], four in Portuguese[110-113], three in French[114-116] and one each in Bulgarian[117], Bosnian[118] and Romanian[119]. Twenty-seven studies reported chorioamnionitis, 38 reported endometritis, 28 reported wound infection, 27 reported sepsis, and 28 reported maternal peripartum infection (Additional Tables of Results).

Description of Study Populations

The 111 studies included data from 46 countries. Four studies were randomised controlled trials[102, 120-122], two were before-after intervention studies[101, 123] and the remainder were observational cohort or cross-sectional studies. Three studies had multiple countries: one covered nine European countries[124], a second involved nine Asian countries[125] and the third had sites in South Asia, Latin America and sub-Saharan Africa[126]. Of the remaining studies, 57 occurred in North America and Europe of which 38 were in the US. There were 14 in Central and South Asia, 12 in East and South-east Asia, 11 in Latin America, seven in sub-Saharan Africa, six in Western Asia and North Africa and one in Australia. Nearly half the studies were of one hospital, but many studies also attempted to capture all births in a country, or a representative sample of them using birth certificate data or national hospital databases. In the regions/countries using such hospital databases (North America, Europe, Japan, Thailand), over 95% of all births are in hospital facilities. In low- and middle-income countries (LMICs), only nine studies (in 10 countries: Tanzania, Nigeria, Egypt, Bangladesh, India, Pakistan, Argentina, Guatemala, Kenya and Zambia) sought to capture population-level data.

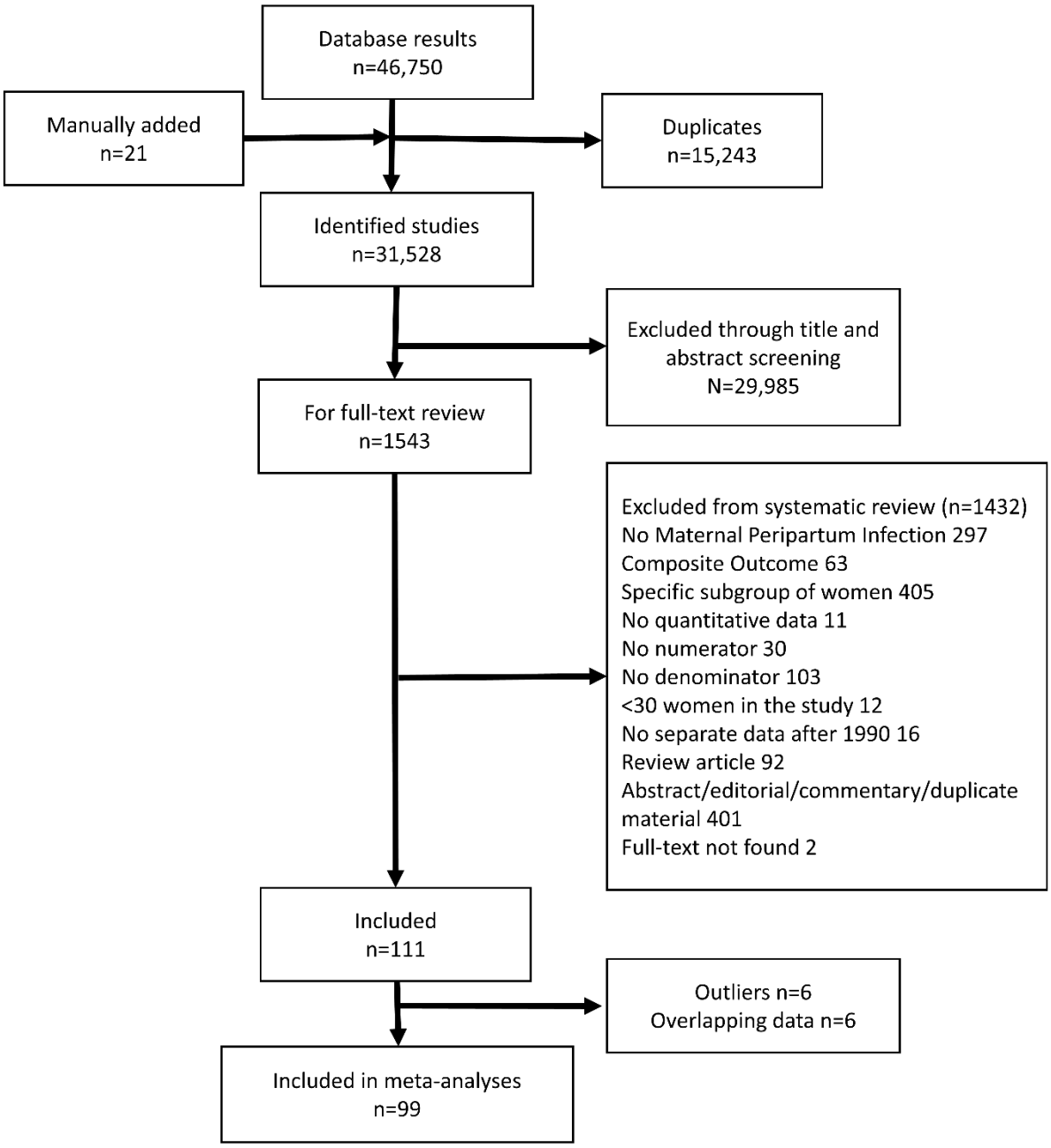


Fig. 2.1: Flow diagram of studies

Study Quality

Table 2.4 shows the quality scores for the studies. When studies had multiple infection outcomes, the lowest score is presented. Of 111 studies, 19% met all five quality-criteria, 37% met four, 22% met three, 14% met two, 7% met one and 2% did not meet any. Only 41% of studies used a standard definition for infection and 37% also measured infection reliably, thereby meeting both measurement criteria. In 13% of studies, there was attrition or missing data in >15% of observations, and 31% of studies had a risk of selection bias. Women or study sites were poorly characterised in 25% of studies.

Incidence of infection

Incidence results are presented separately for the five infection outcomes (Table 2.5). Six studies contributed no data to the meta-analyses because of overlapping populations and dates[127-132]. Heterogeneity was high, as measured by I^2 (>99% for all pooled estimates), but tau^2 values were small and are probably more meaningful for these data since they measure actual between-study variance[133]. We identified six outlier estimates, all with high infection incidence, described below. One single-facility US study of chorioamnionitis in low-risk pregnancies provided no infection definition[134]. Three studies classified as endometritis from Bangladesh, Pakistan, and Turkey relied on self-reported symptoms of pelvic or vaginal infection[135-137]. An Indian study gave no definition for their measure of self-reported puerperal sepsis collected up to six months after delivery[138], and similarly, a Nigerian study gave no definition for their measure of self-reported postpartum infection collected up to three years after giving birth[139]. Removal of these outliers did not change I^2 but led to important reductions in both tau^2 and prediction intervals; therefore, meta-analyses results are presented after removing these outliers.

Table 2.4: Quality of 111 included studies

Yes	
Unclear	
No	

Author (date)	Sampling	Coverage	Definition	Data collection	Sufficient detail
Abramovici (2014)					
Acosta (2013)					
Admaty (2012)					
Ahnfeldt-Mollerup (2012)					
Al-Ostad (2015)					
Andersson (2011)					
Avci (2015)					
Ayzac (2008)					
Bailit (2006)					
Bailit (2013)					
Bakr (2005)					
Balestena (2015)					
Bauer (2013)					
Bear (2016)					
Belfort (2010)					
Ben (2007)					
Benincasa (2012)					
Berg (2009)					
Bianco (2013)					
Bleich (2012)					
Boccardo (2013)					
Bodner (2011)					
Borders (2012)					
Braun (2015)					
Butchon (2014)					
Callaghan (2008)					
Cape (2013)					
Caughey (2007)					
Cavazos-Rehg (2015)					
Charrier (2010)					
Cheng (2007)					
Cheng (2010)					
Chongsuvivatwong (2010)					

Danilack (2015)					
Danish (2010)					
Darmstadt (2009)					
Dasgupta (2014)					
David (2012)					
Debasmita (2010)					
Dimitriu (2010)					
dong (2009)					
Dong (2010)					
Dotters-Katz (2015)					
Dumas (2008)					
Edwards (2015)					
Escosteguy (2013)					
Ezugwu (2011)					
Fassett (2013)					
Fronczak (2005)					
Galyean (2009)					
Geller (2010)					
Getahun (2010)					
Gibson (2014)					
Goff (2013)					
Gozum (2005)					
Grotegut (2008)					
Guendelman (2006)					
Guimaraes (2007)					
Harrison (2015)					
Huda (2012)					
Ivanov (2014)					
Iyengar (2012)					
Jaleel (2009)					
Janssen (2009)					
Jin (2011)					
Jokhio (2005)					
Karlstrom (2013)					
Karolinski (2013)					
King (2012)					
Knowles (2014)					
Kovavisarach (2005)					
Kovavisarach (2010)					
Kuklina (2008)					
Kyser (2012)					

Latif (2013)					
Laws (2014)					
Leth (2009)					
Liu (2007)					
Liu (2010)					
Lulu (2014)					
Luz (2008)					
Lyndon (2012)					
Magann (2008)					
Magann (2011)					
Malloy (2014)					
Maric (2006)					
Matsuda (2011)					
Mayi-Tsonga (2007)					
Nasreen (2007)					
Nelson (2014)					
Ngoc (2005)					
Ngoga (2009)					
Okumura (2014)					
Oladapo (2007)					
Osmundson (2011)					
Pallasmaa (2008)					
Pallasmaa (2015)					
Palmer (2015)					
Panichkul (2007)					
Peret (2007)					
Ramírez-Villalobos (2009)					
Saizonou (2014)					
Sanabria (2011)					
Shah (2011)					
Shazia (2015)					
Shriraam (2012)					
Simoes (2005)					
Tabcharoen (2009)					
Wang (2010)					
Winani (2007)					
Zhang (2005)					

Table 2.5: Summary estimates for all infection outcomes

	All studies		Meta-analyses of all studies (Excluding Outliers)			High-Quality studies		Meta-Analysis of High-Quality studies		
Infection Type	N	Range per 1000	N	Pooled Incidence per 1000 (95% CI)	95% PI*	N	Range per 1000	N	Pooled incidence per 1000 (95% CI)	95% PI*
Chorioamnionitis	28	6-197	21	41 (25-62)	0-180	8	9-126	7	39 (18-68)	0-179
Endometritis	41	0-162	36	14 (9-19)	0-59	6	3-25	6	16 (9-25)	0-60
Wound infection	30	0-109	30	21 (12-32)	0-112	1	12	1	12 (10-15)	-
Sepsis	31	0-38	26	1.1 (0.4-2.1)	0-6	13	0.2-1.3	11	0.5 (0.3-0.7)	0-1.8
Maternal peripartum infection	30	1-181	26	19 (13-28)	0-79	7	2-58	7	11 (3-24)	0-83

*PI – Prediction Interval

Chorioamnionitis

Chorioamnionitis incidence ranged from 6 to 197 per 1000 with a pooled incidence of 41 per 1000 (95% CI 25-62 per 1000) (Table 2.5). The prediction interval was wide, suggesting the incidence in any future study could lie between 0 and 180 per 1000. In North America and Europe, the pooled incidence was 49 per 1000 (Fig. 2.2). Only three studies were conducted in other regions. In the univariate meta-regression (Table 2.6), study extent explained 38% of the heterogeneity, with the highest incidence seen in single-hospital studies. Studies including only singleton deliveries or only term pregnancies also had higher incidence, but almost all of these studies were conducted at single facilities.

Seven high-quality studies (meeting all five quality criteria) had a pooled infection incidence of 39 per 1000. The lowest incidence (9 per 1000) was reported in low-risk women delivering at a hospital in Bangkok, Thailand[140]. The other six estimates were from the US. Two used the US National Inpatient Sample (NIS) database, and recorded a chorioamnionitis ICD-9 code in 17 per 1000 women in 1998-2008[141] and 26 per 1000 in 2008-2010[142]. Two studies from Kaiser Permanente Medical Program (KPMP) hospitals in California also used ICD-9 codes and recorded 35 per 1000 women in 1995-1999[143] and 40 per 1000 in 2010[144]. The highest incidences were reported in studies at single tertiary hospitals: 61 per 1000 in Chicago[145], and 126 per 1000 in California (among women delivering a live, single, term baby)[146].

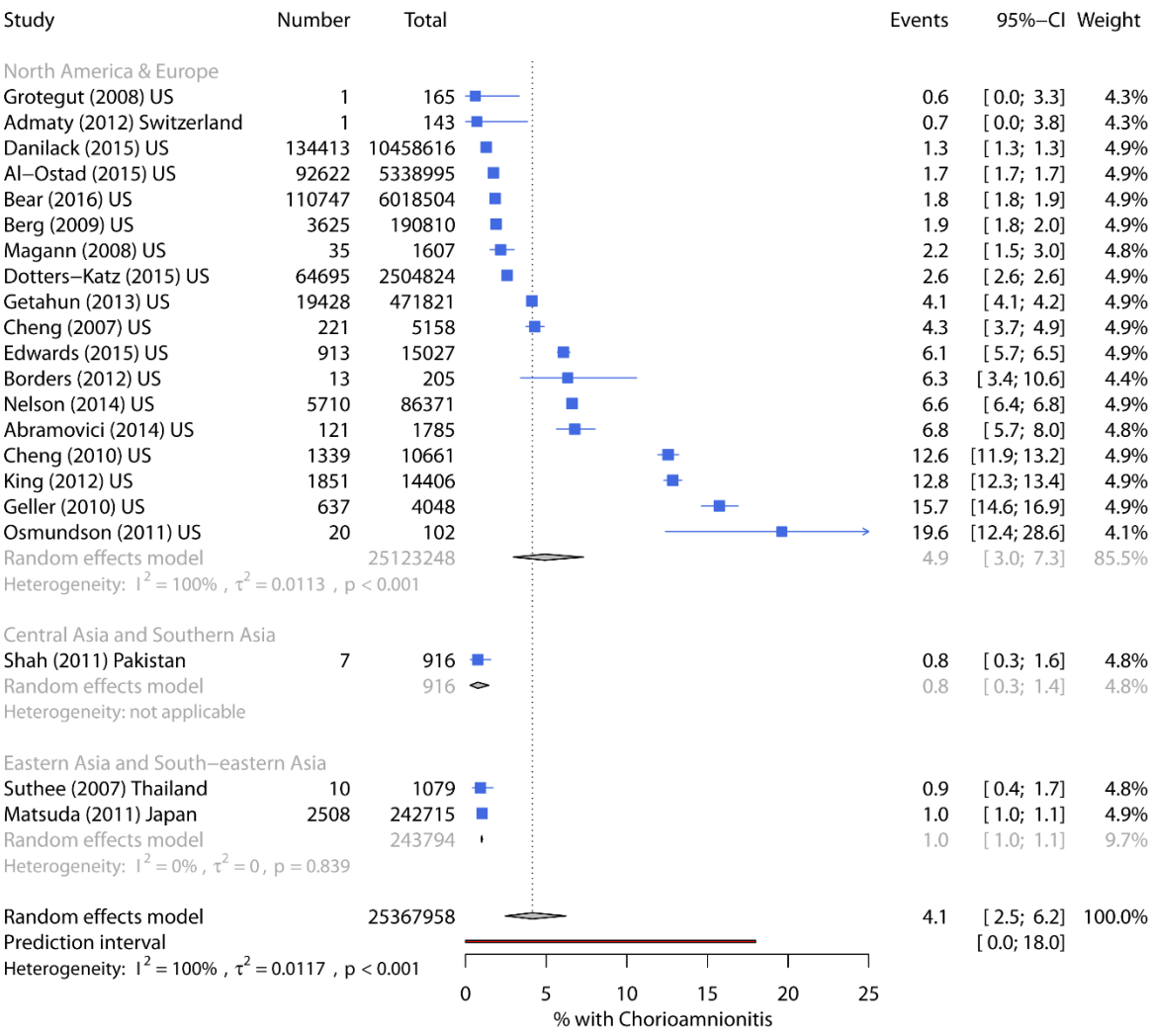


Fig. 2.2: Forest Plot of chorioamnionitis incidence by world region

Table 2.6: Chorioamnionitis univariate meta-regression

Factor		No. of studies	Odds Ratio	95% CI	p-value	R^2 (%)
Region	North America & Europe	18	1			
	Central Asia & South Asia	1	0.17	0.02-1.26		
	East Asia & South-east Asia	2	0.22	0.05-0.87	0.03	23.7
Study extent	Single site	12	1			
	2+ sites	2	0.11	0.02-0.54		
	Network	2	0.32	0.09-1.14		
	State	1	0.29	0.05-1.58		
	National	4	0.28	0.11-0.74	0.007	37.6
Number of foetuses	All pregnancies	8	1			
	Singleton only	13	2.64	1.07-6.53	0.04	13.9
Delivery mode	All deliveries	18	1			
	Vaginal only	3	1.41	0.37-5.43	0.61	0
Gestational age	All gestations	12	1			
	Term only	9	3.36	1.56-7.24	0.002	35.3
Live birth	All deliveries	12	1			
	Live birth only	9	1.16	0.44-3.04	0.77	0
Low risk	All women	16	1			
	Low-risk pregnancy only	5	1.56	0.52-4.69	0.43	0
Diagnosis	ICD9/10	6	1			
	Fever and other signs	7	0.85	0.25-2.95		
	Fever only	8	1.47	0.46-4.74	0.63	0
Data collection	Routine	14	1			
	Study	5	1.62	0.51-5.19		
	Unclear	2	1.29	0.25-6.52	0.71	0

Endometritis

Endometritis incidence ranged from 0-162 per 1000 with a pooled incidence of 14 per 1000 (95% CI 9-19 per 1000) (Table 2.5). The prediction interval suggests a true incidence of up to 59 per 1000 in future studies. Pooled incidence was similar across most world regions ranging from 13-19 per 1000. However, it was much lower in studies from Eastern Asia & South-eastern Asia at 3 per 1000 (Fig 2.3). In univariate meta-regression no variables were associated with incidence (Table 2.7).

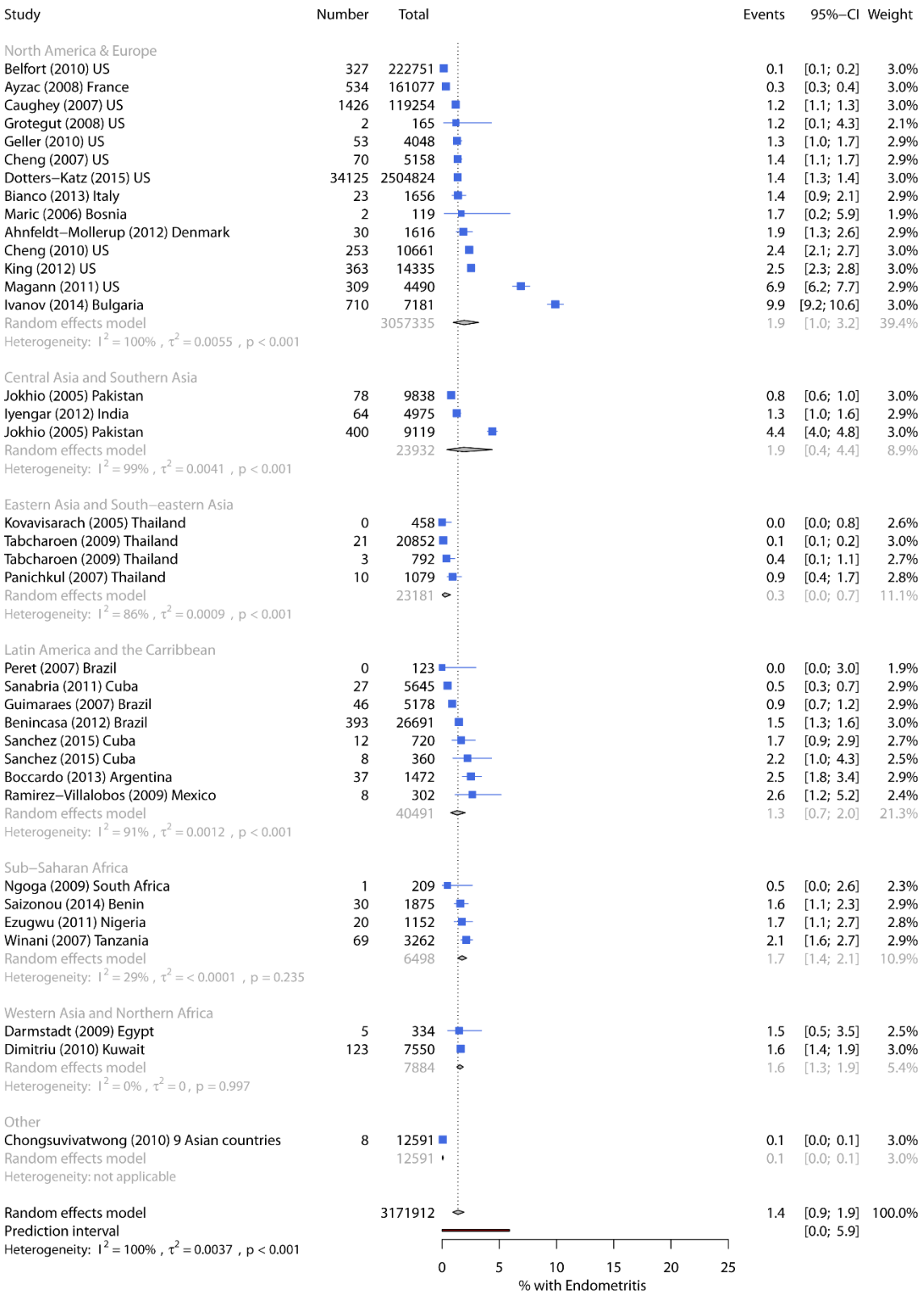


Fig. 2.3: Forest Plot of endometritis incidence by world region

Table 2.7: Endometritis meta-regression

Factor		No. of studies	Odds Ratio	95% CI	p-value	R^2 (%)
Region	North America & Europe	14	1			
	Central Asia & South Asia	3	1.09	0.35-3.46		
	East Asia & South-east Asia	4	0.18	0.06-0.59		
	Latin America & Caribbean	8	0.91	0.39-2.11		
	Sub-Saharan Africa	4	0.99	0.33-2.97		
	West Asia & North Africa	2	1.03	0.25-4.29	0.12	8.0
Study extent	Single site	25	1			
	2+ sites	4	1.82	0.66-4.99		
	Network	2	0.48	0.13-1.81		
	State	2	1.44	0.38-5.51		
	National	2	0.34	0.09-1.29	0.20	6.9
Number of foetuses	All pregnancies	23	1			
	Singleton only	12	1.52	0.75-3.07	0.24	2.6
Delivery mode	All deliveries	31	1			
	Vaginal only	4	0.60	0.19-1.93	0.39	0
Gestational age	All gestations	27	1			
	Term only	8	1.17	0.52-2.64	0.70	0
Live birth	All deliveries	30	1			
	Live birth only	5	1.41	0.55-3.63	0.47	0
Low risk	All women	28	1			
	Low-risk pregnancy only	7	0.72	0.28-1.84	0.49	0
Diagnosis	Clinical	30	1			
	Self-report	5	1.58	0.62-4.02	0.34	0
Data collection	Routine	25	1			
	Study	10	1.25	0.58-2.68	0.57	0
Follow-up*	Hospital discharge	20	1			
	7 days	5	1.13	0.39-3.25		
	8-42 days	9	0.87	0.38-1.96	0.90	0

*Length of follow-up was missing from two studies

Six high-quality studies had a pooled incidence of 16 per 100. The lowest incidence (3 per 1000) was in women delivering vaginally at 66 hospitals in a surveillance network in France[147] with follow-up to 30 days postpartum. The other five studies only reported infections until hospital discharge after childbirth. Endometritis ICD-9 codes were recorded for 14 per 1000 women in the NIS database[142] and 12 per 1000 low-risk deliveries at Kaiser Permanente hospitals in California[143]. Higher infection incidence (24-25 per 1000) was reported in three single-centre studies; two in the US[146, 148] and one in Argentina[106].

Wound Infection

Wound infection incidence ranged from 0-109 per 1000 with a pooled incidence of 21 per 1000 (95% CI 12-32 per 100) (Table 2.5). The prediction interval suggests the incidence could be as high as 112 per 1000 in future studies. Pooled incidence was highest in Eastern Asia & South-eastern Asia (62 per 1000) and lowest in the US & Europe (9 per 1000) (Fig 2.4). In univariate meta-regression, single-site studies were associated with higher infection incidence. Unexpectedly, six studies that only included vaginal deliveries had higher pooled incidence than studies that included all delivery methods. A substantial proportion (44%) of between-study heterogeneity was explained by world region and study extent in multivariable meta-regression (Table 2.8).

Only one study met all five quality criteria and identified 12 per 1000 women with caesarean or episiotomy wound infection from medical records at a single Brazilian hospital[113].

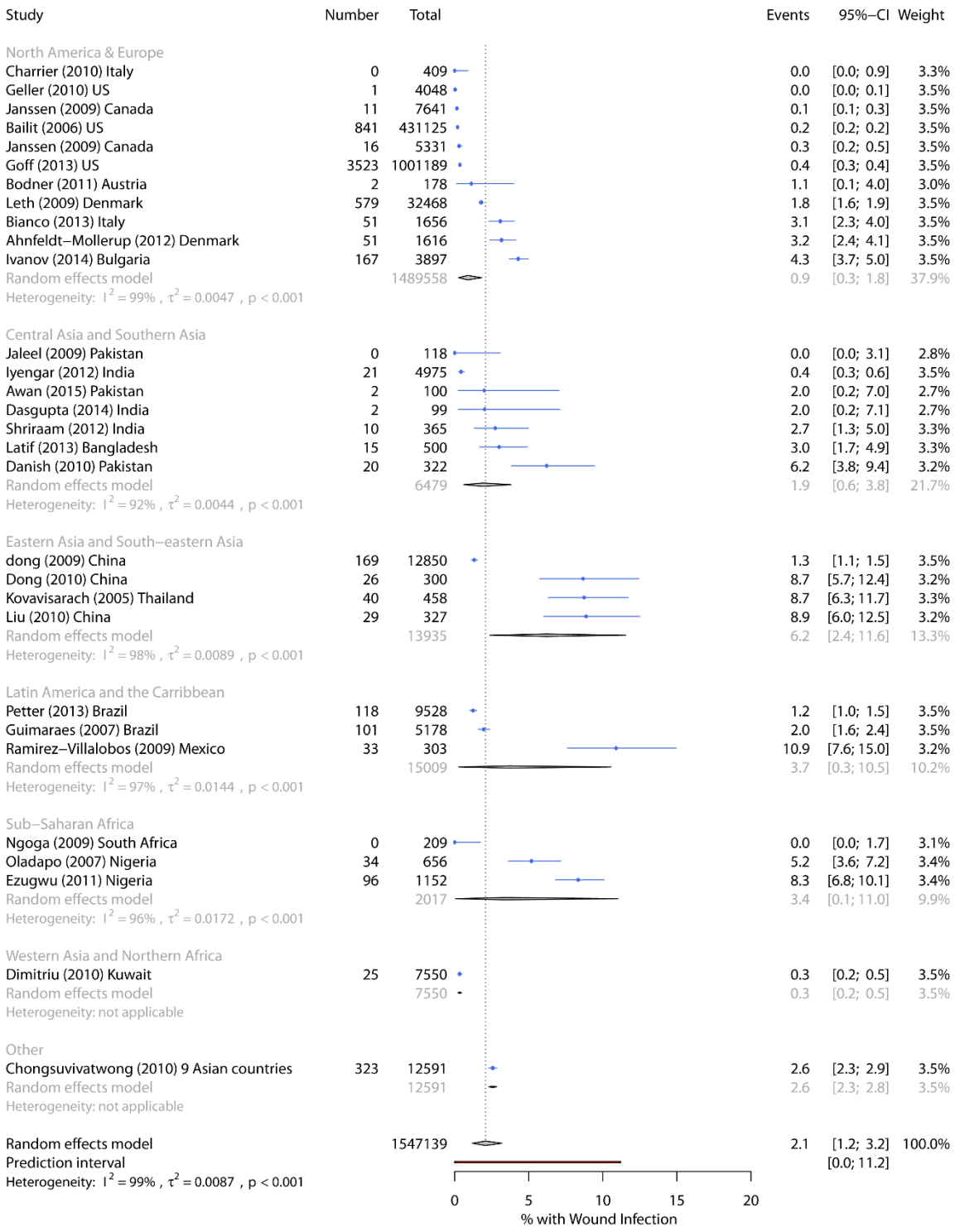


Fig.2.4: Forest Plot of wound infection incidence by world region

Table 2.8: Wound meta-regression

Factor		No. of studies	Odds Ratio	95% CI	p-value	R2 (%)	Adj. OR	95% CI
							R^2=43.78%	
Region	North America & Europe	11	1		0.02	25.2	1	
	Central Asia & South Asia	7	3	0.83-10.82			1.84	0.48-7.12
	East Asia & South-east Asia	4	9.1	2.11-39.20			3.85	0.89-16.72
	Latin America & the Caribbean	3	4.85	0.96-24.52			2.06	0.42-10.06
	Sub-Saharan Africa	3	5.98	1.03-34.69			2.75	0.50-15.22
	Western Asia & Northern Africa	1	0.52				0.22	0.02-2.37
Study extent	Single site	22	1		0.002	37.9		
	2+ sites	2	0.11	0.02-0.80			0.13	0.02-0.94
	State	4	0.13	0.04-0.46			0.24	0.05-1.04
	National	1	0.13	0.01-1.30			0.23	0.02-2.44
Number of foetuses	All pregnancies	21	1					
	Singleton only	8	1.95	0.56-6.75	0.29	3.5		
Delivery mode	All deliveries	24	1					
	Vaginal only	5	4.64	1.21-17.76	0.02	17.8		
Gestational age	All gestations	24	1					
	Term only	5	0.85	0.18-4.08	0.84	0		
Live birth	All deliveries	26	1					
	Live birth only	3	1.31	0.22-7.76	0.76	0		
Low risk	All women	21	1					
	Low-risk pregnancy only	8	0.60	0.17-2.14	0.43	0		
Diagnosis	Clinical	25	1					
	Self-report	4	1.58	0.62-4.02	0.33	0		
Data collection	Routine	16	1					
	Study	8	2.99	0.87-10.25				
	Unclear	5	1.92	0.40-9.19	0.21	5.9		
Follow-up*	Discharge	17	1					
	Day 7	2	3.57	0.42-30.25				
	8-42 days	8	1.26	0.38-4.22	0.50	0		

*Length of follow-up was missing from two studies

Sepsis

Incidence of sepsis, combining systemic inflammatory response syndrome (SIRS), severe sepsis and blood stream infection, ranged from 0-38 per 1000 with pooled incidence of 1.0

per 1000 (95% CI 0.4-2.1 per 1000) (Table 2.5). The prediction interval suggests the incidence could be up to 6 per 1000 in future studies. Pooled incidence was 1.1 per 1000 for SIRS, 0.8 per 1000 for severe sepsis, and 1.0 per 1000 for blood stream infection (Fig. 2.5). The majority of estimates came from the US & Europe, with a pooled incidence of 1.0 per 1000. Latin America had a similar incidence of 0.8 per 1000 while Central & South Asia had slightly more infection (2.7 per 1000) (Fig 2.6). In univariate analysis, there was weak evidence for an association with world region, no evidence for an association with severity, but increased incidence of sepsis with longer follow-up. Women with singleton pregnancies had higher infection incidence but the two studies involved also had longer follow-up periods. Data was too sparse to investigate other factors or conduct multivariable meta-regression (Table 2.9).

Eleven high-quality estimates produced a pooled incidence of 0.5 per 1000. Four high-quality estimates of SIRS used data from the delivery admission: NIS (0.3 per 1000)[149], all Californian hospitals (1.0 per 1000)[4], all hospitals in Thailand (1.3 per 1000)[150], and one reference hospital in Sao Paolo, Brazil (0.4 per 1000)[111]. Incidence of severe sepsis with organ dysfunction was low: NIS (0.1 per 1000)[149], Californian hospitals (0.5 per 1000)[4], and no cases in a near-miss study at one hospital in Gabon[115]. US data from NIS and the National Hospital Discharge Survey (NHDS) estimated blood stream infection at 0.2[142] and 0.7 per 1000[151]. One region in Denmark and 2 hospitals in Ireland followed women until 30 and 42 days postpartum and identified blood stream infection in 0.6[152] and 1.1 per 1000[153] respectively.

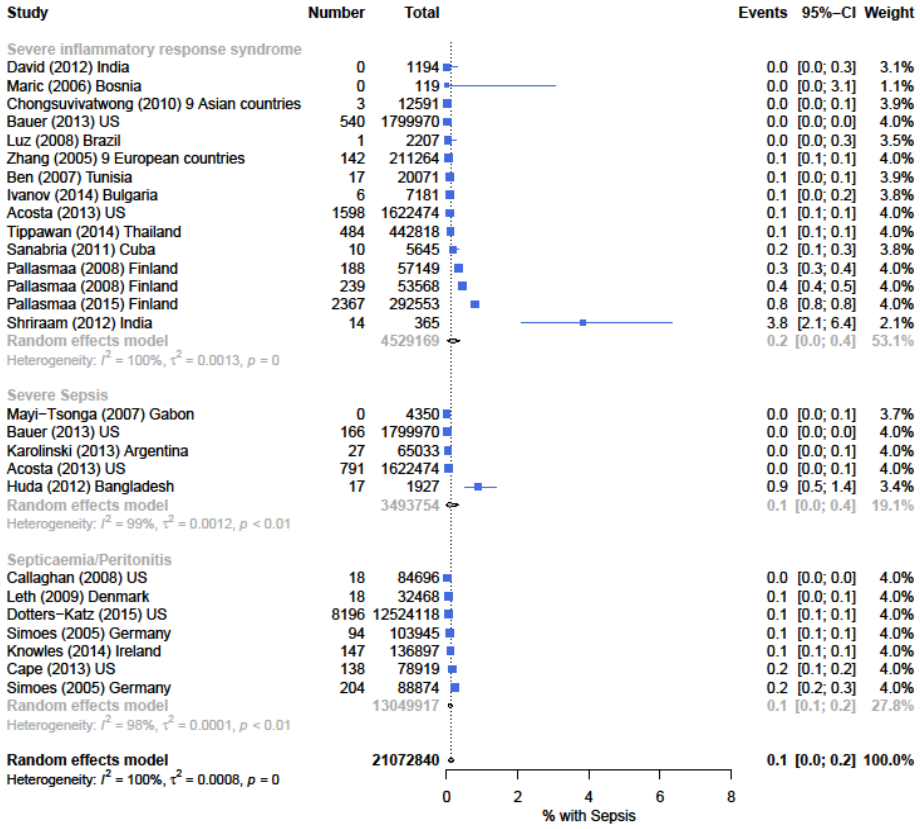


Fig. 2.5: Forest Plot of sepsis incidence by severity

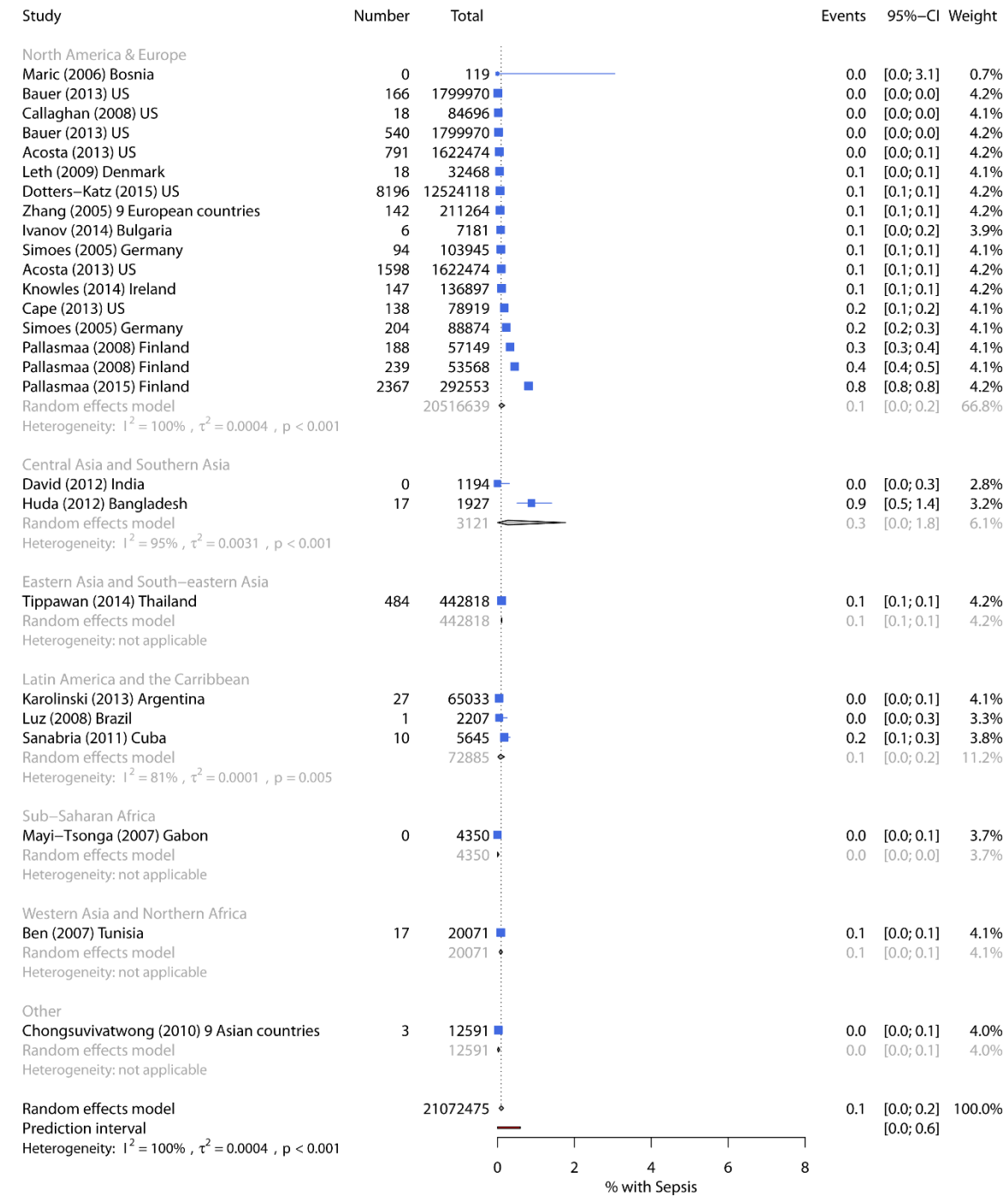


Fig. 2.6: Forest plot of sepsis incidence by world region

Table 2.9: Sepsis Meta-regression

Factor		No. of Studies	Odds Ratio	95% CI	p-value	R^2 (%)
Severity	SIRS*	13	1			
	Severe sepsis	5	0.32	0.08-1.35		
	Septicaemia/Peritonitis	7	0.52	0.15-1.78	0.25	2.6
Region	North America & Europe	16	1			
	Central Asia & South Asia	3	11.00	2.25-53.75		
	East Asia & South-East Asia	1	1.23	0.12-12.50		
	Latin America & The Caribbean	3	0.83	0.18-3.84		
	Sub-Saharan Africa	1	0.13	0.004-4.79		
	West Asia & North Africa	1	0.96	0.09-10.15	0.06	25.1
Study extent	Single site	8	1			
	2+ sites	2	6.84	0.83-56.64		
	Network	2	2.06	0.25-17.12		
	State	6	0.92	0.21-4.08		
	National	7	0.83	0.20-3.50	0.32	2.5
Number of foetuses	All deliveries	23	1			
	Singleton only	2	6.64	1.11-39.63	0.04	13.5
Delivery mode	All deliveries	23	1			
	Vaginal only	2	1.24	0.08-19.58	0.88	0
Gestational age	All gestations	25	-			
	Term only	0				
Live birth	All deliveries	24	1			
	Live birth only	1	0.37	0.02-5.54	0.47	0
Low risk	All women	24	1			
	Low-risk pregnancy only	1	0.42	0.01-14.91	0.64	0
Diagnosis	Clinical	25				
	Self-report	0				
Data collection	Routine	24	1			
	Study	1	2.99	0.87-10.25		
	Unclear	1	1.92	0.40-9.19	0.21	5.9
Follow-up[#]	Discharge/day 7	13	1			
	Day 8-42	10	3.57	1.55-8.22	0.003	27.2

*Systemic inflammatory response syndrome [#]Length of follow-up was missing for two studies

Maternal Peripartum Infection

Incidence of maternal peripartum infection ranged from 1-181 per 1000 with pooled incidence of 19 per 1000 (95% CI 13-28 per 1000) (Table 2.5). The prediction interval suggests the incidence could be up to 79 per 1000 in future studies. Pooled incidence in the US & Europe was 19 per 1000 and in East Asia, 26 per 1000. Other regions contained only

one or two studies (Fig 2.7) and there was no evidence that world region was associated with incidence. In univariate analysis, study extent was strongly associated with incidence. Studies with only low risk pregnancies or vaginal deliveries also showed some evidence of association, although this was lost after adjusting for study extent (Table 2.10); many of these studies used either a broad or poorly described definitions of infection.

Pooled incidence in seven high-quality studies was 11 per 1000. The highest incidence of 58 per 1000 was from a single-facility study in China, using Ministry of Health standard diagnosis of genital tract and caesarean section incision infection[104]. All the other estimates extracted ICD-9 or 10 codes for major/other puerperal infection from state or nationally representative hospital databases with incidence of 2 per 1000 in Canada and Thailand[150, 154], 5 per 1000 using NIS data[155], 8 per 1000 in all NHS hospital deliveries in the UK with follow-up to 42 days[156], and 9 per 1000 using birth certificate data in California[157]. One large US study also included chorioamnionitis and reported 20 per 1000 women with infection[158].

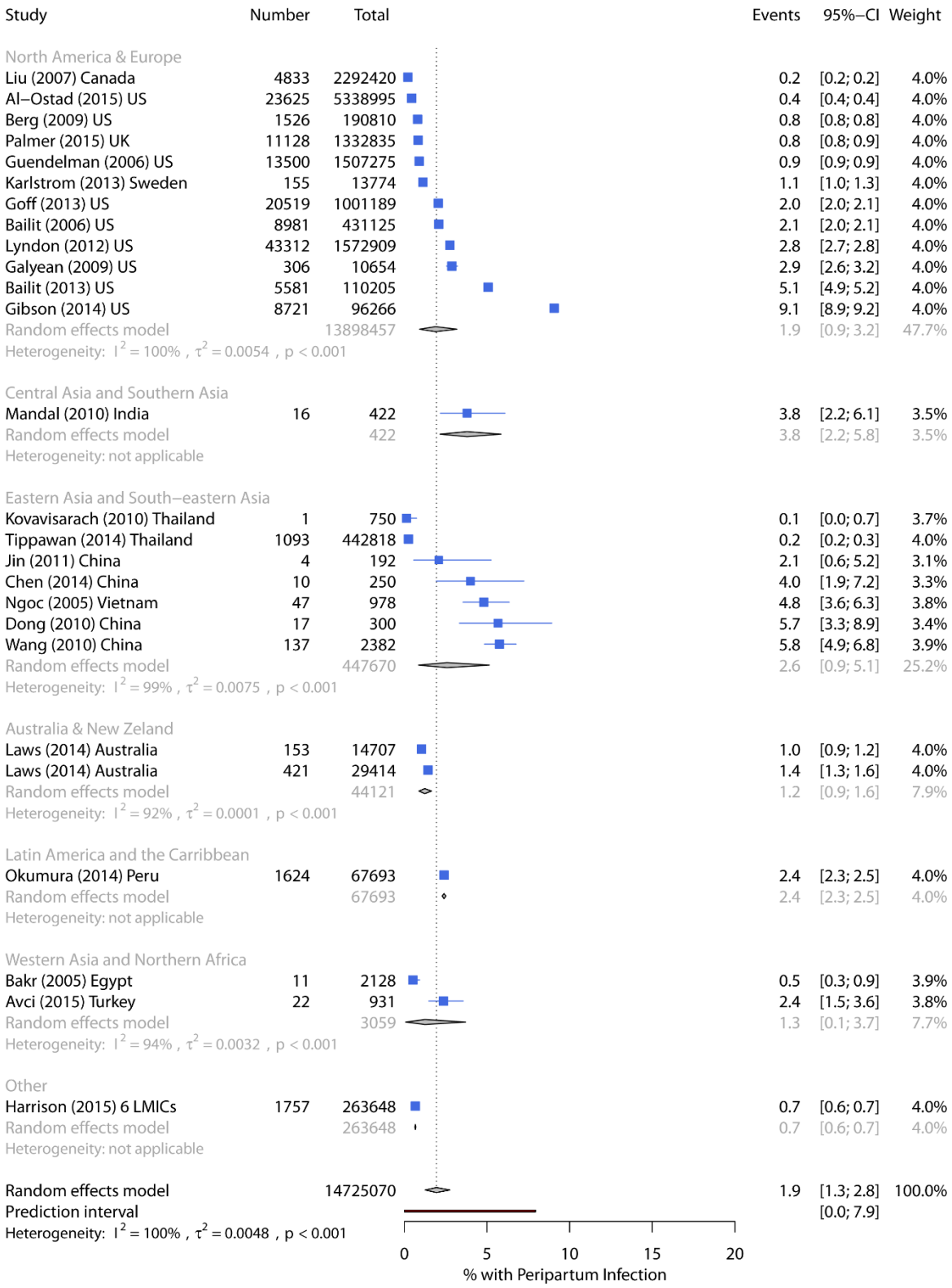


Fig. 2.7: Forest plot of maternal peripartum infection incidence by world region

Table 2.10: Maternal peripartum infection meta-regression

Factor		No. of studies	Odds Ratio	95% CI	p-value	R^2 (%)	Adj. Odds Ratio	95% CI
							R^2=35.7%	
Region	North America & Europe	12	1					
	Central Asia & South Asia	1	2.63	0.24-28.80				
	East Asia & South-East Asia	7	1.37	0.45-4.16				
	Australia & New Zealand	2	0.82	0.15-4.61				
	Latin America & The Caribbean	1	1.64	0.16-17.05				
	West Asia & North Africa	2	0.76	0.13-4.38	0.93	0		
Study extent	Single site	9	1				1	
	2+ sites	5	1.22	0.47-3.17			1.32	0.50-3.48
	Network	1	2.20	0.38-12.80			1.54	0.24-9.87
	State	3	0.72	0.23-2.24			0.88	0.27-2.85
	National	7	0.26	0.10-0.61	0.005	35.6	0.29	0.12-0.70
Number of foetuses	All deliveries	14	1					
	Singleton only	11	1.66	0.71-3.87	0.24	0.7		
Delivery mode	All deliveries	22	1					
	Vaginal only	3	3.83	1.16-12.67	0.03	14.3		
Gestational age	All gestations	17	1					
	Term only	8	0.89	0.36-2.23	0.81	0		
Live birth	All deliveries	20	1					
	Liver birth only	5	1.61	0.57-4.59	0.37	0		
Low risk	All women	19	1				1	
	Low-risk pregnancy only	6	2.34	0.90-6.04	0.08	7.3	1.74	0.71-4.27
Diagnosis	Clinical	24	-					
	Unclear	1						
Data collection	Routine	18	1					
	Study	3	2.67	0.71-10.10				
	Unclear	4	0.74	0.22-2.52	0.28	1.5		
Follow-up	Discharge	20	1					
	Until day 42	5	1.17	0.40-3.41	0.77	0		

2.3.5 Discussion

We systematically reviewed the incidence of maternal peripartum infection and identified 111 studies from 46 countries, representing all world regions from among 31,528 potential studies. Pooled infection incidence in high-quality studies was 39 per 1000 (95% CI 18-68 per 1000) for chorioamnionitis, 16 per 1000 (95% CI 9-25 per 1000) for endometritis, 12 per 1000 (95% CI 10-15 per 1000) for wound infection (one study) and 11 per 1000 (95% CI 3-24 per 1000) for maternal peripartum infection. Pooled incidence of sepsis was 0.5 per 1000 (95% CI 0.3-0.7 per 1000). Studies of composite outcomes had on average a lower incidence than obtained by summing other infection outcomes (11 versus 67 per 1000), probably because they rarely included chorioamnionitis (39 per 1000), but also because co-infections can occur.

Comparing our results to other global estimates is complicated by the different definitions used. The recent 2017 GBD global incidence of maternal infection of 12.1 million women[159] translates to an estimated 82 per 1000 live births[160], but includes mastitis, so is not comparable with ours. Dolea and Stein's older figure of 40 per 1000 for puerperal sepsis[6] excludes surgical site infection but includes urinary tract infection. Our estimates of endometritis, maternal peripartum infection and sepsis are all substantially lower, which may reflect our exclusion of urinary tract infection, or a reduction in infection since 2000. Our identification of source estimates is vastly more comprehensive than either GBD or Dolea and Stein, and we do not rely on modelling. A recently published review of infection following caesarean section in sub-Saharan Africa reports an SSI rate of 156 per 1000 that, at their reported caesarean section rate of 12.4%, corresponds to 19 per 1000 of the total population of women giving birth[161]. This is a little lower than the average incidence (34 per 1000) in our three fairly small, poor-quality African studies but does not include perineal wound infection, and does lie within our prediction interval.

Limitations of included studies

The quality of many studies was poor, with potential for bias. Measurement bias was possible in 63% of studies, primarily because the infection was not defined, or the definition used was too broad and risked over-estimating incidence. This explains part of the between-study heterogeneity observed. Attrition was minimal as most studies were cross-sectional or had short follow-up periods. There was potential selection bias in nearly one-third of studies; most trials did not describe initial selection methods and pair-matched studies produced non-random control groups. However, it is unclear whether and how this

might have affected infection incidence. Restricting the results to high-quality studies made little difference to the pooled incidence for chorioamnionitis or endometritis, but produced lower pooled incidence for the other outcomes, although with similar prediction intervals. This lower incidence may be an under-estimate of infection, as some high-quality studies had narrower outcome definitions than the standards. In addition, only one lower-middle-income and four upper-middle-income countries contributed to high-quality estimates, reducing their generalisability to LMICs.

We explored and quantified the importance of world region and study characteristics on infection risk using meta-regression to explain heterogeneity and better compare study estimates. Unfortunately, our analyses were limited by data sparsity. Beyond North America & Europe, data were scarce, especially from Sub-Saharan Africa and Western Asia & North Africa. We found some evidence for increased wound infection outside North America & Europe, but saw a mixed picture for endometritis, with surprisingly low incidences in East & South-east Asia. In common with other studies, we found higher incidence of SSI in LMICs which could reflect differences in surgical and infection control practices[162]. However, studies outside North America & Europe were also more likely to be at single facilities, use self-reported symptoms and collect data specifically for the study -- all features that relate to higher incidence.

For chorioamnionitis, wound infection and maternal peripartum infection there was evidence that study extent was associated with infection. Pooled incidence was up to five times higher in single-facility studies compared to estimates using nationally-representative databases, although the association was less clear with state-level studies. Large databases relying on routine medical records risk underestimating incidence due to missing or misclassified data. Conversely, studies at single tertiary-level hospitals may represent higher risk populations, especially in LMICs with low facility delivery rates, producing overestimates of population-level incidence. We excluded studies of high-risk women from this review, but chose to retain single-facility studies and regress the effect of study extent on infection because omitting single-facilities would lead to extensive loss of data, especially from LMICs.

Longer follow-up (risk) period was unsurprisingly associated with higher sepsis incidence, and a similar trend was observed with the other outcomes but lacked statistical evidence. This supports the findings of one included study where the majority of infections occurred

after hospital discharge[42]. Unfortunately, the majority of studies only collected data during hospital admission and may therefore have missed many cases.

Expected low risk groups, including live, term, singleton, and vaginal births did not have a lower infection risk compared to studies of all deliveries. This was surprising but as the majority of deliveries, even in population-level studies, are also low-risk, it is difficult to show evidence of a difference. Occasionally there was evidence of higher infection incidence in the studies of low risk groups but numbers were often small and results were confounded by other study design factors.

Strengths and limitations of review

This review's strengths include the very extensive search conducted, and the inclusion of articles in all languages identified. However, studies published after June 2016 have not contributed to the findings. Our review adopted the 2015 WHO definition of maternal peripartum infections and used international standard definitions among its quality criteria. It could be criticised for not restricting included studies to those meeting the full WHO definition, including the specified time period from onset of labour until 42 days postpartum. However, it is telling that none of the studies measured this exact outcome, and very few of those investigating postpartum infection continued until 42 days.

The review reported infection outcomes as an incident risk. This assumes all women were at risk (i.e. free of the infections under consideration) at the start of follow-up; onset of labour or immediately postpartum. However, some studies were unable, or did not seek to, exclude women with existing infections, potentially overestimating the incidence. Some studies only assessed or interviewed women at one time-point after delivery, however, follow-up periods were short, so the chance of missing infections is small. We excluded studies that only assessed high-risk subgroups of women, however, we did not limit our review to population-level studies potentially over-estimating infection incidence as discussed above. Conversely, we did include groups of low-risk women and so our pooled estimates may be an underestimate.

There are arguments against pooling estimates in the presence of extensive heterogeneity. Although I^2 was very high, this is driven by the substantial number of large, precise studies[133]. Tau^2 is a more relevant measure of heterogeneity in this case and values were small. Moreover, we believe that within our outcome groups, each study was attempting to measure the same outcome and therefore the average estimates remain useful although

they should be treated cautiously and not over-interpreted as measures of global incidence.

Conclusion

To our knowledge this is the first global systematic review of maternal peripartum infection incidence. It demonstrates that infection is an important complication of childbirth. Moreover, we found that a large proportion of these infections occurred in labour with implications for the baby and the mother. Postpartum infection incidence appears lower than modelled global estimates, although the difference in definition limits comparability and the proportion of women affected is still considerable. At a time of growing concern about AMR, these findings highlight the importance for clinicians and policy-makers to focus efforts on improved infection prevention practices to reduce this preventable cause of maternal morbidity. Our study provides useful estimates to guide sample size calculations for future intervention research. However, we also highlight the paucity of data from LMICs and the heterogeneity in study designs, quality and infection definitions. Better quality research, using standard definitions and follow-up after hospital discharge, is required to improve comparability between different study settings and to demonstrate the influence of risk factors and protective interventions.

2.3.6 Additional Tables of Results

Studies of Chorioamnionitis

Author	Date	Country	Description	Total women	Chorioamnionitis (%)	Quality
Abramovici (2014)[120]	11/08-06/10	US	Chorioamnionitis extracted from medical records of women in a single-hospital RCT of different oxytocin doses. Low-risk women with vaginal delivery and livebirth at one hospital	1785	6.78	4
Admaty (2012)[163]	03/09-12/10	Switzerland	Signs of chorioamnionitis extracted from maternal medical records for a study of newborn outcomes at different gestational ages in 2 hospitals. Term births only	143	0.70	2
Al-Ostad (2015)[141]	01/98-12/08	US	Study of risk factors for sepsis using National Inpatient Sample (NIS) data representing all hospital deliveries in the US	5338995	1.73	5
Bear (2016)[164]	01/91-12/01	US	Medical record discharge diagnosis at all non-federal hospitals in California for a study of cerebral palsy and maternal infection	6018504	1.84	4
Berg (2009)[165]	01/01-12/05	US	Study of maternal morbidity during hospitalisation for labour using the National Hospital Discharge Survey representing all hospital deliveries in the US.	19986000*	1.50	4
Berg (2009)[165]	01/93-12/97	US	As above	19081000*	1.90	4
Bleich (2012)[134]	01/03-12/08	US	Medical record data on chorioamnionitis from a study of duration of second stage of labour. Women with live births at 1 hospital	21991	19.66	4
Borders (2012)[166]	2009	US	Audit of number of vaginal examinations in labour and routine midwife diagnosis of chorioamnionitis. Term deliveries at one hospital	205	6.34	3

Braun (2016)[144]	01/10-12/10	US	Study of perinatal sepsis in term infants at 13 hospitals in the Kaiser Permanent Medical Program (KPMP), California, and integrated managed care consortium. Medical record data on chorioamnionitis	31112	4.00	5
Caughey (2007)[143]	01/95-12/99	US	Study of maternal complications at 13 KPMP facilities. Medical record data of low-risk, term deliveries	119254	3.49	5
Cavazos-Rehg (2015)[127]	01/09-12/09	US	Study of maternal age and delivery complications using NIS data	4109295	1.67	5
Cheng (2007)[167]	01/91-12/02	US	Medical record data on chorioamnionitis from a study of maternal and newborn outcomes by duration of second stage of labour. Multiparous women with livebirths at term in one hospital.	5158	4.28	4
Cheng (2010)[146]	01/90-07/08	US	Signs of chorioamnionitis extracted from medical records from a study of perinatal outcomes by duration of first stage of labour. Nulliparous women with live, term births at 1 hospital	10661	12.56	5
Danilack (2015)[168]	01/11-12/13	US	Chorioamnionitis on birth certificates of all low-risk women delivering in the US	10458616	1.29	2
Dotters-Katz (2015)[142]	01/08-12/10	US	Study of infection in multiple versus single gestation using NIS data	12524118*	2.58	5
Edwards (2015)[145]	06/06-11/07	US	Signs of chorioamnionitis extracted from maternal medical records for a study of an early warning system for severe sepsis at one hospital.	15027	6.08	5
Geller (2010)[169]	1995-2005	US	Intrapartum fever extracted from medical records for study of maternal outcomes and planned mode of birth at one hospital. Low-risk, nulliparous women delivering at term	4048	15.74	4

Getahun (2010)[129]	01/91-12/07	US	Medical record data for study of effect of chorioamnionitis on childhood asthma at KPMP hospitals. Only includes infants who became health plan members	397852	3.20	3
Getahun (2013)[170]	01/95-12/10	US	Medical record data of temporal trends in chorioamnionitis in KPMP hospitals.	471821	4.12	4
Grotegut (2008)[171]	01/03-06/05	US	Medical record data on obstetric outcomes with false-positive glucose challenge test (GCT) at 1 hospital. Normal GCT only	165	0.61	4
King (2012)[148]	08/95-02/04	US	Maternal and Neonatal morbidity using the perinatal database at 1 hospital. Live births at term.	14406	12.85	4
Magann (2008)[172]	03/04-02/05	US	Obstetric characteristics for prolonged third stage of labour. Source of data unclear. Vaginal deliveries at a naval medical centre	1607	2.18	4
Malloy (2014)[132]	01/08-12/08	US	Birth certificate data for study of chorioamnionitis and newborn outcomes. Live, term births across the US	2224406	0.99	4
Matsuda (2011)[173]	2001-2005	Japan	Data from perinatal registry network of 125 centres.	242715	1.03	4
Nelson (2014)[174]	01/05-12/11	US	Study of obstetric risk factors for newborn complications. Source of data unclear. Live, term births at 1 hospital	86371	6.61	4
Osmundson (2011)[175]	07/06-06/08	US	Medical record data on chorioamnionitis for a sample of low-risk women managed expectantly (not induced) at 39 weeks gestation in 1 hospital	102	19.61	3
Shah (2011)[176]	09/08-11/08	Pakistan	Medical record data on obstetric outcomes of low-risk women at 3 hospitals. Convenience sample of women aged 20-35	916	0.76	2

Suthee (2007)[140]	01/99-12/03	Thailand	Signs of chorioamnionitis extracted from medical records in study of meconium-stained amniotic fluid and maternal infection. Low-risk women with live, term birth at 1 hospital	1079	0.93	5

*Results presented are weighted percentage of US population. In meta-analysis we approximated the sample size at 20% for the NIS[177] and 1% for the NHDS[178].

Studies of Endometritis

Author	Date	Country	Description	Total women	Endometritis (%)	Quality
Ahnfeldt-Mollerup (2012)[179]	05/07-04/08	Denmark	Questionnaire sent to women 28 days after delivering at 1 regional hospital. Report of infection validated with data from General Practice and hospital records	1616	1.86	2
Ayzac (2008)[147]	01/97-12/03	France	Clinical endometritis after vaginal delivery until 30 days postpartum at 66 hospitals in a surveillance network	161077	0.33	5
Belfort (2010)[180]	01/07-12/07	US	Women readmitted with clinical uterine infection up to 42 days postpartum. Medical record data from 114 hospitals representative of the US population	222751	0.15	4
Benincasa (2012)[110]	01/04-12/10	Brazil	Medical record data on clinical puerperal infection at 1 hospital	26691	1.47	3
Bianco (2013)[42]	09/07-09/08	Italy	Telephone calls with women at 30 days after delivery at 1 hospital. Postpartum infections corroborated by hospital and physician visits, wound cultures and antibiotic prescriptions.	1656	1.39	3
Boccardo (2013)[106]	04/10-07/10	Argentina	Medical record data on clinical endometritis in 1 public hospital	1472	2.51	5
Caughey (2007)[143]	01/95-12/99	US	Maternal complications by gestational age. Medical record data on endometritis at 13 Californian hospitals in an insurance programme (KPMP)	119254	1.20	5
Cavazos-Rehg (2015)[127]	01/09-12/09	US	Maternal age and delivery complications using NIS data	4109295	0.36	4
Cheng (2007)[167]	01/91-12/02	US	Maternal and newborn outcomes by duration of 2nd stage of labour in multiparous women. Medical record data at 1 hospital	5158	1.36	4
Cheng (2010)[146]	01/90-07/08	US	Perinatal outcomes by duration of 1st-stage of labour in nulliparous women. Medical record data at 1 hospital	10661	2.37	5

Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	Clinical data on maternal and foetal complications collected by checklist until day 5 postpartum in 12 teaching hospitals in Asia. Vaginal deliveries only	12591	0.06	2
Darmstadt (2009)[181]	06/01-07/01	Egypt	Study of clean delivery-kit use in 1 urban and 2 rural areas. Infection diagnosed by nurse at week 1 postnatal home visit	334	1.50	4
Dimitriu (2010)[119]	1/1/06-1/9/09	Kuwait	Medical record data of puerperal infection at 1 hospital	7550	1.63	2
Dotters-Katz (2015)[142]	01/08-12/10	US	Endometritis in single and multiple gestation using NIS data	12524118*	1.36	5
Dumas (2008)[128]	01/01-12/04	France	Clinical endometritis after vaginal delivery until 30 days postpartum at 44 hospitals in a surveillance network	49786	0.23	4
Ezugwu (2011)[182]	09/08-12/08	Nigeria	Medical record data on obstetric outcomes, including genital sepsis, at 1 hospital during the period of free maternal care.	1152	1.74	1
Fronczak (2005)[135]	11/93-05/95	Bangladesh	Multi-stage probability sampling of women in slum areas of Dhaka. Pelvic infection identified at interviews conducted at home at 72 hours, 7 days and, with examination by a doctor, 14-22 days postpartum	1506	14.01	3
Geller (2010)[169]	1995 -2005	US	Medical record data on maternal outcomes and planned mode of birth among nulliparous, low-risk women at 1 hospital	4048	1.31	4
Ghani (2007)[136]	1/7/05-31/7/05	Pakistan	Self-reported symptoms of vaginal infection during interview at home by trained nurse/midwife. Simple random sample of postpartum women in the Khyber Agency	1000	16.20	3
Gozum (2005)[137]	05/00-06/00	Turkey	Vaginal infection until 6 weeks postpartum, reported during interviews with mothers attending for 2 month infant immunisations at 1 primary care unit	112	14.29	1

Grotegut (2008)[171]	01/03-06/05	US	Medical record data on obstetric outcomes with false-positive glucose challenge test (GCT) at 1 hospital. Normal GCT only	165	1.21	4
Guimaraes (2007)[183]	12/00-07/03	Brazil	Puerperal infection among women at 1 maternity hospital, followed until 30 days postpartum using the National Nosocomial Infection Surveillance System	5178	0.89	4
Ivanov (2014)[117]	01/11-12/13	Bulgaria	Medical record data on puerperal infection at 1 hospital.	7181	9.89	3
Iyengar (2012)[184]	01/07-12/10	India	A field site in rural Rajasthan. Clinical uterine infection diagnosed during home visits by trained nurse-midwives at 2-3 days and 6-9 days postpartum	4975	1.29	4
Jokhio (2005)[121]	05/98-10/98	Pakistan	Cluster RCT of traditional birth attendant (TBA) training in Larkana District. Lady Health Workers were trained to recognise complications during their routine monthly visits. Women with trained TBA	9838	0.79	3
Jokhio (2005)[121]	As above	As above	As above; women without trained TBA	9119	4.39	3
King (2012)[148]	08/95-02/04	US	Maternal and Neonatal morbidity using the perinatal database at 1 hospital	14335	2.53	5
Kovavisarach (2005)[122]	11/01-02/02	Thailand	RCT of perineal shaving vs hair cutting on maternal and neonatal outcomes among low-risk women with vaginal delivery at 1 hospital	458	0.00	3
Magann (2011)[185]	01/07-07/08	US	Medical record data on obesity and peripartum complications at 2 hospitals	4490	6.88	4
Maric (2006)[118]	1/04-12/04	Bosnia	Medical record data on puerperal complications until 42 days postpartum in nulliparous women at 1 hospital. Vaginal deliveries	119	1.68	2
Ngoga (2009)[186]	Start 12/03	South Africa	Medical record data on pregnancy outcomes in morbidly obese vs a matched sample of normal weight women at 1 hospital. Women with body mass index (BMI) 20-25	209	0.48	2

Sanchez (2015)[109]	01/12-12/13	Cuba	Maternal age and obstetric complications using medical record data at 1 hospital. Each month, first 30 women aged 25-30 enrolled.	720	1.67	2
Sanchez (2015)[109]	As above	As above	As above. Each month, the first 15 women over 35 enrolled	360	2.22	2
Suthee (2007)[140]	01/99-12/03	Thailand	Medical record data on meconium-stained amniotic fluid and maternal infection among low-risk women at 1 hospital	1079	0.93	4
Peret (2007)[112]	07/01-09/03	Brazil	Puerperal morbidity in HIV-infected vs pair-matched non-infected women at 1 hospital; diagnosed before discharge and at a scheduled visit with researchers at 7-15 days postpartum. HIV negative women	123	0.00	3
Ramírez-Villalobos (2009)[187]	04/03-12/03	Mexico	Puerperal complications after hospital discharge among women with vaginal delivery at 1 hospital. Self-reported symptoms collected by trained interviewers at a clinic or home visit at day 7 postpartum	302	2.65	3
Saizonou (2014)[116]	07/09-02/10	Benin	Peripartum infection up to 7 days postpartum at 1 hospital. Diagnosed by doctor or midwife supervised by public health doctor	1875	1.60	4
Sanabria (2011)[108]	01/07-12/09	Cuba	Medical record data on puerperal complications at 1 hospital	5645	0.47829938	1
Tabcharoen (2009)[188]	01/97-12/06	Thailand	Medical record data on pregnancy outcomes after age 40 at 1 hospital. Women aged 20-34	20852	0.10	4
Tabcharoen (2009)[188]	As above	As above	As above; women age 40+	792	0.38	4
Winani (2007)[189]	Start 01/2000	Tanzania	Cord infection and puerperal sepsis with clean delivery kits in 2 rural districts. Home visit at day 5 by village health workers with suspected infection confirmed at health facility	3262	2.12	4

*Results presented are weighted percentage of US population. In meta-analysis we approximated the sample size at 20% for the NIS.[177]

Studies of Wound infection

Author	Date	Country	Description	Total women	Wound Infection (%)	Quality
Ahnfeldt-Mollerup (2012)[179]	05/07-04/08	Denmark	Questionnaire sent to women 28 days after delivering at 1 regional hospital. Report of infection validated with data from General Practice and hospital records	1616	3.16	2
Awan (2015)[190]	10/10-09/11	Pakistan	Feto-maternal outcomes in overweight versus normal weight in 1 hospital. Data source unclear. Results for normal weight (18.5-24.9)	100	2.00	0
Bailit (2006)[191]	01/01-12/01	US	Study of quality of obstetric care. Birth certificate record data from California	431125	0.20	4
Bianco (2013)[42]	09/07-09/08	Italy	Telephone calls with women at 30 days after delivery at 1 hospital. Postpartum infections corroborated by hospital and physician visits, wound cultures and antibiotic prescriptions	1656	3.08	3
Bodner (2011)[192]	11/05-01/09	Austria	Maternal and neonatal outcomes for elective caesarean and planned vaginal delivery. Data source unclear. Low-risk women at 1 hospital. Planned vaginal deliveries only	178	1.12	2
Charrier (2010)[193]	05/04-10/04	Italy	Study of clean versus sterile vaginal delivery at 2 hospitals. Signs of perineal infection in hospital from direct observation and medical records. Telephone interview at 20-30 days postpartum for reported infection diagnosis, symptoms and antibiotic use	409	0.00	4
Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	Clinical data on maternal and foetal complications collected by checklist until day 5 postpartum in 12 teaching hospitals in Asia. Vaginal deliveries only	12591	2.57	1
Danish (2010)[194]	05/98-11/99	Pakistan	Pregnancy outcome in booked versus unbooked women at 1 hospital. Data collection poorly described	322	6.21	0

Dasgupta (2014)[195]	10/10-09/11	India	Pregnancy outcomes in obesity at 1 hospital. Data source unclear. Results for normal BMI (<25kg/m2)	99	2.02	1
Dimitriu (2010)[119]	01/06-09/09	Kuwait	Medical record data of puerperal infection at 1 hospital	7550	0.33	2
Dong (2009)[101]	01/01-11/04	China	Study of infection prevention control intervention at 1 hospital. Medical record data of perineal and caesarean wound infections in the control group	12850	1.32	4
Dong (2010)[102]	07/08-08/08	China	Controlled trial of hand washing method for vaginal deliveries at 1 hospital. Perineal infection data collected by the study doctor	300	8.67	4
Ezugwu (2011)[182]	09/08-12/08	Nigeria	Medical record data on obstetric outcomes, including wound sepsis, at 1 hospital during the period of free maternal care	1152	8.33	1
Geller (2010)[169]	1995-2005	US	Medical record data on maternal outcomes and planned mode of birth among nulliparous, low-risk women at 1 hospital	4048	0.02	4
Goff (2013)[158]	01/08-12/09	US	Medical record data from the Perspective database; 355 hospitals accounting for approximately 20% of all hospital admission in the US	1001189	0.35	4
Guimaraes (2007)[183]	12/00-07/03	Brazil	Surgical site and episiotomy infection among women at 1 maternity hospital, followed until 30 days postpartum using the National Nosocomial Infection Surveillance System	5178	1.95	4
Ivanov (2014)[117]	01/11-12/13	Bulgaria	Medical record data on puerperal infection at 1 hospital. Results for perineal wound infection after vaginal delivery	3897	4.29	3
Iyengar (2012)[184]	01/07-12/10	India	A field site in rural Rajasthan. Perineal wound infection diagnosed during home visits by trained nurse-midwives at 2-3 days and 6-9 days postpartum	4975	0.42	4
Jaleel (2009)[196]	01/06-04/08	Pakistan	Pregnancy outcomes in obesity at 1 private maternity home. Data source unclear. Results for control group (BMI 18.5-22.9)	118	0.00	1

Janssen (2009)[197]	01/00-12/04	Canada	Medical record data. Low risk women in British Colombia planning to delivery with a midwife at home or hospital	7641	0.14	3
Janssen (2009)[197]	01/00-12/05	Canada	As above. Low risk women planning to delivery with a physician in hospital	5331	0.30	3
Kovavisarach (2005)[122]	11/01-02/02	Thailand	RCT of perineal shaving versus hair cutting on maternal and neonatal outcomes in low-risk women with vaginal delivery at 1 hospital. Perineal wound infection. Unclear if up to day 4 or 42	458	8.73	3
Latif (2013)[198]	01/00-06/00	Bangladesh	Medical record data of outcomes in primigravidae at 1 hospital	500	3.00	3
Leth (2009)[152]	01/01-12/05	Denmark	Wound infection up to 30 days postpartum identified through the laboratory system, regional prescription database and National Hospital Registry. All deliveries in County of Aarhus	32468	1.78	4
Liu (2010)[103]	01/05-12/06	China	Clinical study data on abdominal and perineal wound infection and body mass index at 1 hospital. Results for BMI<25	327	8.87	3
Ngoga (2009)[186]	12/03	South Africa	Medical record data on pregnancy outcomes in morbidly obese vs a matched sample of normal weight women at 1 hospital. Women with BMI 20-25	209	0.00	2
Oladapo (2007)[199]	01/90-12/05	Nigeria	Medical record data on wound infection. Vaginal deliveries at 1 hospital	656	5.18	3
Petter (2013)[113]	01/09-12/10	Brazil	Medical record data on episiotomy and caesarean wound infections among women at 1 hospital	9528	1.24	5
Ramírez-Villalobos (2009)[187]	04/03-12/03	Mexico	Episiotomy infection after hospital discharge among women with vaginal delivery at 1 hospital. Self-reported symptoms collected by trained interviewers at a clinic or home visit at day 7 postpartum	303	10.89	3
Shriraam (2012)[138]	11/08-02/09	India	Self-reported wound infection up to 42 days postpartum using pre-tested questionnaire at up to 6 months after delivery. All	365	2.74	2

			women delivered in previous 6 months in rural community of Tamil Nadu			

Studies of Sepsis

Author	Date	Country	Description	Total women	Sepsis (%)	Quality
Acosta (2013)[4]	01/05-12/07	US	Medical record data for all admissions for delivery of a live birth in California. Sepsis coded as septicaemia or sepsis	1622474	0.10	5
Acosta (2013)[4]	01/05-12/07	US	As above. Severe sepsis, also coded as septic shock or sepsis with prolonged length of stay, transfer to intensive care or death	1622474	0.05	5
Bauer (2013)[149]	01/98-12/08	US	Maternal sepsis during hospitalisation for delivery using NIS data. Sepsis coded as septicaemia or SIRS	8999852*	0.03	5
Bauer (2013)[149]	01/98-12/08	US	As above. Severe sepsis coded as sepsis plus organ dysfunction	8999852*	0.01	5
Belfort (2010)[180]	01/07-12/07	US	Medical record data on women readmitted with postpartum infection up to 42 days postpartum at 114 hospitals, representative of the US population	222751	0.01	3
Ben (2007)[114]	01/99-12/03	Tunisia	Medical record data on all severe (near-miss) puerperal infection at one hospital using SIRS criteria	20071	0.08	4
Callaghan (2008)[151]	01/91-12/03	US	Septicaemia and hospital stay of 3+ days using data on delivery hospitalisations from the National Hospital Discharge Survey	423480	0.02	5
Cape (2013)[200]	01/00-12/08	US	Bacteraemia from 7 days before until 30 days after delivery using the microbiology database at one hospital. Restricted to women with a diagnosis of chorioamnionitis, endometritis or wound infection	78919	0.17	4

Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	Clinical data on maternal and foetal complications including peritonitis, collected by checklist until day 5 postpartum in 12 teaching hospitals in Asia. Vaginal deliveries only	12591	0.02	1
David (2012)[201]	01/05-12/10	India	Medical record data on puerperal sepsis during hospitalisation for delivery, in a midwife-run labour room at one urban health centre	1194	0	2
Dotters-Katz (2015)[142]	01/08-12/10	US	Study of infection in multiple versus single gestation using NIS data. Codes for septicaemia and bacteraemia	12524118*	0.07	5
Goff (2013)[158]	01/08-12/09	US	Medical record data from the Perspective database; 355 hospitals accounting for approximately 20% of all hospital admission in the US. Codes for septicaemia, septic shock, bacteraemia, SIRS	1001189	0.13	5
Huda (2012)[202]	01/08-12/08	Bangladesh	Medical record data from 30 hospitals on genital infection and signs of shock, from labour until 32 days postpartum	1927	0.88	4
Ivanov (2014)[117]	01/11-12/13	Bulgaria	Medical record data on puerperal infection, including sepsis, at 1 hospital	7181	0.08	3
Karolinski (2013)[203]	06/08-05/09	Argentina	Medical record data from 25 hospitals in the Perinatal network of Buenos Aires on life-threatening puerperal sepsis until 42 days postpartum	65033	0.04	3
Knowles (2014)[153]	01/05-12/12	Ireland	Medical and laboratory records at 2 maternity hospitals of blood stream infection secondary to genital tract infection until 42 days postpartum	136897	0.11	5
Kuklina (2008)[155]	01/98-12/04	US	Sepsis coded as septicaemia, septic shock or SIRS with/without organ dysfunction during hospitalisation for delivery using NIS data	28084407	0.03	5

Leth (2009)[152]	01/01-12/05	Denmark	Blood stream infection up to 30 days postpartum identified through the laboratory system, regional prescription database and National Hospital Registry. All deliveries in County of Aarhus	32468	0.06	5
Luz (2008)[111]	10/05-07/06	Brazil	Positive blood culture and SIRS or organ dysfunction, collected from medical records during admission for delivery at one hospital	2207	0.05	5
Lyndon (2012)[131]	01/05-12/07	US	Medical record data of maternal sepsis from all live singleton births at hospitals in California	1572909	0.09	4
Maric (2006)[118]	01/04-12/04	Bosnia	Medical record data on puerperal sepsis following vaginal delivery until 42 days postpartum in nulliparous women at 1 hospital	119	0	2
Mayi-Tsonga (2007)[115]	06/06-12/06	Gabon	Audit of near-miss at one hospital. Medical record data on septic shock of pelvic origins	4350	0	5
Pallasmaa (2008)[204]	01/97-12/97	Finland	Puerperal sepsis and peritonitis in all singleton births in Finland using the national hospital discharge registry	57149	0.33	4
Pallasmaa (2008)[204]	01/02-12/02	Finland	Puerperal sepsis and peritonitis in all singleton births in Finland using the national hospital discharge registry	53568	0.45	4
Pallasmaa (2015)[205]	01/07-12/11	Finland	Puerperal sepsis, peritonitis and re-operation in all singleton births in Finland using the national hospital discharge registry	292553	0.81	4
Sanabria (2011)[108]	01/07-12/09	Cuba	Medical record data on puerperal complications including sepsis among women delivering at 1 hospital	5645	0.18	1

Shriraam (2012)[138]	11/08-02-09	India	Self-reported puerperal sepsis up to 42 days postpartum using pre-tested questionnaire at up to 6 months after delivery. All women delivered in previous 6 months in rural community of Tamil Nadu	365	3.84	2
Simoes (2005)[206]	01/98-12/98	Germany	Postpartum septicaemia in the Perinatal database for all women delivering in hospitals in Baden-Wurttemberg State	103945	0.09	3
Simoes (2005)[206]	01/01-12/01	Germany	Postpartum septicaemia in the Perinatal database for all women delivering in hospitals in Baden-Wurttemberg State	88874	0.23	3
Tippawan (2014)[150]	10/10-09/11	Thailand	Medical record data on puerperal sepsis in all hospital deliveries in the country using the National Health Security Office data	442818	0.11	5
Zhang (2005)[124]	01/95-02/98	9 European countries	Data collected from medical records on sepsis (infection with SIRS) at the time of birth. Survey usually covered the hospitals in one region of each country for 12 months	211264	0.07	3

*Results presented are weighted percentage of US population. In meta-analysis we approximated the sample size at 20% for the NIS[177]

Studies of Maternal Peripartum Infection

Author	Date	Country	Description	Total Women	Maternal Peripartum Infection (%)	Quality
Al-Ostad (2015)[141]	01/98-12/08	US	Risk factors for sepsis mortality using NIS data. Unspecified codes for puerperal infection	5338995	0.44	4
Andersson (2011)[139]	05/09-11/09	Nigeria	Self-reported symptoms of infection up to 42 days postpartum. Stratified random sampling to provide state-level representation for 2 Nigerian states	14890	18.11	1
Avci (2015)[207]	03/12-03/13	Turkey	Maternal obesity and perinatal outcomes at one hospital. Definition and data collection methods for postpartum infection not specified	931	2.36	2
Bailit (2006)[191]	01/01-12/01	US	Birth certificate record data from California. ICD-9 codes for major postpartum infection, postpartum fever, GU tract infection and wound complications	431125	2.08	4
Bailit (2013)[208]	03/08-02/11	US	Medical record data from a stratified random selection of days at 25 hospitals in a network of Maternal-Fetal Medicine Units. Peripartum infection in low-risk women defined as Chorioamnionitis, postpartum endometritis or postpartum wound infection	110205	5.06	4
Bakr (2005)[123]	01/02-06/02	Egypt	Study of vaginal chlorhexidine and maternal morbidity at one hospital. Medical record data from the pre-intervention period. Postpartum infection defined as puerperal sepsis, or fever plus offensive vaginal discharge, infected wound, retained products of conception or secondary PPH	2128	0.52	4
Berg (2009)[165]	01/01-12/05	US	Maternal morbidity during hospitalisation for labour using the National Hospital Discharge Survey representing all hospital deliveries in the US. ICD-9 codes for major puerperal infection	19986000*	0.50	4

Berg (2009)[165]	01/93-12/97	US	As above	19081000*	0.80	4
Chen (2014)[100]	2011	China	Random sample of 250 medical records of low-risk deliveries at one hospital. Textbook definition of puerperal infection	250	4.00	4
Dong (2010)[102]	07/08-08/08	China	Controlled trial of hand washing method for low-risk vaginal deliveries at 1 hospital. Data collected by study doctor on puerperal infection (undefined)	300	5.67	4
Galyean (2009)[209]	07/02-12/03	US	Multiparous women with live singleton delivery at four hospitals in California. Serious post-partum infections requiring aminoglycosides from a perinatal outcomes database	10654	2.87	3
Gibson (2014)[210]	01/02-12/08	US	Outcomes in elective induction of low-risk pregnancies at 12 clinical centres and 19 hospitals. Medical record data on infection; intrapartum fever, chorioamnionitis, endomyometritis and wound separation	96266	9.06	3
Goff (2013)[158]	01/08-12/09	US	Medical record data from the Perspective database; 355 hospitals accounting for approximately 20% of all hospital admissions in the US. ICD-9 codes for chorioamnionitis and major puerperal infection	1001189	2.05	5
Guendelman (2006)[157]	01/96-12/98	US	Database of birth certificate and hospital discharge records for 93% of deliveries in California. ICD-9 codes for major puerperal infection.	1507275	0.90	5
Harrison (2015)[126]	01/10-12/13	6 LMICs	7 rural communities in Argentina, Guatemala, India, Kenya, Pakistan and Zambia, under the Global Network. Undefined postpartum maternal infection from medical records and a study visit at 42 days	263648	0.67	3
Jin (2011)[105]	03/05-03/10	China	Study of gestational diabetes in one hospital. Undefined puerperal infection collected in a sample of women without diabetes for a single-facility study of gestational diabetes	192	2.08	3

Karlstrom (2013)[211]	01/97-12/06	Sweden	Register of all facility births in the country. Postpartum infection (undefined) after spontaneous onset of labour at term	13774	1.13	4
Kovavisarach (2010)[212]	11/06-12/07	Thailand	Women aged 20-34 delivering at one hospital. Puerperal infection with undefined definition or data collection methods.	750	0.13	2
Kuklina (2008)[155]	01/98-12/04	US	NIS database. ICD-9 codes for puerperal infection and pyrexia of unknown origin	28084407*	0.52	5
Kyser (2012)[130]	01/06-12/06	US	Medical record data from 1045 hospitals in 11 states. Undefined postpartum infection using ICD-9 codes	1678809	0.72	4
Laws (2014)[213]	01/01-12/09	Australia	Undefined postpartum infection from linked birth records and hospital admission records up to 1 year postpartum. Women intending to deliver at 8 birthing centres	14707	1.04	4
Laws (2014)[213]	01/01-12/09	Australia	As above. Women intending to deliver at 8 co-located hospitals	29414	1.43	3
Liu (2007)[154]	04/91-03/05	Canada	Low-risk planned vaginal deliveries at all acute-care hospitals in Canada, excluding Quebec and Manitoba. Medical record data of major puerperal infection from ICD-9 codes	2292420	0.21	5
Lyndon (2012)[131]	01/05-12/07	US	Medical record data of livebirths at hospitals in California. Unspecified ICD-9 codes for maternal infection	1572909	2.75	4
Mandal (2010)[214]	01/06-12/08	India	Maternal obesity and pregnancy outcome at one hospital. Combined endometrial and wound infection at 6 weeks postpartum visit in low-risk non-obese women	422	3.79	1
Ngoc (2005)[215]	01/01-07/01	Vietnam	Clinical data collected at 6-week postpartum study visit after vaginal delivery at two hospitals. Serious postpartum infection defined as physician-diagnosed sepsis or clinical symptoms of endometritis, pelvic abscess, or chorioamnionitis	978	4.81	3
Okumura (2014)[107]	01/00-12/00	Peru	Perinatal Information System database from one hospital. ICD-10 codes for puerperal infection	67693	2.40	4

Palmer (2015)[156]	04/10-03/12	UK	Database of all NHS hospital deliveries. ICD-10 codes for puerperal infection or sepsis within 42 days of birth	1332835	0.83	5
Tippawan (2014)[150]	10/10-09/11	Thailand	Medical record data on puerperal sepsis in all hospital deliveries in the country using the National Health Security Office data. ICD-10 code for other puerperal infection	442818	0.25	5
Wang (2010)[104]	01/07-12/08	China	Medical record data from one hospital. Postpartum intrauterine infection defined as fever, headache, dizziness, abnormal lochia, genital tract or caesarean wound infection	2382	5.75	5

*Results presented are weighted percentage of US population. In meta-analysis we approximated the sample size at 20% for the NIS[177] and 1% for the NHDS[178]

Chapter 3: Methods used to identify and define maternal peripartum infection: further analysis of studies included in a systematic literature review

3.1 Introduction

The published systematic literature review in Chapter 2 identified marked heterogeneity in all pooled estimates of infection. This was only partially explained by factors tested in the meta-regression, including certain aspects of study design. Less than one fifth of studies (19%) met all quality criteria, and only 41% used one of the standard infection definitions. As presented in Chapter 1, measurement of infection incidence relies on a standard case definition for the infection, combined with methods to identify all cases within a given a population. To understand how these two elements of measurement were handled by researchers, I examined the studies included in the systematic review in more detail. I present a narrative review of the data collection methods used and the infection definitions applied, and consider the strengths of limitations of the different approaches.

3.2 Methods

I selected three of the five infection outcomes to explore in more detail; endometritis, wound infection and sepsis, but not maternal peripartum infection or chorioamnionitis. Endometritis and wound infection were chosen because they both occur in the postpartum period, potentially requiring some form of follow-up to identify all cases. Sepsis was selected as an important cause of maternal mortality. No studies used the actual term 'maternal peripartum infection' or met the exact definition, therefore it was deemed of little benefit to examine studies with this outcome. All studies of chorioamnionitis were hospital-based and the vast majority were in the US, therefore further exploration was considered unlikely to add any information of interest.

3.2.1 Outcome definitions

Table 3.1 presents the standard definitions for endometritis and wound infection, the adapted version used for this chapter, and the explanation for any difference. Allowances were made for studies that relied on self-reported symptoms, or had limited access to laboratory tests or the potential to identify organisms. The standard definition for sepsis was listed in the main results of Chapter 2.

3.2.2 Analysis

For each selected outcome, I present a table with the data collection methods and infection definition for each study. I summarise data collection according to length of follow-up (delivery admission only versus post-discharge follow-up) and data source (routine record data, clinical research data or self-reported data). I summarise definitions based on whether they meet the standard definitions detailed in the review, whether they are narrower with potential to miss cases, or broader and therefore likely to over-estimate risk.

I describe the infection incidence range for groups of studies, related to data collection or infection definition. However, as there are few studies within each of these groups, I have not performed any statistical analysis.

I present a graphical summary of the data using Sankey diagrams. Traditionally, these diagrams demonstrate flows of energy or change over time, with arrows going in one direction and the width of the line proportional to the flow rate. However, I have used the software (sankeymatic) to simply describe the relationship between data collection method and infection definition, with each study contributing a similar width, and the colour of the lines representing either the income-level of the study country or the incidence of infection.

Table 3.1: Standard definitions and adaptation for purpose of review

Infection	Standard definition (source)	Adapted definition	Explanation
Caesarean Section Surgical Site Infection (SSI)	**SSI-Surgical site infection (CDC*[92])** Superficial incisional SSI must meet the following criteria: Involves only skin and subcutaneous tissue of the incision AND Patient has at least one of the following: 1. Purulent drainage from the superficial incision OR 2. Organisms identified (further detail not reported here) OR 3. Incision is deliberately opened by a surgeon/attending physician/other designee and microbiologic testing not performed AND patient has least one of pain or tenderness, localised swelling, erythema, heat. OR 4. Diagnosis by the surgeon/attending physician/other designee Deep incisional SSI must meet the following criteria: Involves deep soft tissues of the incision AND Patient has at least one of the following; 1. Purulent drainage from the deep incision OR 2. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated AND organisms identified AND patient has at least one of fever (>38C), localized pain or tenderness OR 3. An abscess or other evidence of infection involving the deep incision detected on gross anatomical or histopathological exam or imaging. Organ/Space SSI must meet the following criteria: Infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure AND Patient has at least one of the following; 1. Pus drainage from a drain that is placed into the organ/space OR 2. Organisms are identified from fluid or tissues in the organ/space OR 3. An abscess or other evidence of infection involving the organ/space AND Meets criterion for a specific organ/space infection – This Includes Endometritis	At the site of the caesarean wound either: Purulent drainage OR Organisms identified OR Wound reopened and local signs of infection OR Abscess.	Organisms, imaging, measurement of temperature not required. Studies did not specify depth of infection, therefore this detail was not included in the adapted definition

Perineal wound infection	**EPIS-Episiotomy infection (CDC*[92])** Episiotomy infections must meet at least ***one*** of the following criteria: 1. Postvaginal delivery patient has purulent drainage from the episiotomy 2. Postvaginal delivery patient has an episiotomy abscess	This definition was applied to both episiotomy wounds and perineal tears. Purulent drainage OR Abscess at the site of the wound	No specific definition for perineal wound infection, therefore used episiotomy infection.
Endometritis	**EMET-Endometritis (CDC*[92])** Endometritis must meet at least one of the following criteria: 1. Patient has organism(s) identified from endometrial fluid or tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing. 2. Patient has at least two of the following signs or symptoms: fever (>38.0°C), pain or tenderness (uterine or abdominal)*, or purulent drainage from uterus. * With no other recognized cause	Organisms identified from endometrial fluid/tissue OR Two of more of the following: Fever, abdominal/pelvic/uterine pain or tenderness, or foul-smelling or pus vaginal discharge OR	No study reported endometrial sampling. Measurement of temperature not required.

*CDC – Centres for Disease Control and Prevention

3.3 Results

Overall, 73 studies provided data on 96 outcomes (Fig 3.1). In many studies, data collection was conducted in a way that risked under-estimating peripartum infection. For example, data was limited to the admission for childbirth in 38 (52%) studies and possibly in a further seven (10%) studies with unclear methods. This would have missed any later infections. Additionally, passive postpartum follow-up, relying on hospital readmission records, carried the risk of missing women who attended a different facility, or did not attend at all, especially in cases of milder disease, in LMICs, or in single-centre studies. The methodologic features of the studies are summarized in Figure 3.2 below.

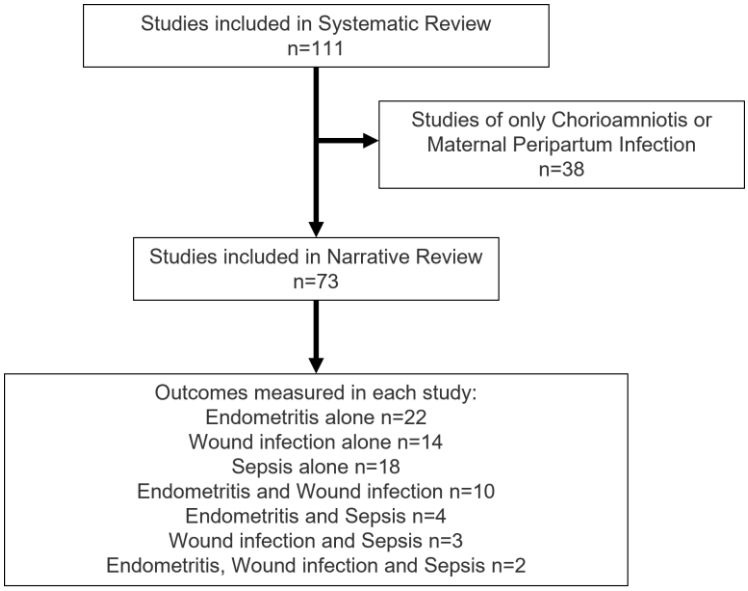


Figure 3.1: Flow diagram

For the 28 studies (38%) with active follow-up, a variety of methods were used, including clinic visits, home visits, postal questionnaires, telephone interviews, or a combination of these. In four studies, hospitals conducted routine surveillance, although the methods are not described. Length of follow-up varied from five to 42 days, limiting the comparability of results, and many studies (10 of 28) had only one follow-up contact with the risk of missing infection at other times. There was the risk of misclassification bias when relying on self-reported data, which was the case in 9 (12%) studies.

Only 23 (22%) of the 106 outcomes met one of the standard infection definitions, and 38 (36%) provided no clear definition at all. Misclassification also occurs when a standard definition is not used.

3.3.1 Endometritis

There were 38 studies providing data on endometritis (Table 3.2): 16 were conducted in HICs, 13 in upper-middle income (UMI) countries, six in lower-middle income (LMI) countries, two in low-income countries (LICs), and one in nine Asian countries of which three were UMI, five were LMI and one was an LIC.

Data collection methods

In 21 studies, data was collected from routine hospital records during the admission for delivery. In some of these studies it is possible that readmission records were also included but this is not clear from the study description. In the RCT of perineal shaving versus hair cutting in Thailand, *Kovavisarach and colleagues* also examined women with suspected infection and performed investigations[122]. The studies reported 0 to 98.9 cases of endometritis per 1000 women, with 16/21 studies reporting infection of <20 per 1000.

Ten studies collected clinical data after the delivery admission. *Belfort et al* collected routine medical record data on hospital readmission in the US, from discharge after delivery until day 42 postpartum, reporting 1.5 per 1000 women with endometritis[180]. In four studies, surveillance after discharge was conducted by the hospitals themselves to day 30 or 42, although no detail was provided on the methods used[118, 128, 147, 183]. *Guimaraes et al* utilised the national surveillance programme in Brazil[183] while *Ayzac et al* and *Dumas et al* worked with surveillance networks in France[128, 147]. Postpartum endometritis was reported at 2.3 to 16.8 per 1000 women. Clinical follow-up was conducted by research teams in five studies, all occurring in LMICs, and found 0-21.2 per 1000 women with endometritis. *Peret et al* invited women in Brazil to the research clinic at day 7-15[112]. In three studies home visits were conducted by clinicians or nurses up to 9 days postpartum[125, 181, 184], and in Tanzania, *Winani et al* conducted a trial of clean delivery kits assessed by a lay-worker home visit at day 5, with cases of suspected infection confirmed by a clinician or nurse at the local health facility[216].

The final seven studies (five conducted in LMICs), collected self-reported data, and describe an infection risk ranging from 13.9 to 162 per 1000, with three studies reporting a risk of over 140 per 1000 women. In three studies the data was collected through lay-worker interviews in women's homes. In Pakistan, *Ghani et al* measured vaginal infection and *Jokhio et al* assessed a traditional birth attendant intervention, although neither specified the end of follow-up[121, 136], and in Bangladesh, *Fronczak et al* assessed postpartum morbidity to day 22[135]. *Ramirez-Villalobos et al* interviewed women at their research clinic in Mexico on day 7[187] and *Gozum et al* arranged interviews at child immunisation clinics in Turkey at around 2

months[137]. *Ahnfeldt-Mollerup et al* sent a postal questionnaire to women in Denmark at day 28[217] and *Bianco et al* conducted telephone interviews with women in Italy at day 30[42].

Infection definitions

Three studies met the CDC definition of endometritis. The criteria were specified by *Ayzac et al* within a French hospital surveillance network[147] and by *Fronczak et al* in Bangladesh[135]; they found 3.3 and 140.1 per 1000 cases of infection respectively. In Brazil, *Guimaraes et al* stated that the CDC definition was used (although the specific criteria were not listed), and identified 8.9 cases of endometritis per 1000 women[183].

Six studies used ICD-9 or ICD-10 codes although none of them specified which code numbers they used to define endometritis. Five of these studies were conducted in the US and extracted the data from hospital records; four from the delivery admission[127, 143, 148, 218] and one from readmissions after delivery[180]. The sixth study, by *Chongsuvivatwong et al*, assessed postpartum complications in teaching hospitals in 9 Asian countries and involved researchers collecting clinical data in hospital and at home, until day 5 postpartum[125].

Two US studies, using hospital records at the time of birth, defined endometritis as fever and uterine tenderness[146, 171]. The cases therefore meet the CDC definition, but the studies could miss cases by excluding uterine discharge as a symptom.

Eleven studies used a broader definition than the CDC, potentially including women who without endometritis. In nine of these studies, all three CDC signs were included, but either a) only one symptom/sign was required[216], b) the combination of symptoms/signs was not specified[136, 187] or c) additional signs or investigations were added. These additional indications were delayed uterine involution[112, 128, 184], tachycardia[110], heavy vaginal bleeding[184], raised white blood cell count[140] and a pelvic ultrasound scan suggestive of infection[106]. These are all potential signs of infection, but do not strictly meet the CDC criteria. In Pakistan, *Jokhio et al* specified only one of either fever OR discharge[121], and *Darmstadt et al*, assessing clean delivery kits in Egypt, specified perineum pain, instead of abdominal or uterine pain, implying cases could be missed and non-cases included[181].

There was no attempt to define infection in 12 of the studies[108, 109, 117-119, 137, 167, 169, 182, 185, 186, 188], and in a further four, the diagnostic criteria used were unclear[42, 116, 122, 217]. Of these 16 studies, 10 were conducted in LMICs and 12 only collected data until women were discharged after giving birth.

Table 3.2: Definitions for Endometritis

Author	Date	Country	World Bank income level	Data collection	Details on data collection	Definition	Details on definition	Infection per 1000 women
Ahnfeldt-Mollerup (2012)[179]	05/07-04/08	Denmark	HIC	Self-report	Questionnaire day 28. Searched GP and hospital records for validation. One third of diagnoses from self-report alone.	Unclear/No definition	Asked if they had an infection and where it was, including 'uterus'. If in contact with GP or hospital then clinical diagnosis used instead, as given by physician.	18.6
Ayzac (2008)[147]	01/97-12/03	France	HIC	Hospital surveillance	Medical records during hospital stay. Surveillance to day 30. Each hospital used their own method – not described	CDC	At least 2 of: fever (≥38°C), abdominal pain, uterine tenderness, or purulent cervical discharge	3.3
Belfort (2010)[180]	01/07-12/07	US	HIC	Medical records for readmission	Readmission to hospital from discharge to day 42	ICD-9	Codes not specified	1.5
Benincasa (2012)[110]	01/04-12/10	Brazil	UMI	Medical records at time of birth		Broader than CDC	Puerperal infection, mainly endometritis. Unspecified combination of isolation of organisms in the endometrium, fever (≥38°C), tachycardia, purulent uterine discharge and abdominal pain accompanied by uterine sensitivity	14.7
Bianco (2013)[42]	09/07-09/08	Italy	HIC	Self-report	Telephone call at day 30. Searched medical records for validation. 12% diagnosed from self-report alone	Unclear/No definition	States definitions of postpartum infections were derived from CDC definitions. Details not provided. Self-reported 'signs and symptoms of infection' not specified.	13.9
Boccardo (2013)[106]	04/10-07/10	Argentina	HIC	Medical records at time of birth	Researchers followed-up laboratory and ultrasound findings	Broader than CDC	At least 2 of: fever (≥38°C), uterine or lower abdominal tenderness, offensive vaginal or cervical discharge or transvaginal ultrasound suggestive of infection	25.1
Caughey (2007)[143]	01/95-12/99	US	HIC	Medical records at time of birth		ICD-9	Codes not specified	12.0

Cavazos-Rehg (2015)[127]	01/09-12/09	US	HIC	Medical records at time of birth		ICD-9	Methods list codes for major puerperal infection. Results only presented for endometritis	3.6
Cheng (2007)[167]	01/91-12/02	US	HIC	Medical records at time of birth		Unclear/No definition	Endometritis – no further detail	13.6
Cheng (2010)[146]	01/90-07/08	US	HIC	Medical records at time of birth		Narrower than CDC	Fever (≥38.5°C) and uterine fundal tenderness	23.7
Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	3 UMI, 5 LMI, 1 LIC	Clinical research follow-up	Clinical data collected on a checklist, in hospital and at home until day 5. No details on how this was done, or by whom	ICD-10	Codes for endometritis not specified	0.6
Darmstadt (2009)[181]	06/01-07/01	Egypt	LMI	Clinical research follow-up	Home visit by nurse within 7 days	Broader than CDC	At least 2 of: Fever (≥38.5°C), abnormal vaginal discharge, perineum pain	15.0
Dimitriu (2010)[119]	1/1/06-1/9/09	Kuwait	HIC	Medical records at time of birth		Unclear/No definition	Endometritis – no further detail	16.3
Dotters-Katz (2015)[142]	01/08-12/10	US	HIC	Medical records at time of birth		ICD-9	Codes for endometritis not specified	13.6
Dumas (2008)[128]	01/01-12/04	France	HIC	Hospital surveillance	Medical record during hospital stay. Surveillance to day 30. Each unit used their own method – not described	Broader than CDC	Fever plus 1 of: purulent cervical discharge, pelvic pain or delayed uterine involution.	02.3
Ezugwu (2011)[182]	09/08-12/08	Nigeria	LMI	Medical records at time of birth		Unclear/No definition	'Genital sepsis' – no further detail	17.4
Fronczak (2005)[135]	11/93-05/95	Bangladesh	LMI	Self-report	3 interviews conducted at home at day 3, 7 and 14-22. Clinical examination at day 14-22 detected fewer signs of pelvic infection. Results presented for self-reported infection.	CDC	At least 2 of: fever, abdominal tenderness, foul vaginal discharge, occurring at least 3 days after delivery	140.1

Geller (2010)[169]	1995 -2005	US	HIC	Medical records at time of birth		Unclear/No definition	Endometritis diagnosed by a clinician and recorded in the medical record	13.1
Ghani (2007)[136]	1/7/05-31/7/05	Pakistan	LMI	Self-report	Nurse interview conducted at home. Timing not specified	Broader than CDC	Unspecified combination of fever, lower abdominal pain, foul smelling vaginal discharge	162.0
Gozum (2005)[137]	05/00-06/00	Turkey	UMI	Self-report	Interview at child immunisation clinic at 2 months. Questions related to 6-weeks postpartum	Unclear/No definition	Interview questions/diagnostic criteria not reported. Results presented for 'vaginal infection'	142.9
Grotegut (2008)[171]	01/03-06/05	US	HIC	Medical records at time of birth		Narrower than CDC	Fever (≥38°C) and uterine tenderness	12.1
Guimaraes (2007)[183]	12/00-07/03	Brazil	UMI	Hospital surveillance	National Nosocomial Infection Surveillance System to day 30. Reported to follow CDC system but not further details provided	CDC	Reports CDC definition used but does not give further details	8.9
Ivanov (2014)[117]	01/11-12/13	Bulgaria	UMI	Medical records at time of birth		Unclear/No definition	Endometritis – no further details	98.9
Iyengar (2012)[184]	01/07-12/10	India	LMI	Clinical research follow-up	2 home visits by nurse-midwives at day 2-3 and 6-9	Broader than CDC	Fever (≥38°C) plus 1 of: lower abdominal pain, abnormal vaginal discharge, delayed uterine contraction, heavy vaginal bleeding	12.9
Jokhio (2005)[121]	05/98-10/98	Pakistan	LMI	Self-report	Routine monthly home visits by lay workers. Timing of infection data not specified	Broader than CDC	Fever or foul-smelling vaginal discharge	43.9 (control group)
King (2012)[148]	08/95-02/04	US	HIC	Medical records at time of birth	Perinatal database comprised of medical charts matched to administration records with ICD-9 codes	ICD-9	Codes for infection not specified	25.3
Kovavisarach (2005)[122]	11/01-02/02	Thailand	UMI	Medical records and research data at time of birth	Research doctors performed pelvic examination and took cervical swabs if infection diagnosed before hospital discharge at day 4.	Unclear/No definition	'Puerperal infection' – no detail on how infection diagnosed or how results of examination and swabs were used	0.0

Magann (2011)[185]	01/07-07/08	US	HIC	Medical records at time of birth		Unclear/No definition	Postpartum endometritis – no further detail	68.8
Maric (2006)[118]	1/04-12/04	Bosnia	UMI	Hospital surveillance	Surveillance to day 42. No details provided	Unclear/No definition	Endometritis – no further detail	16.8
Ngoga (2009)[186]	Start 12/03	South Africa	UMI	Medical records at time of birth		Unclear/No definition	Endometritis – no further detail	04.8
Peret (2007)[112]	07/01-09/03	Brazil	UMI	Clinical research follow-up	Visit to research clinic at day 7-15. Also diagnosed during admission for delivery – unclear if this was by researchers or from medical records	Broader than CDC	Fever plus 1 of: delayed uterine contraction, abnormal smelling vaginal discharge, uterine tenderness on examination	0.0
Ramírez-Villalobos (2009)[187]	04/03-12/03	Mexico	UMI	Self-report	Interview at research clinic visit on day 7. Women who did not attend were visited at home	Broader than CDC	Unspecified combination of: fever and shivering, uterine pain, foul-smelling vaginal discharge	26.5
Saizonou (2014)[116]	07/09-02/10	Benin	LIC	Medical records at time of birth	Diagnosed by doctor or midwife under supervision of Public Health doctor, up to day 7.	Unclear/No definition	Peripartum infection defined as any fever excluding malaria. Endometritis reported in results – no further detail of diagnosis	16.0
Sanabria (2011)[108]	01/07-12/09	Cuba	UMI	Medical records at time of birth	Possibly readmissions also included by methods unclear	Unclear/No definition	Endometritis – no further details	4.8
Sanchez (2015)[109]	01/12-12/13	Cuba	UMI	Medical records at time of birth	Birth records and statistics department for maternal and child health in the hospital	Unclear/No definition	Endometritis – no further detail	16.7 (aged 25-30)
Suthee (2007)[140]	01/99-12/03	Thailand	UMI	Medical records at time of birth		Broader than CDC	Fever (≥38°C on 2 occasions at least 4 hours apart) plus 1 of: uterine tenderness, foul smelling vaginal discharge or white blood cell count more than 15000/mm3	9.3
Tabcharoen (2009)[188]	01/97-12/06	Thailand	UMI	Medical records at time of birth	Medical records and hospital statistics database	Unclear/No definition	Endometritis – no further detail	1.0 (aged 20-34)
Winani (2007)[189]	Start 01/2000	Tanzania	LIC	Clinical research follow-up	Home visit by lay worker at day 5. Suspected infection confirmed by clinician/nurse at local health facility	Broader than CDC	One of the following: fever, lower abdominal pain, foul vaginal discharge	21.2

3.3.2 Wound infection

There were 29 studies providing data on wound infection (Table 3.3). Ten were conducted in HICs, nine in UMI countries, nine in LMI countries and one in nine Asian countries as described above[125].

In 13 studies, clinical data was collected during the admission for delivery. Eleven of these studies used routine hospital records; in their RCT, *Kovavisarach et al* also examined women with suspected infection and performed wound swabs[122]; and in a trial of hand washing methods in China, *Dong et al (2010)* assessed the women themselves[102]. Nine of the studies measured both abdominal and perineal wound infection; seven described infection risks of less than 20 per 1000[101, 113, 119, 158, 169, 186, 191], *Latif et al* at a teaching hospital in Bangladesh described a risk of 30 per 1000[198] and *Ezugwu et al* at a teaching hospital in Nigeria reported the highest risk of 83.3 per 1000[182]. The other four studies identified perineal infection risks of 42.9-87.3 per 1000[102, 117, 122, 199], with more infection detected in the controlled trials by *Kovavisarach et al* and *Dong et al (2010)* than in the two studies using routine medical record data.

Four studies collected clinical data after the delivery admission. Risk of wound infection was reported at 19.5 per 1000 by *Guimaraes et al* in Brazil[183], and 17.8 per 1000 by *Leth et al* using Danish national and regional databases up to day 30 postpartum[152]. Risk of perineal infection was reported at 25.7 per 1000 by *Chongsuvivatwong et al's* multi-country Asian study[125] and 4.2 per 1000 by *Iyengar et al* in India, assessed during home visits by nurse-midwives up to day 9[184]. In addition, *Liu et al* examined women in a Chinese hospital and identified 88.7 per 1000 with wound infection, but it was unclear if data collection continued after hospital discharge and if so for how long[103].

Five studies, three in HICs, collected self-reported data. Three of these studies describe a risk of wound infection ranging from 27.4-31.6 per 1000. *Bianco et al* in Italy[42] and *Ahnfeldt-Mollerup et al* in Denmark[217] used telephone and postal questionnaires respectively, and *Shriraam et al* interviewed women in India up to 6 months postpartum, asking about the first 42 days[138]. The other two studies describe perineal infection: no infection was identified by *Charrier et al* in Italy during telephone interviews at 20-30 days postpartum[193], and a risk of 108.7 per 1000 episiotomy infections was identified by *Ramirez-Villalobos et al* in Mexico[187].

A further six studies, two from HICs, had unclear data collection methods[190, 192, 194-197]. They were hospital-based studies, so data were probably collected from the medical records during the delivery admission. Infection risks ranged from 0-62.1 per 1000 women.

Infection definitions

Five studies closely met the standard definition of wound infection. Two of these, based in Brazil, stated that they used the CDC definition although the specific criteria were not mentioned: *Petter et al* identified 1.24 wound infection during the delivery admission[113] and *Guimaraes et al* identified 1.95% using national surveillance[183]. In Italy, *Bianco et al* derived definitions from CDC and specifically included purulent discharge, identifying 30.8% infection[42] and in China, *Liu et al* measured purulent discharge or incision and drainage of the wound, identifying a high risk of infection at 88.7 pe 1000[103]. *Charrier et al*, also in Italy, did not identify any perineal infection when asking women about purulent discharge or abscess[193].

Four studies used ICD-9 or -10 codes although none of them specified the code numbers used. Three studies from North America identified up to 3.5 per 1000 women with wound infection[158, 191, 197] and *Chongsuvivatwong et al* identified 25.7 per 1000 with perineal infection in Asia[125].

Two studies used definitions that are narrower than the CDC standard, potentially missing cases. In India, *Shriraam et al* estimated 27.4 pe 1000 women with wound infection based solely on purulent discharge[138] and in Mexico, *Ramirez-Villalobos et al* estimated 108.9 per 1000 with episiotomy infection based on self-reported symptoms of pus, pain, warmth and redness[187].

Four studies included signs of infection based on the CDC definition but also used additional criteria that may have over-estimated infection risk. Wound infection was reported at 20.2 per 1000 by *Leth et al,* including gaping of the episiotomy wound[152], and 17.8 per 1000 by *Dasgupta et al* in South India, including antibiotic prescription after hospital discharge following caesarean section[195]. Two studies of perineal wound infection included pain and redness with or without purulent discharge: *Kovavisarach et al's* RCT identified 87.3 per 1000 with infection in Thailand and *Iyengar et al* identified 4.2 per 1000 in India[122, 184].

The remaining 14 studies provided no clear definition; ten of these were conducted in LMICs. Four of the studies also had unclear data collection methods and nine only collected data until hospital discharge after delivery. Eleven reported wound infection risk of 0-83.3 per 1000[101, 119, 169, 182, 186, 190, 192, 194, 196, 198, 217], and the other three reported perineal infection risk of 42.9-86.7 per 1000[102, 117, 199].

Table 3.3: Definitions for Wound Infection

Author	Date	Country	Income level	Data Collection	Details of data collection	Infection definition	Details of definition	Wound Infection Per 1000 women
Ahnfeldt-Mollerup (2012)[179]	05/07-04/08	Denmark	HIC	Self-report	Questionnaire day 28. Searched GP and hospital records for validation. One third of diagnoses from self-report alone.	Unclear/No definition	Asked if they had an infection and where it was, including 'wound'. If in contact with GP or hospital then clinical diagnosis used instead, as given by physician.	31.6
Awan (2015)[190]	10/10-09/11	Pakistan	LMI	Unclear	Data collected on a predesigned proforma – but not clear where the information came from	Unclear/No definition	Wound infection – no further detail	20.0
Bailit (2006)[191]	01/01-12/01	US	HIC	Medical records at time of birth	Birth certificate data linked to hospital discharge data	ICD-9	Codes not specified	2.0
Bianco (2013)[42]	09/07-09/08	Italy	HIC	Self-report	Telephone call at day 30. Searched medical records for validation, including wound cultures and antibiotics. 12% diagnosed from self-report alone	CDC	States definitions of postpartum infections were derived from CDC definitions including SSI. Full details not provided but includes fever and wound discharge	30.8
Bodner (2011)[192]	11/05-01/09	Austria	HIC	Unclear	Hospital-based study so probably from medical records at time of birth	Unclear/No definition	Abdominal or episiotomy wound infection – no further detail	11.2
Charrier (2010)[193]	05/04-10/04	Italy	HIC	Self-report	Telephone interview at 20-30 days Data also collected during hospital stay by direct observation and from medical records.	CDC	Episiotomy and perineal wound infection: drainage of pus or abscess. Women were asked about symptoms, diagnosis by physician and antibiotic administration	0.0
Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	3 UMI, 5 LMI, 1 LIC	Clinical research follow-up	Clinical data collected on a checklist, in hospital and at home until day 5. No details on how this was done, or by whom	ICD-10	Minor and major wound infection – codes not specified	25.7
Danish (2010)[194]	05/98-11/99	Pakistan	LMI	Unclear	Hospital-based study so probably from medical records at time of birth	Unclear/No definition	Wound infection – no further detail	62.1

Dasgupta (2014)[195]	10/10-09/11	India	LMI	Unclear	Hospital-based study so probably from medical records. Included infection to day 7 but no methods described to follow women after hospital discharge	Broader than CDC	Discharge from caesarean wound and episiotomy wound gape	20.2
Dimitriu (2010)[119]	01/06-09/09	Kuwait	HIC	Medical records at time of birth		Unclear/No definition	Wound infection – no further detail	3.3
Dong (2009)[101]	01/01-11/04	China	UMI	Medical records at time of birth		Unclear/No definition	Perineum or caesarean wound infection – no further detail	13.2
Dong (2010)[102]	07/08-08/08	China	UMI	Research data at time of birth	Clinical data collected by study doctor	Unclear/No definition	Perineal infection using hospital diagnostic criteria – no details provided	86.7
Ezugwu (2011)[182]	09/08-12/08	Nigeria	LMI	Medical records at time of birth		Unclear/No definition	'Wound sepsis' – no further detail	83.3
Geller (2010)[169]	1995-2005	US	HIC	Medical records at time of birth		Unclear/No definition	Wound infection as determined by the hospital clinician	0.2
Goff (2013)[158]	01/08-12/09	US	HIC	Medical records at time of birth		ICD-9	Wound infection – codes not specified	3.5
Guimaraes (2007)[183]	12/00-07/03	Brazil	UMI	Hospital surveillance	National Nosocomial Infection Surveillance System to day 30. Reported to follow CDC system but no further details provided	CDC	Reports CDC definition used for surgical site and episiotomy infection, but does not give further details	19.5
Ivanov (2014)[117]	01/11-12/13	Bulgaria	UMI	Medical records at time of birth		Unclear/No definition	Perineal wound infection after vaginal delivery – no further details	42.9
Iyengar (2012)[184]	01/07-12/10	India	LMI	Clinical research follow-up	2 home visits by nurse-midwives at day 2-3 and 6-9	Broader than CDC	Perineal infection – perineal pain and pus or redness on examination	4.2
Jaleel (2009)[196]	01/06-04/08	Pakistan	LMI	Unclear	Hospital data so probably medical records at time of birth	Unclear/No definition	Wound infection – no further detail	0.0

Janssen (2009)[197]	01/00-12/04	Canada	HIC	Unclear	Hospital and home births included. Unclear who diagnosed infection or length of follow-up	ICD-10	Wound infection – codes not specified	1.4 – planned midwife. 3.0– planned doctor
Kovavisarach (2005)[122]	11/01-02/02	Thailand	UMI	Research data at time of birth	Women with infection were examined by the authors (doctors) and wound swab performed	Broader than CDC	Perineal wound infection – pain and erythema, with or without purulent discharge	7.3
Latif (2013)[198]	01/00-06/00	Bangladesh	LMI	Medical records at time of birth		Unclear/No definition	Wound infection – no further details	30.0
Leth (2009)[152]	01/01-12/05	Denmark	HIC	Clinical follow-up using routine data	Data to day 30, from hospital laboratory information system, regional prescription database and National Hospital Registry.	Broader than CDC	One of the following: positive wound culture or abscess OR re-operation due to wound infection OR dicloxacillin antibiotic after hospital discharge following caesarean section	17.8
Liu (2010)[103]	01/05-12/06	China	UMI	Clinical research follow-up – time not specified	Clinical data collected by a study doctor.	CDC	Abdominal and perineal wound infection – purulent discharge OR needs incision and drainage	88.7
Ngoga (2009)[186]	12/03	South Africa	UMI	Medical records at time of birth		Unclear/No definition	Abdominal wound infection and episiotomy sepsis – no further details	0.0
Oladapo (2007)[199]	01/90-12/05	Nigeria	LMI	Medical records at time of birth	Average hospital stay 5-6 days in early 1990s and 2-3 days from late 1990s	Unclear/No definition	Wound infection (abdominal or episiotomy) – no further details	51.8
Petter (2013)[113]	01/09-12/10	Brazil	UMI	Medical records at time of birth	Identified from regular communication on infection and notification to the hospital Infection Control service. Assumed until discharge after delivery	CDC	Surgical site infection according to the national nosocomial infection surveillance system which follows CDC definitions: endometritis, surgical wound infection, or episiotomy infection following an obstetric procedure. Details not provided.	12.4

Ramírez-Villalobos (2009)[187]	04/03-12/03	Mexico	UMI	Self-report	Interview at research clinic visit on day 7. Women who did not attend were visited at home	Narrower than CDC	Episiotomy infection – purulent discharge, pain, warmth and redness. (Simple complications with pain, bleeding and separation were excluded)	108.9
Shriraam (2012)[138]	11/08-02/09	India	LMI	Self-report	Structured questionnaire on the postpartum period (to day 42), delivered up to 6 months postpartum	Narrower than CDC	Wound with purulent discharge	27.4

3.3.3 Sepsis

There were 27 studies providing data on sepsis (SIRS, severe sepsis or blood stream infection) (Table 3.4). Sixteen were conducted in HICs, seven in UMI countries and 4 in LMI countries.

Data collection methods

In over half (14/27) of studies, clinical data was collected from routine hospital records relating to the admission for delivery. Twelve of these studies reported a sepsis risk of 0-2.3 per 1000[4, 108, 111, 114, 117, 124, 131, 149, 155, 158, 201, 206]. *Dotters-Katz et al*[218] and *Callaghan et al*[151] used two different databases of nationally representative US hospital data to identify blood stream infection of 0.7 per 1000 and 0.2 per 1000 (including a marker of severity) respectively.

Eleven studies collected clinical data after the delivery admission of which seven (five from HICs) used hospital record data, both at birth and during readmission. *Pallasmaa et al (2008 and 2015)* used the Finnish National hospital discharge registry and described sepsis incidence to day 42 postpartum, increasing over time from 3.3 per 1000 to 8.1 per 1000[204, 205]. Three studies reported risk of severe sepsis: *Mayi-Tsonga et al* identified no cases in their audit of maternal near-miss in Gabon[115], *Karolinski et al* identified a risk of 0.4 per 1000 in their study of life-threatening complications up to 42 days in Argentina[203] and *Huda et al* identified a risk of 8.8 per 1000 up to 42 days in Bangladesh[202]. The final two studies reported blood stream infections: *Cape et al* identified 1.7 per 1000 with infection up to 30 days postpartum at a teaching hospital in the US[200] and *Knowles et al* identified 1.1 per 1000 up to day 42 at two tertiary maternity hospitals in Ireland[153].

Belfort et al, using readmission data in the US, reported sepsis risk of 0.1 per 1000 up to 42 days postpartum[180]. *Maric et al* identified no cases of puerperal sepsis at a Bosnian hospital conducting its own surveillance to 42 days[118]. *Leth et al*, in Denmark, identified 0.6 per 1000 women with blood stream infection up to day 30 postpartum[152] and *Chongsuvivatwong et al* identified a peritonitis risk of 0.2 per 1000 in Asia[125].

Only *Shriraam et al* in India collected self-reported data, identifying an extremely high risk of 38.4 per 1000 women with postpartum/puerperal sepsis occurring until day 42[138]. *Tippawan et al* reported 1.1 per 1000 with sepsis from National Health Security Office data in Thailand, although the data collection methods were unclear[150].

Sepsis definitions

The 27 studies present results for SIRS/sepsis, severe sepsis and blood stream infection. *Acosta et al*[4] and *Bauer et al*[149] report results separately for sepsis and severe sepsis, thereby creating a total of 29 outcomes assessed in the 27 studies Over half (15/29) of these definitions used ICD-9 and 10 codes, but three did not use codes that fully met one of the sepsis definitions, and two did not list the code numbers. Their results are reported together with the studies that presented clinical definitions.

Five definitions met the criteria for SIRS/sepsis, three using ICD codes and two specifying SIRS criteria correctly. Infection risks ranged from 0.3-1.1 per 1000[4, 114, 124, 149, 150]. *Chongsuvivatwong et al* reported 0.2 per 1000 women with peritonitis in Asia; a definition likely to miss many cases of sepsis as well as including non-septic women[125]. The two studies by *Pallasmaa et al* used ICD-10 codes for peritonitis as well as puerperal sepsis, potentially including non-septic women and identifying a higher proportion of cases (3.3-8.1 per 1000)[204, 205]. Eight studies, including two using ICD codes and five from LMICs, provided no definition. One was the study by *Shriraam et al* which identified 38.4 per 1000 with puerperal/postpartum sepsis using self-reported data[138]. The other seven studies report sepsis risks ranging from 0-2.3 per 1000[108, 117, 118, 131, 180, 201, 206].

Four definitions met the criteria for severe sepsis. Three of the studies were conducted in HICs and used ICD codes, identifying a low risk of disease (0.1-0.5 per 1000)[4, 149, 203]. The fourth study, by *Huda et al* in Bangladesh, identified a much higher risk (8.8 per 1000) using clinical criteria[202]. *Mayi-Tsonga et al* in Gabon included signs of severe disease but their definition was broader than the standard and included the vague descriptor of 'general state impaired'[115]. However, no cases were reported.

Kuklina et al and *Goff et al*, both utilising large US databases, selected ICD-9 codes that met the definitions for combined SIRS and severe sepsis, reporting 0.3 per 1000 and 1.3 per 1000 women with disease respectively[155, 158]. *Luz et al* also measured SIRS with and without signs of severity at a teaching hospital in Brazil, but narrowed the definition to those with a positive blood or swab culture; they reported a risk of 0.5 per 1000[111].

Finally, four studies, all from HICs, met the definition for blood stream infection, one using ICD codes, with risks ranging from 0.6-1.7 per 1000[152, 153, 200, 218]. *Callaghan et al* narrowed the definition to only include cases of blood stream infection with prolonged admission, reporting a risk of 0.2 per 1000[151].

Table 3.4: Definitions for Sepsis

Author	Date	Country	Income level	Data Collection	Details of data collection	Infection type	Definition	Details of definition	Sepsis cases per 1000 women
Acosta (2013)[4]	01/05-12/07	US	HIC	Medical records at time of birth	Live births only	Sepsis	Meets definition	ICD-9 Septicaemia (038.1–038.9) or sepsis (995.91)	1.0
Acosta (2013)[4]	01/05-12/07	US	HIC	Medical records at time of birth	Live births only	Severe sepsis	Meets definition	ICD-9 Severe sepsis (995.92) or Sepsis (as above) plus prolonged length of stay or transfer to intensive care or death. Septic shock (785.52)	0.5
Bauer (2013)[149]	01/98-12/08	US	HIC	Medical records at time of birth	NIS data	Sepsis	Meets definition	ICD-9 Septicaemia (038.0, 038.1, 038.11, 038.12, 038.19, 038.2, 038.2, 038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 112.5). Septicaemia during labour (659.3x). SIRS without organ dysfunction (995.91).	0.3
Bauer (2013)[149]	01/98-12/08	US	HIC	Medical records at time of birth	NIS data	Severe sepsis	Meets definition	ICD-9 SIRS with organ dysfunction (995.92). Septic shock (785.52). Severe sepsis defined as a code for sepsis plus a code for acute organ dysfunction, hypotension or hypoperfusion (multiple codes listed)	0.1
Belfort (2010)[180]	01/07-12/07	US	HIC	Medical records for readmission	Readmission to hospital from discharge to day 42	Sepsis	Unclear/No definition	ICD-9 codes not specified	0.1
Ben (2007)[114]	01/99-12/03	Tunisia	UMI	Medical records at time of birth	Medical record data on all severe (near-miss) puerperal infection at one hospital using SIRS criteria.	Sepsis	Meets definition	Called 'Severe (near-miss) puerperal infection)' - SIRS criteria specified	0.8

Callaghan (2008)[151]	01/91-12/03	US	HIC	Medical records at time of birth	National Hospital Discharge Survey	Blood stream infection	Narrower	ICD-9. Septicaemia (038) and hospital stay of 3+ days	0.2
Cape (2013)[200]	01/00-12/08	US	HIC	Medical records at birth and readmission postpartum	Hospital laboratory and medical records from 7 days antepartum to 30 days postpartum	Blood stream infection	Meets definition	Positive blood culture plus clinical diagnosis of chorioamnionitis, endometritis or wound infection. (Cultures taken if fever ≥100.4°F and signs of infection)	1.7
Chongsuvivatwong (2010)[125]	09/01-09/04	9 Asian countries	3 UMI, 5 LMI, 1 LIC	Clinical research follow-up	Clinical data collected on a checklist, in hospital and at home until day 5. No details on how this was done, or by whom. Results for vaginal deliveries only	Sepsis	Narrower	ICD-10 code for peritonitis	0.2
David (2012)[201]	01/05-12/10	India	LMI	Medical records at time of birth	Vaginal deliveries only	Sepsis	Unclear/No definition	Puerperal sepsis – no further detail	0.0
Dotters-Katz (2015)[218]	01/08-12/10	US	HIC	Medical records at time of birth	NIS	Blood stream infection	Meets definition	ICD-9 Septicaemia (038.x) or bacteraemia (790.7)	0.7
Goff (2013)[158]	01/08-12/09	US	HIC	Medical records at time of birth	Perspective database	Sepsis and severe sepsis	Meets definition	ICD-9 Septicaemia (038) infection in labour (659.3) septic shock (785.52) bacteraemia (790.7) SIRS (959.9). Excluded antepartum conditions (codes with a 5th digit of '3')	1.3
Huda (2012)[202]	01/08-12/08	Bangladesh	LMI	Medical records at birth and readmission postpartum	From labour until 32 days postpartum	Severe sepsis	Meets definition	Septic shock or septicaemia: Genital source of infection and fever (≥38.3 °C) or hypothermia, and tachycardia (≥110/min) or tachypnoea (≥ 30/min). Plus, low blood pressure or confusion or unconsciousness or scanty urine output	8.8
Ivanov (2014)[117]	01/11-12/13	Bulgaria	UMI	Medical records at time of birth	Medical record and laboratory data	Sepsis	Unclear/No definition	Sepsis – no further details	0.8

Karolinski (2013)[203]	06/08-05/09	Argentina	HIC	Medical records at birth and readmission postpartum	Admissions with life-threatening complications up to 42 days postpartum. Denominator is live-births at the same facilities.	Severe sepsis	Meets definition	ICD-10 Life-threatening puerperal sepsis: O85 plus admission to intensive care, or emergency hysterectomy or organ dysfunction	0.4
Knowles (2014)[153]	01/05-12/12	Ireland	HIC	Medical records at birth and readmission postpartum	Medical and laboratory records, infection prevention and control team records and annual clinical report. From labour until 42 days postpartum	Blood stream infection	Meets definition	Positive blood cultures and same organisms cultured from genital tract.	1.1
Kuklina (2008)[155]	01/98-12/04	US	HIC	Medical records at time of birth	NIS	Sepsis and severe sepsis	Meets definition	ICD-9 Septicaemia (038x) Septic shock (785.5) SIRS without/with organ dysfunction (995.91/2)	0.3
Leth (2009)[152]	01/01-12/05	Denmark	HIC	Clinical research follow-up using routine data	Data to day 30, from hospital laboratory information system, regional prescription database and National Hospital Registry.	Blood stream infection	Meets definition	Positive blood cultures and concomitant antibiotics	0.6
Luz (2008)[111]	10/05-07/06	Brazil	UMI	Medical records at time of birth	Cases identified daily by a trained nurse and data extracted from clinical records by the researcher	Sepsis and severe sepsis	Narrower	SIRS criteria plus positive blood culture or positive swab culture. With/without organ dysfunction or hypotension.	0.5
Lyndon (2012)[131]	01/05-12/07	US	HIC	Medical records at time of birth	Live, singleton births only	Sepsis	Unclear/No definition	ICD-9 Maternal sepsis – codes not specified	0.9
Maric (2006)[118]	01/04-12/04	Bosnia	UMI	Hospital surveillance	Surveillance to day 42. No details provided. Nulliparous vaginal deliveries only	Sepsis	Unclear/No definition	Puerperal sepsis – no further detail	0.0
Mayi-Tsonga (2007)[115]	06/06-12/06	Gabon	UMI	Medical records at birth and readmission postpartum	Audit of near-miss cases throughout pregnancy and postpartum	Severe sepsis	Broader	Fever (≥38°C) plus hypotension or altered consciousness or general state impaired	0.0

Pallasmaa (2008)[204]	01/97-12/97 and 01/02-12/02	Finland	HIC	Medical records at birth and readmission postpartum	National hospital discharge registry to day 42 postpartum	Sepsis	Broader	ICD-10 Puerperal sepsis (O85) or generalised peritonitis (K65.0) or peritonitis unspecified (K65.9)	1997 – 3.3 2002 – 4.5
Pallasmaa (2015)[205]	01/07-12/11	Finland	HIC	Medical records at birth and readmission postpartum	National hospital discharge registry to day 42 postpartum	Sepsis	Broader	ICD-10 Puerperal sepsis or peritonitis or re-operation for infection	8.1
Sanabria (2011)[108]	01/07-12/09	Cuba	UMI	Medical records at time of birth	Unclear if readmission also included	Sepsis	Unclear/No definition	Sepsis – no further detail	1.8
Shriraam (2012)[138]	11/08-02-09	India	LMI	Self-report	Structured questionnaire on the postpartum period (to day 42), delivered up to 6 months postpartum	Sepsis	Unclear/No definition	Postpartum sepsis/puerperal sepsis – no further detail	38.4
Simoes (2005)[206]	01/98-12/98 and 01/01-12/01	Germany	HIC	Medical records at time of birth	Perinatal database	Sepsis	Unclear/No definition	Septicaemia – no further details	1998 – 0.9 2001 – 2.3
Tippawan (2014)[150]	10/10-09/11	Thailand	UMI	Unclear	National Health Security Office data	Sepsis	Meets definition	ICD-10 Puerperal sepsis (O85)	1.1
Zhang (2005)[124]	01/95-02/98	9 European countries	HIC	Medical records at time of birth	Unclear if readmission also included. Two-weekly data collection by trained researchers.	Sepsis	Meets definition	SIRS criteria specified	0.7

3.4 Summary and Discussion

Half of all studies (38/73) measured outcomes during the delivery admission, potentially missing many cases of infection. However, infection incidence across these studies was wide, not clearly related to the definitions used, and incidence risks did not appear to be higher when hospitals surveyed women for a longer period, except for blood stream infections. This could reflect the different contexts where studies occurred, poor follow-up methods that continued to miss cases, or unclear reporting of study methods with longer follow-up than I accorded them.

The majority of data came from routine medical records, especially, and most appropriately, in the studies of sepsis. However, infection was also diagnosed by researchers within hospitals, and data was collected postpartum using a variety of follow-up methods: home visits, clinic visits, postal questionnaires and telephone calls. Higher risks of endometritis were described by studies collecting self-reported data, in particular by lay-workers in LMICs. This could reflect a real increased risk in these settings or a more complete follow-up programme, however, it could also indicate an overdiagnosis of infection based on a non-clinical judgement of women's symptoms (misclassification).

In comparison, incidence of wound infection was not higher in studies using self-reported data. Instead, some of the highest risks were reported when infection was diagnosed by research doctors. An example of this is seen by comparing the three Chinese studies. The largest of these utilised medical record data on all women delivering at one hospital within a 4-year period to estimate an abdominal and perineal wound infection risk of 13.2 per 1000. This compares to a risk of 88.7 per 1000 in a small cohort of 360 women being examined for infection by research doctors and a risk of perineal infection of 86.8 per 1000 in the 300-woman control arm of a trial of hand washing. This may be an example of confirmation bias, with over-diagnosis of infection by researchers specifically looking for it. Alternatively, it could indicate that studies using routine data are missing cases of infection.

Studies of sepsis were more likely to use a standard definition compared to those measuring the other outcomes, with 15 out of 29 estimates meeting the definition compared to only three and five of 29 for endometritis and wound infection respectively. A higher proportion of the sepsis studies were conducted in high-income countries and the vast majority used hospital records, which is both unsurprising and appropriate given the severity of the condition and the expectation that most women will be admitted to hospital. The higher compliance with a standard definition was also due to the provision of appropriate ICD-code numbers which were missing in studies of the other two outcomes.

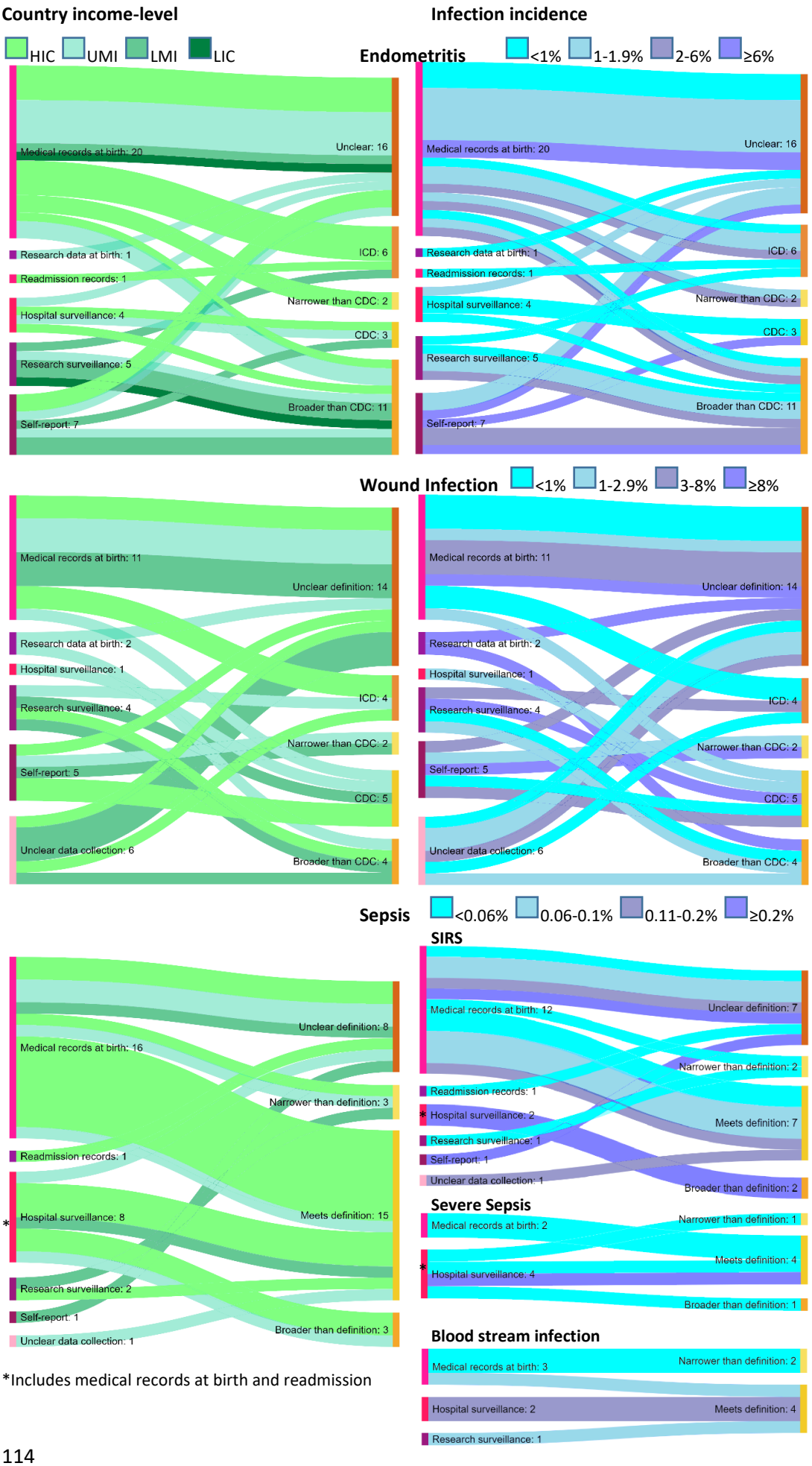
Studies of sepsis that used broader or narrower definitions than the standard appeared to have higher and lower risk of disease respectively, after accounting for the three severities of outcome (Fig. 3.1). However, this was not the case for endometritis or wound infection (Fig. 3.1). Studies of endometritis were particularly prone to using a broader definition than CDC, and although incidence did not appear higher this carries the risk of over-estimating the outcome.

A substantial proportion of all outcomes had no clear definition, and this was a greater problem for endometritis and wound infection (42% and 48% respectively) compared to sepsis (27%). This lack of a definition occurred with all forms of data collection, and in countries from all income-levels.

3.4.1 Conclusion

This narrative review illustrates some of the limitations in the way maternal peripartum infection has been measured, however, it also demonstrates that good practice is possible. Standard definitions were applied in both hospital and community settings, and some studies managed to conduct active follow-up for four to six weeks postpartum using a variety of methods. Studies of sepsis had the advantage of being able to rely on hospital records, because of the severity of disease. Postpartum follow-up of endometritis and wound infection is more challenging and greater care is needed to retain women and avoid misclassification.

Fig 3.2: Illustration of data collection methods and infection definitions for each study



*Includes medical records at birth and readmission

Chapter 4: Postnatal surveillance methods – literature review and synthesis

4.1 Introduction

In the previous chapters, the systematic review of peripartum infection revealed two major challenges in the measurement of childbirth-related maternal infection. The first relates to the variety of definitions used, resulting in studies measuring potentially different outcomes. Tackling this requires the creation and use of standard definitions that can be applied across different settings. The second relates to the identification or detection of all cases in a population. The majority of study outcomes were identified from medical records, and half of them did not describe follow-up periods beyond the childbirth admission. The effect of this limited surveillance is not evident from the review because of the many other differences in the studies. However, individual studies clearly demonstrate a high proportion of postnatal maternal infections are missed by failing to conduct thorough surveillance after hospital discharge[42, 219]. European SSI surveillance reports not only find just a small proportion of infections (16% in 2010-11) are diagnosed during hospitalisation, but also that countries with more intensive surveillance methods identify more infections[220, 221].

The systematic review provided some examples of post-childbirth data collection, however, there are studies of postnatal surveillance which do not measure infection or did not meet the inclusion criteria for the review but can help inform the design of future surveillance. As well as research design, they can also inform routine surveillance and provide insights into maternal postnatal care provision. I therefore reviewed these studies to describe the proportion of postnatal women successfully retained in follow-up, comparing different surveillance methods. My secondary objective was to describe any methodological details or interventions that contributed to successful surveillance.

4.2 Methods

I conducted a literature search in March 2021 for studies that collected health data on women or newborns after birth. In Medline I combined postnatal terms (postpartum or postnatal or postpartum period/ or postnatal care/ or caesarean section) with terms for surveillance (surveillance or public health surveillance/ or population surveillance/). I included English language, peer-reviewed articles. All quantitative study designs were included. I excluded articles published before 2007 as the aim was to learn about the coverage and challenges of current methods of surveillance. I excluded studies that did not

specify the proportion of the study population retained in follow-up, or provide details of their follow-up methods, and articles that only reported mortality outcomes because different methods are required for collection of morbidity data. I also excluded any articles already included in the systematic review presented in the previous chapter. I examined the reference lists from these articles for any additional studies not identified above. In addition, I retained some studies that did not meet the criteria above but provided insights into novel ways of conducting maternal postnatal care, or explored women's experiences of care during this period.

For each study I extracted data on the study population, length of postnatal follow-up, health condition of interest, method of data collection and percentage of women/newborns reached. For studies of maternal postnatal infection, I extracted the proportion of infections occurring after hospital discharge, when available. In addition, I documented information on interventions implemented to provide or improve postnatal follow-up and care, and on women's experiences and desires regarding health and support in the postnatal period.

4.3 Results

4.3.1 Overview of surveillance studies

I identified 28 studies providing data on postnatal surveillance methods (Table 4.1); four from North America[222-225] (three from the US), nine from Europe[219, 226-233] (1 Kosovo), two from Latin America[234, 235] (both Brazil), three from Asia[236-238] and seven from SSA[239-245].

In addition, three studies covered multiple countries; one had sites in SSA, Asia and Latin America[246], the second had sites in SSA and Latin America[247] and the third had sites in SSA and South Asia[248]. There were two cross-sectional studies, five controlled trials (four of which were cluster-randomised) and one before-after evaluation. The remaining 18 studies were prospective cohorts. The sample sizes ranged from 193 to 187,501.

4.3.2 Outcomes measured

The most common outcome was SSI, measured by twelve studies; three from SSA[242-244], one from Latin America[234] and the remainder from Europe or North America[219, 224, 225, 227-229, 231, 233]. Five of these studies reported on a range of surgical procedures of which caesarean section was one[219, 228, 229, 242, 244], and seven included only caesarean section patients. In the majority (10) of these studies, women were followed-up for a month (28-30 days), in line with the CDC definition of SSI as occurring up to 30 days after surgery. One Canadian study of SSI following caesarean section collected data at 42 days as this was when women

returned for a standard postnatal visit[224]. One UK study collected data on post-caesarean wounds supplied by community midwives, who discharged women after an average of 15 days postnatal[233].

Seven of the studies of SSI reported the proportion of all infection cases diagnosed after discharge. Among four studies of various surgical procedures, post-discharge infection ranged from 73% to 88%[228, 229, 242, 244]. The median day of diagnosis was 15 in a Kenyan RCT[244] and 13 in the Norwegian national surveillance system for Healthcare Associated Infections (NOIS)[228]. There were three studies of post-caesarean SSI. A UK study followed women on average for 15 days and reported 84% of infections occurring post-discharge[233]. An Italian study diagnosed 89% of infections post-discharge with median day of onset of 9.5[227], and in a Tanzanian study, the median day of onset was 8 and all infections were identified after discharge[243]. Two other studies of caesarean SSI reported similar median times to infection of 7 days (Kosovo)[231] and 10 days (Brazil)[234].

Various other maternal outcomes were assessed by seven studies: blood pressure[223], perineal morbidity[230], pelvic pain[226], infection[232], depression[237], direct maternal morbidities[248], and near-miss criteria[238]. One study was interested in pregnancy outcomes and postnatal mortality[246], and two were interested in health service utilization for maternal postnatal care[240, 245]. Six studies, five in LMICs, were interested in newborn care and illness, including two that specifically surveyed breastfeeding practices[222, 235, 236, 239, 241, 247].

4.3.3 Data collection methods

Telephone methods

Seven of the 28 studies aimed to collect data on all participants using telephone calls; two were conducted in HICs[225, 229], two in SSA[242, 243], two in Brazil[234, 235], and one in India[238]. Five measured SSI at 28-30 days, one (Brazilian) study measured exclusive breastfeeding at 30-45 days[235] and an Indian call centre collected data on near-miss criteria between day 8-42[238]. Across the seven studies, 63-91% of the intended populations were reached at least once by telephone. The best performing surveillance was conducted in Switzerland[229], involving five calls to each woman at around one month postnatal. In a Tanzanian study, 84% of women provided one or more telephone number and were called up to two times on three separate occasions, reaching 87% of them at least once[243]. The Indian call centre telephoned up to three times to reach 86% of all women[238]. The usual reason for not reaching a woman by telephone was no telephone number in their records, therefore, among women with a telephone number the success would be considerably higher. Fieldworkers visited women

who could not be reached by telephone, giving an overall coverage of 98%. A study in the US called up to three times on three separate days, reaching 82% of women at least once, and 65% on all three occasions[225]. Among all SSI identified, 26% were detected solely by telephone surveillance because these women did not return to the study hospital so were missed by standard hospital record surveillance. In Sudan, participants provided two telephone numbers and were called on four occasions, reaching 78%[242]. It is not specified whether they were called more than once on each day. Among the identified SSI, 43% were detected solely by telephone surveillance. Two Brazilian studies had the lowest coverage using telephone methods. One study of post-caesarean SSI made up to five calls on two occasions, reaching 67% of women at least once[234]. The other study was conducted in the Western Brazilian Amazon with a population that was 28% rural. They made 'several attempts' to contact women from day 30-45 to interview them about breastfeeding and reached 63% of them.

A small RCT in the US used text messaging to collect twice daily blood pressure measurements from women with hypertensive disease[223]. In the first 10 days postnatal, 92% of women sent at least one blood pressure reading by text message. In the control arm, only 44% of women visited the hospital clinic for a blood pressure recording during this period.

Telephone calls were used to supplement postal questionnaires in two national surveillance systems. The NOIS module for SSI sent a postal questionnaire at 25 days after surgery, followed by a reminder letter and then a telephone reminder, and reached 88% of women post-caesarean section[228]. Data was also collected from hospital records, however, 23% of infections were purely based on patient reports. A study of breastfeeding in the US used data from the Pregnancy Risk Assessment Monitoring System (PRAMS)[222]; a survey of maternal behaviours, attitudes and experiences between 2-6 months postnatal[249]. A postal questionnaire is sent up to three times, with one reminder after the first time. Women who do not respond are called up to 15 times and the questionnaire conducted by telephone. States are allowed to provide an incentive for completing the questionnaire. In 2014, weighted response rates among participating states ranged from 47% to 74% with a median of 61%. The relatively low response may reflect the length of the questionnaire which takes around 20 minutes to complete and some difficulty in locating women's telephone number within routine data. Among women who responded, 20% completed the questionnaire by telephone interview, but this was higher for harder to contact demographics including ethnic minorities, adolescents and those with lower educational levels.

A cluster RCT (cRCT) of surgical patients in Kenya[244] and a cohort of post-caesarean women in Italy[227] measured SSI at clinic visits, supplemented by telephone calls when required. In both cases, surveillance data was captured for 94% of women. Further details of the methods used and the proportion of women requiring telephone calls is not provided.

Three non-surveillance studies explored the potential of telehealth in the provision of obstetric care. Two recent US studies were conducted in the context of the COVID-19 pandemic. One article details the management of high-risk pregnancies using a combination of telehealth and in-person consultations[250]. They advise that postpartum care can be safely carried out for stable patients using a video call, including examination of a caesarean scar, lactation consultation, and Blood Pressure (BP) monitoring with the use of a home BP cuff. A second study specifically describes the remote management of obstetric patients with COVID, primarily through twice daily nurse telephone calls[251]. They were able to manage 86% of women entirely through telehealth and suggest that telehealth models could have a role in improving access to both ante- and postnatal care, especially for women with barriers to attendance such as geography, transport, childcare and work.

An Irish study assessed women's willingness to pay for three hypothetical forms of post-caesarean SSI surveillance; a standard mobile telephone application (app), an integrated app, and a telephone helpline[252]. The standard app would provide information about Caesarean Section (CS) and SSI, allow women to enter symptoms and record vital signs and generate advice based on the results, e.g. to contact their general practitioner. The integrated app, in addition to the above, would involve a midwife reviewing the results and telephoning the woman if necessary. The helpline would allow the woman to call a midwife directly during a 2-hour period each day. Almost half of women preferred the integrated app, with the standard app the least popular option. However, based on women's willingness to pay, the standard app was the only cost-beneficial method, due to the higher costs of staffing the integrated app and helpline.

Postal questionnaires

The 3 studies using postal questionnaires alone had a wide range of response rates. An older study from the UK, published in 2007, sent a questionnaire at 12 months, followed by a single reminder, to assess perineal morbidity[230]. Responses were received from only 33% of women. A Swedish study had a 60% response rate from a questionnaire on postpartum infection sent at 8 weeks postnatal[232]. The best response rate was from a Norwegian study of postpartum pelvic pain that accessed women recruited to the MoBa study[253]. They

received an 85% and 73% response rate for a questionnaire sent at 6 and 18 months respectively[226]. All women giving birth at 50+ hospitals in Norway were eligible for the cohort study but by 2005 only 43% had consented. Therefore, the relatively high response rates are among a self-selecting group of interested women.

Home visits

Postpartum home visits were implemented by seven of the 28 surveillance studies; six in LMICs and one in the UK. Three of these studies introduced visits by existing community workers to improve newborn care practices or morbidity. Studies in Bangladesh[236] and Ghana[241] evaluated the outcome using cluster RCTs. Three visits were planned in the first 7-8 days and at least one visit occurred in 73% and 63% of cases respectively. The third study in Malawi used a before-after evaluation. only 11% of participants received a visit in the first 72 hours[239]. Many of the community workers lived outside their catchment areas and they all had other responsibilities, both in the community and at the local health centre, which the authors suggest led to the low level of early visits. The other four studies used home visits to assess various maternal outcomes. In a UK cohort study, community midwives measured post-caesarean SSI during routine home visits, returning records on 88% of participating women[233]. In a multi-site study in South Asia and SSA, fieldworkers assessed maternal morbidity during pregnancy and at one week and 7-11 weeks postpartum[248]. Among the 125,716 pregnant women enrolled at an antepartum visit, 91% were visited postpartum. Among In a cohort study in Kenya, trained interviewers visited women twice during pregnancy and once in the first 6 weeks postnatal to assess intentions and utilisation of maternal health services[240]. Among all enrolled women, 89% were visited postnatally. However, among women remaining in the study in the third trimester of pregnancy, 97% were visited after delivery. In another large cRCT in Bangladesh, women were enrolled in pregnancy and assessed for depressive symptoms at 6 months postnatal during a home visit by trained interviewers[237]. 96% of consenting women contributed depression data. Among women without data, two thirds were not met.

Hospital visits

Two HIC studies collected data on post-caesarean SSI when women returned for routine clinic visits. In Kosovo, 77% of women attended for a 30-day visit with loss occurring due to women attending more local clinics, being out of the country or withdrawing[231]. In Canada, 81% of women returned for a 6-week visit[224]. A multi-country cohort study in Latin America and SSA invited women to visit the study site at 90-days to collect neonatal data[247]. On average, 69% of women attended. Attendance was higher if women could walk to the site or

had lower transportation costs. The authors concluded that involving local health facilities would increase follow-up in future studies.

A before-after study in Burkina Faso sought to improve attendance and quality of maternal postnatal care by integrating it into child vaccination clinics[245]. Day 6-10 visits increased from 21% to 49% with a similar increase in women being examined (17% to 40%). Only 26% received advice on topics such as family planning and breast feeding, although this was a marked improvement from before the intervention (8%).

Records and reports

A multi-country cohort, involving sites in Latin America, SSA and South Asia, collected data from hospital records, birth attendants and village elders to determine pregnancy outcomes and postnatal mortality for 98% of participants[246]. A large cohort in the Netherlands also used health record data, conducting a retrospective examination of admission and Outpatient department records from all facilities, or using a health registration card, to detect SSI[219]. This 'mandatory' surveillance was used for 75% of surgical cases and detected 2.6 times more cases of SSI than less intensive methods that relied predominantly on (re)admission to the original surgical facility.

4.3.4 Qualitative research on postpartum care provision

Two qualitative studies, in the US[254] and Australia[255], explored women's challenges and concerns regarding postnatal care. The US study used free-text comment data from PRAMS, while the Australian study conducted in-depth interviews with 15 women. Women in both studies expressed a need for psychosocial support, including peer support from mothers' groups as well as input from health professionals. They also revealed a desire for more information or education, especially about caring for their baby, including reassurance for small, everyday concerns.

4.4 Summary and Discussion

Follow-up of women after birth is performed as part of routine care; to monitor the health of mother and baby, and provide education and advice. The two qualitative studies identify a strong desire from women for sources of information and support during the postnatal period; although both were conducted in HICs and may not be generalisable to low-income settings. Follow-up is also performed for surveillance purposes; either routinely by a hospital, network or country, or for research purposes. The literature reveals a wide variety of methods for conducting this surveillance, with differing levels of success ranging from 11% to 96%.

Postal questionnaires were used only in HIC studies, delivering a very mixed response of 33% to 85%. Home visits, conducted primarily in LICs, also had diverse results. As part of a trial, visits from interviewers could reach as many as 96% of women participants. However, when added to the workload of existing community health workers, a smaller proportion of women were visited, dropping as low as 11% in one study. When the cost of transport and the opportunity costs of staff time are also considered, home visits may be of limited value in routine surveillance. However, an economic analysis of the Malawi programme suggested a scaled-up intervention would be cost-effective if it resulted in a 1% reduction in neonatal mortality rate[256].

Visits by women to health facilities offer a potentially simple, low-cost method for postnatal surveillance or care. However, the one study carried out in multiple LMICs achieved only 69% follow-up, and an attempt to improve postnatal visits in Burkina Faso resulted in less than half of women attending, even with the intervention. In addition, this method is likely to differentially exclude poorer women, and those living in more remote locations. Use of existing health records also appears a low-cost option for surveillance, of particular value for severe morbidity when women are more likely to return to a health facility. However, both low- and high-income studies demonstrate the need to involve data from the whole range of healthcare providers, including community health workers, lower-level facilities and outpatient clinics. For routine surveillance, a system will need to be established to link health records and reports from these different sources.

Telephone calls performed well across both LMICs and HICs, reaching 63% to 91% of participants. Most studies reported calling on multiple occasions and some requested more than one telephone number. When combined with other modalities such as hospital visits or postal questionnaires, telephone calls proved an important addition, capturing a substantial percentage of infection that would otherwise have been missed. They were particularly useful for reaching sectors of the population that were considered harder-to-reach. In addition to traditional telephone calls, text messaging, video calls and mobile apps show potential in HICs.

Table 4.1: Studies with quantitative data on postnatal surveillance

Study	Location	Design	Number of women	Study outcome	Method	Details	Response	Other comments
Halwani 2016[225]	US	Prospective cohort	193	CS[a] SSI[b]	Telephone	Phoned day 7, 14, 30. 3 calls each day.	82.4% at least once. 65% all 3 days.	26% diagnosed solely by telephone.
Lima 2016[234]	Brazil	Prospective cohort	528	CS[a] SSI[b]	Telephone	Phoned within 15 days and at 15-30 days. 5 calls each time.	67% once. 45% before day 15.	170 lost to follow-up, 5 died. 71% diagnosed within 15 days. Mean day 12, median day 10
Nguhuni 2017[243]	Tanzania	Prospective cohort	374 (316 with telephone access)	CS[a] SSI[b]	Telephone	Phoned day 5, 12, 28. 2 calls each day.	87% at least once	100% diagnosed post-discharge. Median day 8. Calls 3-5 mins. Cost $0.5
Elbur 2013[242]	Sudan	Prospective cohort	1769	SSI[b] (CS[a] 39%)	Telephone	Phoned day 7, 14, 21, 28	78.4% (78% women vs 85% men)	20.8% lost, 0.8% died. 88% diagnosed post-discharge. 43% diagnosed by telephone
Troillet 2017[229]	Switzerland	Prospective cohort (national survey)	187,501	SSI[b]	Telephone	Phoned up to 5 times at 1 month	91% for CS	86.5% diagnosed post-discharge. SSI incidence 1.6%
Mosquera 2019[235]	Brazil	Prospective Cohort	1523	Exclusive breastfeeding	Telephone	Followed to day 30-45. No other details.	63% (3% invalid phone number)	
Gass 2018[238]	India	Prospective cohort (call centre)	157,689	Near-miss maternal morbidity	Telephone and field worker visit	Phoned 3 times from day 8-21. If no response, then fieldwork visit.	86% reached by phone	
Hirshberg 2018[223]	US	RCT	206	BP monitoring in severe hypertensive disease	Text message (vs clinic visit)	Asked to text 2 BP readings each day for 10 days	92.2% at least 1 reading (vs 43.7% attended the clinic)	
Lower 2013[228]	Norway	Prospective cohort (Norwegian	21,772	SSI[b]	Postal questionnaire or telephone	Letter after 25 days, reminder letter, then phone call	91% (88% for CS).	81% diagnosed post-discharge (83% for CS). Median day 13.2

		surveillance - NOIS)						95% of all hospitals participated
Ahluwalia 2012[222]	US	Prospective cohort (Pregnancy Risk Assessment Monitoring System – PRAMS)		Breastfeeding	Postal questionnaire or telephone	Letter sent 3 times, plus one reminder. Non-responders phoned up to 15 times	Breastfeeding study selected sites with >70% response	Median state-level response of 61%. 20% of questionnaires conducted by phone.
Nthumba 2010[244]	Kenya	cRCT	3317	SSI[b] (CS[a] 18%)	Clinic visit or telephone	Followed to 30 days. No further details	94%	72.9% diagnosed post-discharge. Median day 15
Ferraro 2016[227]	Italy	Prospective cohort	3685	CS[a] SSI[b]	Routine clinic visit or telephone	Followed to 30 days. No further details	94%	89.0% diagnosed post-discharge. Median day 9.5
Williams 2007[230]	UK	Retrospective cross-sectional survey	2,100	Perineal morbidity	Postal questionnaire	Letter at 12 months. Reminder after 3 weeks	23%	
Axelsson 2013[232]	Sweden	Prospective cohort	11,124	Postpartum infection	Postal questionnaire	One letter at 8 weeks	60%	
Bjelland 2016[226]	Norway	Cross-sectional survey	20,248	Postpartum pelvic pain	Postal questionnaire	Letter at 6 and 18 months	84.8% (6 months), 72.5% (18 months)	
Darmstadt 2009[236]	Bangladesh	cRCT	10,006 newborns	Neonatal illness	Home visits by Community Health Workers	Visits day 2, 5 and 8	73% at least once	Median 4 assessments per neonate. 4% referred.
Kirkwood 2013[241]	Ghana	cRCT	6029	Newborn care practices	Home visits by community-based surveillance volunteers	Visits day 1, 3, 7	63% at least once	
Callaghan-Koru 2013[239]	Malawi	Before-after evaluation	903 (before) 900 (after)	Newborn knowledge and care practices	Home visits by lay worker	Visits day 1, 3 and 8	10.9% visited within 72 hours	

Ward 2008[233]	UK	Prospective cohort	6,297	CS[a] SSI[b]	Home visits by midwives	Routine community midwife visits. Mean follow-up 15 days.	88% returned midwife records	84% post-discharge.
Aftab 2021[248]	Bangladesh, India, Pakistan, DRC, Ghana, Kenya, Zambia, Tanzania	Prospective cohort	125,716	Direct maternal morbidity and mortality, stillbirth, and neonatal death	Home visits by fieldworkers	Visits week 1 and 7-11. Also 3 visits during pregnancy.	91% visited at least once postpartum	
Creanga 2016[240]	Kenya	Prospective cohort (Demographic Surveillance Site)	1185	Intentions re maternal health service utilization	Home visits by trained interviewers	Visit up to 6 weeks postpartum. Also 2 visits during pregnancy.	97% visited from 3rd trimester to 6 weeks postpartum	94% intended PNC, 52% achieved it. More likely to achieve it if polygamous relationship, husband (vs woman) making health decisions, delivery complications. Less likely if stillbirth or poor experience of birth.
Surkan 2017[237]	Bangladesh	cRCT	59,666	Postpartum depression	Home visits by trained interviewers	Visits at 3 and 6 months.	96% with depression data at 6 months	
Zejnullahu 2019[231]	Kosovo	Prospective cohort	325	CS[a] SSI[b]	Routine clinic visit	Visit at 30 days	77% of eligible patients	Loss due to attending local clinic, being out of the country or withdrawal. Median diagnosis [223]day 7
Ng 2015[224]	Canada	Prospective Cohort	8442	CS[a] SSI[b]	Routine clinic visit	Visit at 6 weeks. Also used records from delivery, readmission, and emergency department visits	81% visited the clinic. 85% with data.	96% detected by clinic visit. 3% emergency department. 2% readmission
Madhi 2018[247]	Panama, Dominican Republic, South	Prospective Cohort	3243	Neonatal follow-up	Visit to study site	Visit at day 90	69%	Attendance more likely if women walked or had lower transportation costs.

	Africa, Mozambique							
Yugbare 2018[245]	Burkina Faso	Before after survey	757 (before) 754 (after)	Maternal postpartum care	Clinic visit for child vaccination	Maternal care integrated into child vaccination clinics	Day 6-10 maternal visit increased from 21% to 49%. Physical exam increased from 17% to 40%. Health promotion advice increased from 8% to 26%. Day 45-90 visit increased from 3% to 17%.	
Goudar 2012[246]	Argentina, Guatemala, India, Kenya, Pakistan, Zambia	Prospective cohort	72,848	Pregnancy outcome and postnatal mortality	Health reports	Birth attendant reports, hospital records, telephone reports from village elders, to day 42	98%	
Koek 2015[219]	Netherlands	Prospective cohort (PREZIES Dutch surveillance network)	105,607	SSI[b]	Registration card or medical records (Mandatory surveillance group)	Includes records of admission, readmission, outpatients at any facility, to day 30 (for CS).	75% CS had mandatory surveillance.	Mandatory vs 'other' methods detected 1.55% SSI vs 0.60%. (Other methods primarily included admission and readmission records at delivery hospital only). Surveillance to 21 days reduced SSI detection by 11%

[a]CS – Caesarean Section. [b]SSI – Surgical Site Infection

Chapter 5: Postnatal Telephone Surveillance Methods

5.1 Introduction

The systematic review of peripartum infection incidence presented in chapter 2 revealed only occasional use of standard infection definitions, a sparsity of data from LMICs and a frequent lack of follow-up beyond the first few days after childbirth. Literature on postnatal surveillance, presented in chapter 4, showed good response rates from telephone surveillance in both LMICs and HICs, suggesting this method has potential to assist research in this field. Exploring this method further, and identifying factors that enhance telephone surveillance coverage, can improve the quality of future research.

In response, I chose to conduct a postnatal telephone surveillance study to explore the feasibility of this method of surveillance, and to estimate incidence of postnatal infection. I adapted standard definitions of the infections of interest, as described below. I also explored potential risk factors for infection and possible early consequences. As described in the introduction to this thesis, neonatal infection is intimately related to infection in the mother, therefore I also collected data on the health of the newborn.

For the systematic review I studied maternal peripartum infections, namely chorioamnionitis, postpartum endometritis, childbirth-related wound infection (caesarean and perineal) and sepsis (where specified, as a result of one of the above). The telephone surveillance study diverted a little from the above group of infections. Endometritis and wound infections were both included. However, it focussed primarily on women's experience after childbirth and did not ask about features of chorioamnionitis, although data was extracted from hospital records on infection in labour. In addition, I included UTI, which had been excluded from the review. While conducting the review I discovered many studies of peripartum infection and the ICD codes for puerperal infection included UTI. Risk of UTI is increased by urinary catheterisation during childbirth, and it is therefore appropriate to measure it alongside other childbirth-related infections. Diagnosis of sepsis is based on clinical signs and I did not attempt to diagnose it on self-reported symptoms. Instead, I hoped that by measuring the above infections I would also capture cases of severe disease and sepsis arising from them.

5.2 The CLEAN Study

The postnatal telephone surveillance study was conducted as a sub-study of the CLEAN study. The CLEAN study was a pilot evaluation of a training in environmental hygiene for maternity units that ran from April 2018 to July 2019 in three high-volume public hospitals in Dar es Salaam, Tanzania. The project was a collaboration between the London School of Hygiene and Tropical Medicine (LSHTM), the Ifakara Health Institute (IHI), Tanzania, and the Soapbox Collaborative. Muhimbili University of Health and Allied Sciences was contracted directly by IHI as a training institution.

Ten days of formative observation was conducted from August to September 2018. This was followed by the preparatory intervention stage; engagement with hospital managers, selection of *cleaning champions* by each hospital, and adaptation of the TEACH CLEAN training package. Training of *champions* and subsequent training of cleaners at each hospital took place from 7th to 28th January 2019. Data was collected on environmental cleaning and microbiological cleanliness of surfaces in the maternity wards from 28th October 2018 until 24th May 2019.

The two CLEAN study hospitals with highest delivery volume were selected for telephone surveillance. Amana and Temeke public hospitals are the regional referral hospitals for Ilala and Temeke municipalities respectively, both serving an urban population. There are a total of 28 regional referral hospitals in Tanzania of which three serve Dar es Salaam. In the 2012 census Ilala had a population of over 1.2 million and Temeke of nearly 1.4 million. Both hospital maternity units record approximately 1,000 births each month.

5.3 Postnatal Telephone Surveillance Study

5.3.1 Eligibility and recruitment

Telephone surveillance took place from March to June 2019, during the final weeks of the CLEAN study, and after the training of cleaners had been completed. Women were recruited from 19th March to 2nd May 2019, and telephone interviews were conducted between 26th March and 14th June.

At each hospital, two trained research nurses recruited women from Monday to Thursday each week for eight weeks, excluding public holidays. For pragmatic reasons, the nurses were not asked to work over the weekend, and Fridays were used to pass recruitment details to the nurses conducting telephone interviews (as detailed below). However, women recruited on Mondays would have given birth on Sunday day or night, ensuring weekend deliveries

were included in the sample population. Women were randomly selected each day, with the aim of achieving a representative sample.

The planned recruitment number increased gradually from 12 to 20 women per hospital per day during the study period, with the expectation that the nurses would become more efficient at recruitment, data collection and telephone interviews as the study progressed. I designed a sampling form in Open Data Kit (ODK) and installed it on tablet devices which were provided to each nurse. Every morning, they created a sampling frame of all women who gave birth from 7am the previous day until 7am that morning. Using the delivery register on labour ward, they manually counted the total number of deliveries and the number of caesarean sections during the 24-hour period and entered this data, together with the planned recruitment number for the day. The ODK form calculated the number of women with a vaginal delivery and with a caesarean section that they should aim to recruit that day, ensuring the same proportion of caesarean deliveries in the sample as in the hospital population.

The nurses used the Random Number Generator Plus tablet application (manufactured by RandomAppsInc and offered by Google Commerce Ltd since 2nd January 2016) to randomly select the specified number of women for each delivery mode from the delivery register. After completing this, they generated a new set of random numbers to select up to eight additional women to recruit in place of any who were unavailable or ineligible. Eligible women were aged 18 years or older, had access to at least one mobile phone and gave birth in the hospital. Women who required admission to the ICU were not eligible for recruitment because the hospitals considered them too unwell to consent and did not want the research nurses entering these units.

Eligible women were located on the postnatal wards on the same morning they were sampled. They were individually counselled about the project, provided with written information and asked for signed consent to participate. If a woman could not read or write, a family member or another woman on the ward was asked to witness her thumbprint consent. Women were asked to provide up to three telephone numbers for follow-up; one or two numbers of their own and at least one number of a close relative or neighbour.

5.3.2 Telephone schedule and protocol

Every Friday the research nurses working at the hospitals attended the IHI offices in Dar es Salaam to pass on the details of all the women recruited that week. They created a simple

index card for each woman with her name, telephone number, delivery mode and scheduled interview dates. The cards were filed by date, under the planned day-7 interview date.

Two further research nurses, stationed at IHI offices, interviewed each woman by telephone in Kiswahili at 7 and 28 days after recruitment. To increase the response rate, women were called multiple times over the course of a week, on all the telephone numbers provided. The nurses were instructed to make up to four telephone call attempts to reach each woman per scheduled interview; the first call on the morning of the scheduled interview, a second call later the same day, a third call the next day and a fourth call after seven days. At each attempt, the nurses were expected to call each of the woman's telephone numbers. If they reached a relative/friend, they asked for a suitable time and telephone number to call back to speak to the woman. If the woman answered but was occupied, they arranged a suitable time to call back. The outcome of every attempted call was documented on the back of the woman's index card and the card was moved to the next call-date in the filing system. After conducting the day-7 interview, or making four failed call attempts, the card was moved to the day-28 interview date. After both interviews, the cards were retained until all data collection and cleaning was complete.

5.3.3 Data collection

I designed ODK forms to collect individual women's data from their hospital records and at telephone interview. The text on the forms was translated into Kiswahili and the research nurses had the option to view the form in Kiswahili or English. They entered the data anonymously on tablets, using unique identification numbers allocated to each woman at recruitment. The hospital-based research nurses extracted data from each woman's paper case-notes as soon as possible after she was discharged from hospital. Maternal factors included maternal age, gestational age, parity, HIV status, pregnancy complications (diabetes, hypertensive disorders, ante-partum haemorrhage), complications during labour and delivery (premature rupture of membranes (PROM), induction or augmentation of labour, operative delivery, post-partum haemorrhage (PPH)), infection during labour or postpartum and the name and reason for any antibiotic prescription. Newborn factors included number of foetuses, occurrence of stillbirth, Apgar score at five minutes, use of resuscitation, development of sepsis, admission to a neonatal unit, details of any antibiotic prescription and vital status at discharge.

Each telephone call attempt was entered into ODK with six possible outcomes of the call: 1) interview completed, 2) no answer, 3) incorrect number, 4) relative/friend answered, 5)

woman left the study, 6) inconvenient time to speak. When an interview occurred, the nurses documented whether they had used the first, second, or third telephone number provided by the woman. ODK was programmed to save the date and time a new entry was started and completed.

Interviews consisted primarily of closed questions regarding the history and ongoing presence of specific symptoms of infection in both mother and newborn, the day symptoms started, care-seeking behaviour, medication received, and readmission to hospital. Short, open questions were asked about any problem for mother or newborn since birth, and the diagnosis given if they sought care for that problem. Maternal depression and functionality were assessed at day 28 only. Depression was assessed using a 5-item modified Edinburgh Postnatal Depression Scale (EPDS), validated in South Africa where it gave the best overall performance compared to longer and shorter versions of the EPDS[257]. Functionality was assessed according to the ease of conducting five common postpartum activities: breastfeeding, washing oneself, housework, carrying the baby and caring for the baby. I chose not to use a formal functioning assessment tool such as the WHO Disability Assessment Schedule because a pilot study of its use in pregnancy and postpartum women suggested it was not optimal for this population and a tool that asked more specifically about infant care would be more relevant[258]. In addition, it was important to make the interview too long and detract from the focus on infection.

Women with infection symptoms were advised to attend a health-facility if they hadn't already done so. In cases of maternal depression or neonatal death, women were offered referral to social welfare liaison for counselling and support.

5.3.4 Defining infection

I aimed to collect data on the following maternal postnatal infections: caesarean SSI, perineal wound infection, endometritis, and UTI. I also collected data on newborn infections: possible severe bacterial infection (pSBI) and umbilical cord infection. I combined the self-reported symptoms of infection collected during telephone interview to establish the diagnosis. In addition, research nurses extracted infection diagnoses recorded in the maternal hospital case-notes at the time of childbirth, including any infection occurring during labour.

To determine the symptom combinations, I started with international definitions of each specific infection. However, these are a guide for clinicians and researchers, usually in high-income hospital settings and combine symptoms, signs, investigations and physician's diagnosis and treatment. pSBI is intended for primary care health facilities in LMICs and is

therefore based purely on signs, although these are still expected to be assessed by someone trained. Therefore, I adapted the definitions to exclude the results of investigations or the diagnosis and management of clinicians, and instead to rely entirely on symptoms and signs that could be self-reported by women. Table 5.1 presents the original definition, the adapted definition used in this study, and the explanation for the adaptation.

5.3.5. Research nurse training

Together with my co-investigator at IHI, I developed training materials and trained the six research nurses for six days in all aspects of sampling, recruitment and data collection, including the use of ODK. We used role-play to practice the consent procedure and telephone interviews, and I created dummy maternal case-notes to practice data extraction into the ODK forms. Under our supervision, the nurses spent one day at each of the two study hospitals where they met with ward staff, agreed the best time and location to counsel and consent women, and developed a system to mark the case-notes of recruited women to allow easier identification after discharge. In addition, they piloted the recruitment and data-extraction tools on 24 women. The two nurses allocated to telephone interviews spent an additional two days of training conducting pilot interviews with the same 24 women. I amended the ODK data-collection forms in response to some small issues identified during the pilot.

5.3.6 Study size

I aimed to recruit 900 women so that with an estimated loss of 10% I would have 95% confidence to estimate a maternal infection risk of 30 per 1000 (+/- 12 per 1000).

Table 5.1: Adaptation of infection definitions used in telephone surveillance

Infection	Standard definition (source)	Adapted definition	Explanation
Caesarean Section Surgical Site Infection (SSI)	**SSI-Surgical site infection (CDC[a92])** Superficial incisional SSI must meet the following criteria: Involves only skin and subcutaneous tissue of the incision AND Patient has at least one of the following: 1. Purulent drainage from the superficial incision OR 2. Organisms identified (further detail not reported here) OR 3. Incision is deliberately opened by a surgeon/attending physician/other designee and microbiologic testing not performed AND patient has least one of pain or tenderness, localised swelling, erythema, heat. OR 4. Diagnosis by the surgeon/attending physician/other designee Deep incisional SSI must meet the following criteria: Involves deep soft tissues of the incision AND Patient has at least one of the following; 1. Purulent drainage from the deep incision OR 2. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated AND organisms identified AND patient has at least one of fever (>38C), localized pain or tenderness OR 3. An abscess or other evidence of infection involving the deep incision detected on gross anatomical or histopathological exam or imaging. Organ/Space SSI must meet the following criteria: Infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure AND Patient has at least one of the following; 1. Pus drainage from a drain that is placed into the organ/space OR 2. Organisms are identified from fluid or tissues in the organ/space OR 3. An abscess or other evidence of infection involving the organ/space AND Meets criterion for a specific organ/space infection – This Includes Endometritis	At the site of the caesarean wound either: Pus discharge OR Wound breakdown AND one of more of pain, swelling, or redness OR Two of more of fever, abdominal pain, foul-smelling or pus vaginal discharge	**Superficial and deep SSI** We did not ask women to differentiate between skin/subcutaneous and deep tissues. Excluded laboratory or image tests (organisms, image of abscess), clinical diagnosis and management (incision deliberately re-opened, placement of drain) Only remaining criteria is pus from the incision. Therefore, included wound dehiscence combined with localised signs of infection (in the absence of microbiologic testing or deliberate wound opening) **Organ/space SSI** Criteria 1-3 rely on further investigations or clinical management. Therefore, as endometritis meets criteria for specific organ infection, all women meeting the definition of endometritis following caesarean section were included as SSI

Urinary Tract Infection (UTI)	**Diagnosis of Bacterial UTI in Adult Women (SIGN[b259])** The prior probability of bacteriuria in otherwise healthy women who present with symptoms of acute UTI is estimated at between 50-80%. If dysuria and frequency are both present, then the probability of UTI is increased to >90% and empirical treatment with antibiotic is indicated. Initiation of antibiotic treatment should be guided by the number of symptoms of UTI that are present. • Consider empirical treatment with an antibiotic for otherwise healthy women aged less than 65 years presenting with severe or ≥3 symptoms of UTI. • Use dipstick tests to guide treatment decisions in otherwise healthy women under 65 years of age presenting with mild or ≤2 symptoms of UTI. Signs of UTI: dysuria, frequency, urgency, polyuria, fever, suprapubic tenderness, flank or back pain	Women with either Pain passing urine AND urinary frequency, OR Three of the following: Pain passing urine, urinary frequency, urinary urgency, fever, abdominal pain.	Urine dipstick tests not included Included the criteria of 3 signs. Only lower UTI signs were included. Abdominal pain was considered more understandable for women than suprapubic tenderness. Polyuria was omitted as there was possible confusion with urinary frequency. Also diagnosed UTI based on dysuria and frequency due to high probability of infection
Perineal wound infection	**EPIS-Episiotomy infection (CDC[a92])** Episiotomy infections must meet at least ***one*** of the following criteria: 1. Postvaginal delivery patient has purulent drainage from the episiotomy 2. Postvaginal delivery patient has an episiotomy abscess	At the site of a perineal wound, at least one of the following criteria: Pus discharge OR Wound breakdown AND either Pain or Swelling	No specific definition for perineal wound infection, therefore used episiotomy infection. Criteria 2 excluded – women not expected to self-identify an abscess in the perineal region Wound dehiscence and localised signs of infection (similar to SSI) also included as women may not observe pus, and these are considered signs of infection in other studies

Endometritis	**EMET-Endometritis (CDC[a92])** Endometritis must meet at least one of the following criteria: 1. Patient has organism(s) identified from endometrial fluid or tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing. 2. Patient has at least two of the following signs or symptoms: fever (>38.0°C), pain or tenderness (uterine or abdominal)*, or purulent drainage from uterus. * With no other recognized cause Report as an organ space SSI if a C-section was performed on a patient with chorioamnionitis, and the patient later develops endometritis.	Two of more of the following: Fever, abdominal pain, or foul-smelling or pus vaginal discharge, Where abdominal pain is not explained by UTI and vaginal discharge is not explained by perineal wound infection In women with caesarean section, endometritis was counted as an organ space SSI	Criteria 1 excluded – relies on laboratory test Criteria 2: Measurement of temperature not required. Tenderness removed as difficult to self-assess 'Abdominal' pain considered appropriate term to include pelvic/uterine pain 'Purulent' defined for a lay audience as 'foul-smelling or pus' Considered possible for women to confuse vaginal discharge and pus from perineal wound, therefore, if the woman meets the above criteria for perineal wound infection the vaginal discharge was discounted. UTI counted as 'other recognised cause' of abdominal pain.
Mastitis	**BRST-Breast infection or mastitis (CDC[a92])** A breast abscess or mastitis must meet at least ***one*** of the following criteria: 1. Patient has organism(s) identified from affected breast tissue or fluid obtained by invasive procedure by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment for example, not Active Surveillance Culture/Testing. 2. Patient has a breast abscess or other evidence of infection on gross anatomic or histopathologic exam. 3. Patient has fever (>38.0°C) and local inflammation of the breast, ***AND*** Physician initiates antimicrobial therapy within 2 days of onset or worsening of symptoms	At least one of the following: Swollen, hard area of the breast OR Both painful, red breast AND fever	Criteria 1 excluded – relies on laboratory test Criteria 2 – breast abscess defined for patient as 'swollen, hard area' Criteria 3 – Measurement of temperature not required. Local inflammation defined for patient as 'painful and red' Requirement for antimicrobial therapy excluded

pSBI	**Clinical predictors of severe illness requiring hospital admission (YICSS[c80])** One or more of: Temperature ≥37.5 Temperature <35.5 Respiratory rate ≥60 Severe chest indrawing History of convulsions History of difficulty feeding Movement only when stimulated	At least one of the following: Fever, very cold (low temperature), very fast breathing, chest indrawing (sucking in the ribs when breathing), convulsions/fits, poor feeding/not feeding, OR only moving when stimulated	All the signs were used but measurement of temperature was not required and respiratory rate was not counted.
Umbilical cord infection	**UMB-Omphalitis (CDC[a92])** Omphalitis in a newborn (≤30 days old) must meet at least ***one*** of the following criteria: 1. Patient has erythema OR drainage from umbilicus **And at least *one* of the following:** Organism(s) identified from drainage or needle aspirate by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing OR Organism(s) identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing. 2. Patient has erythema AND purulence at the umbilicus	Redness around the umbilical cord stump OR Pus discharge from umbilical cord stump	Criteria 1 applied without the need for microbiological testing

[a]CDC – Centres for Disease Control and Prevention. [b]SIGN – Scottish Intercollegiate Guidelines Network. [c]YICSS – Young Infant Clinical Signs Study

5.3.7 Data management – how quantitative variables were handled and grouped

Data was cleaned and analysed using STATA 15.1. In the hospital dataset, 23 identification (ID) numbers were entered twice, with different data for each observation, indicating that one set of data had been entered using the wrong ID number. The research nurses attempted to confirm the correct data for each of these ID from the original hospital records and the other entry using the same ID was dropped from the dataset. When this was not possible, the two entries were compared, matching values were retained, and other data was dropped. In the telephone data, two interviews were entered using the same ID number in the case of one day-7 and three day-28 interviews. I attempted to confirm the correct entry by comparing with the other sources of study data available for the ID. When this wasn't possible, I followed the same procedure as for hospital data and kept any values that were the same in both entries but dropped values that were discordant.

Hospital record data was explored for unexpected and missing values. Age was grouped as 18-19, 20-24, 25-29 and 30+. Gravidity and parity were compared for inconsistencies, corrected where possible or data dropped when the true value could not be determined. Gestational age was grouped as pre-term (<37 weeks), or term (37-42 weeks). Pregnancy induced hypertension, pre-eclampsia and eclampsia were combined to create a binary variable for all hypertensive disorders. Where necessary, records were corrected for women delivering by caesarean section to indicate the presence of intravenous catheterisation.

Data on twin and triplet pregnancies were inconsistent between data sets. Out of 840 women with hospital case-note data, 22 were documented to have twin pregnancies and one was documented with triplets. Five of the second twins were reported stillborn. Of the remaining 18 women, 12 were interviewed but only six provided information about the second twin. This was partly due to an error in the ODK programming that was later corrected. Due to the large proportion of missing data, only data from the first baby was used in analyses.

No stillbirths were recorded by the nurses extracting data at Temeke. Excluding second twins for the reasons above, eleven stillbirths were reported at Amana of whom ten of the women have interview data. Two of these babies are documented as alive at interview and details about newborn health is provided. Of the remaining eight deaths, the woman gave a reason consistent with stillbirth in seven cases ('died in the womb' or 'premature'). In one case the mother reported meconium aspiration as cause of death which suggests the baby breathed

at birth and was not stillborn. In addition, women reported four additional babies who 'died in the womb'; three at Temeke and one at Amana. Due to these inconsistencies, the frequency of stillbirth was not reported, and stillbirth was not analysed as a risk factor of maternal infection.

The 5-item EPDS gave a score out of 15. In the full 10-item scale a score of ≥13/30 is considered the highest recommended cut-off for probable depression. I therefore generated a binary variable with the closest equivalent score of ≥6/15 indicating probable depression. I initially hoped to create a combined score from the maternal function questions, but exploration using a correlation matrix and Crohnbach's alpha did not show sufficient correlation. Instead, I analysed recoded the response to each question as a binary variable of any versus no difficulty in performing the function.

Statistical analyses are described in detail in the two chapters that follow.

5.3.8 Ethics

The study was approved by the Tanzanian National Institute for Medical Research on 27/2/19 (Ref: NIMR/HQ/R.8c/Vol.1/654), IHI Institutional Research Board on 3/12/18 (Ref: IHI/IRB/AMM/No: 13-2018) and LSHTM Research Ethics Committee on 5/2/19 (Ref: 16204). Written informed consent was obtained from women on the postnatal wards. Willingness to continue in the study was confirmed at the start of each telephone interview. There was no public or patient involvement in the study design or interpretation of results.

5.3.9 Funding

The CLEAN study, on which I was a co-investigator, was funded by the MRC. However, telephone surveillance was not part of the original proposal to the MRC, and I successfully sought additional funding from The Soapbox Collaborative. My proposal was reviewed by two independent reviewers, external to Soapbox and the CLEAN study. The grant of £12,000 paid for ethics approvals, staff costs, transport, training, supplies and equipment necessary to conduct the study. In addition, a research degree travel scholarship from LSHTM funded my own travel expenses for three weeks at the beginning of the study, and for a further week of results' dissemination in July 2019.

Chapter 6: Coverage of telephone surveillance for postnatal infections in Dar es Salaam

6.1 Introduction

The first paper of results from the fieldwork conducted in Dar es Salaam addresses question 4 of this PhD relating to the feasibility of postnatal telephone surveillance in this setting. Specifically, it explores the factors associated with coverage and efficiency in an attempt to inform future research using this method of data collection.

I developed the initial concept and design for the study which I refined after helpful input from Oona Campbell, Wendy Graham, and Alex Aiken. I developed the questionnaires, programmed them in ODK and trained the research nurses to carry out the data collection. After the first week of data collection I returned to the UK and handed over day-to-day supervision to the local principal investigator, Dr Mulokozi. I held weekly video calls with the research nurses to discuss any issues that arose. They submitted the ODK data each week and I conducted preliminary analyses for completeness and cleanliness which I fed back to the nurses. This led to improvements in compliance with study protocols.

I wrote the analysis strategy and cleaned and analysed the data. I received statistical support from Andrea Rehman to develop the regression models used.

6.2 Cover Sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	310061	**Title**	Dr
First Name(s)	Susannah		
Surname/Family Name	Woodd		
Thesis Title	Measurement, incidence and risk factors of Maternal Peripartum Infection		
Primary Supervisor	Professor Oona Campbell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Pilot and Feasibility Studies
Please list the paper's authors in the intended authorship order:	Susannah L Woodd, Andrea M. Rehman, Oona M R Campbell, Alexander M Aiken, Wendy J Graham, Joseph Hokororo, Asila Kagambo, Warda Martiasi, Giorgia Gon, Abdunoor M Kabanywanyi
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the initial concept and design for the study which I refined after receiving input from other authors. I developed the questionnaires, programmed them in ODK and trained the research nurses to carry out the data collection. I had weekly remote meetings with the nurses, checked data weekly and liaised with the local principal investigator. I wrote the analysis strategy and cleaned and analysed the data. I received statistical support to develop the regression models used. I wrote the first draft of the paper and made revisions based on co-author's feedback

SECTION E

Student Signature	[redacted]
Date	8/12/21

Supervisor Signature	[redacted]
Date	10/1/22

6.3 Manuscript 2. Coverage of telephone surveillance for postnatal infections in Dar es Salaam: a prospective cohort study

6.3.1 Abstract

Introduction

Postnatal infection surveillance is important to understand the burden of disease and improve infection prevention through feedback to healthcare staff. Community surveillance is necessary but difficult, especially in low- and middle-income countries. Mobile telephone interviews offer a possible solution. We explored factors associated with successful telephone contact in a cohort of postnatal women delivering in maternity units in Dar es Salaam, Tanzania.

Methods

We recruited women who gave birth at two tertiary hospitals between 15th March and 9th May 2019 and interviewed them by telephone at 7 and 28 days postnatal. Women provided at least two telephone numbers (one belonging to a friend/relative) and were called up to four times over seven days for each interview. We used generalised estimating equation regression models to explore factors associated with successful contact and interview length.

Results

We recruited 879 women, made 2,987 attempted telephone calls and conducted 1,492 interviews with 791 (90%) women. Research nurse compliance with the protocol (four call attempts made on the scheduled days) improved over the study period. Success at contacting women was maintained between day-7 (84%) and day-28 (86%) interviews and was not associated with women's age, delivery mode or hospital. Women not reached at day-7 often subsequently reported that their telephone was not charged. 29% of interviewed women were not reached at the first attempted call and 11% of women were interviewed on the second or third telephone number provided. Interviews lasted on average six minutes and became shorter during the study period.

Conclusion

Postnatal women were successfully contacted by telephone, regardless of age or delivery mode, and program managers should consider telephone methods for infection surveillance and postnatal community follow-up. Multiple calls to more than one telephone number increased success. Alerting women to the expected call-day, or providing credit to return a missed call may further increase the chance of successful contact.

6.3.2 Introduction

Pregnancy-related sepsis is estimated to cause 11% of maternal mortality[7] and prevention is a high priority in the WHO's vision of good quality care for pregnant women[1]. Detecting all cases of infection is important for both individual patient management, and to increase understanding of the extent of the problem, and hence assist in advocacy and policy-level priority setting. Infection surveillance, with feedback to health professionals, is also an effective way to improve infection control practices and reduce morbidity[260, 261]. The majority of severe maternal infections occur postpartum, often after women have been discharged home following childbirth[42], therefore community surveillance is necessary to detect all cases of infection. Indeed, European surveys typically demonstrate that countries with more intense surveillance identify a higher incidence of post-caesarean infection, a paradoxical situation meaning that more limited surveillance systems are liable to under-estimate infection incidence rates[220].

Despite the clear need for good infection surveillance, there are practical challenges to conducting it, and limited evidence about the most effective methods to use. Comparisons of methods in high-income countries produce inconsistent results[262]. In LMIC settings, where the vast majority of maternal deaths occur, the range of feasible surveillance methods is limited. Low literacy and poor postal networks make self-completed questionnaires impractical. Home visits are resource-intensive and there are limited computerised, comprehensive, linked healthcare databases. Consequently, many studies only report infection occurrence up to the time of hospital discharge following facility childbirth[85].

Thanks to extensive mobile phone network coverage, mobile telephone-based surveillance is a possible solution for many LMICs. In India, a postpartum call centre managed to survey 86% of 157,689 enrolled women by telephone, and demonstrated excellent consistency in responses when women were called twice[238]. Telephone surveillance has also been successfully used to increase detection of post-caesarean surgical site infection (SSI) in both high- and low-income settings, either alone or in addition to a postal questionnaire[225, 242, 263]. There are few validity studies but two in sub-Saharan Africa found among 202 post-caesarean women in Tanzania and 89 post-operative patients in Kenya, phone surveillance had 72% and 70% sensitivity respectively, and 100% specificity to detect an SSI compared to diagnosis by a clinician[243, 264].

In addition to infection surveillance, telephone calls are being used to provide aspects of routine maternal healthcare in the context of COVID-19. In a global survey of maternal healthcare workers, the first few days postpartum were cited as a time when women needed more support and telehealth was frequently used to deliver it[265]. In addition, advice and guidance on neonatal care delivered by telephone was believed to have avoided possible morbidity and mortality.

We have used mobile telephone surveillance in urban Tanzania to estimate 7-day postnatal infection incidence of 67 per 1000 mothers and 62 per 1000 newborns[266]. In this paper we interrogate the telephone call data further to explore the factors associated with successfully contacting women by telephone, and the characteristics of the interview calls. Our aim is to increase understanding about how to effectively conduct telephone-based surveillance in Tanzania, and potentially in other LMIC settings; this has relevance to the current falls in utilisation of services owing to the COVID-19 pandemic.

6.3.3 Methods

We conducted postnatal telephone surveillance from March to June 2019 as a sub-study of the CLEAN study, a pilot evaluation of training in environmental cleaning in the hospital setting[86]. The study was a collaboration between London School of Hygiene and Tropical Medicine (LSHTM) and Ifakara Health Institute (IHI) and was based at Amana and Temeke Public Regional Hospitals in Ilala and Temeke municipalities in Dar es Salaam city, Tanzania. Each facility recorded approximately 1,000 births per month.

Research nurses (two per hospital) recruited eligible women from postnatal wards every Monday to Thursday, excluding public holidays. Eligible women were aged 18 years or older, with access to at least one mobile telephone and providing signed or witnessed thumbprint consent. Women were asked to provide up to three mobile telephone numbers; one or two of their own and one for a relative or neighbour. The planned recruitment number increased gradually from 24 to 40 women per day during the study period, with the expectation that research nurses would become more familiar and efficient with the study tools over time. We planned to recruit 912 women over eight weeks and conduct 1824 interviews (Table 6.1) in order to have 95% confidence to estimate a maternal infection risk of 30 per 1000 $\pm$ 12 per 1000 with 80% power, allowing for 10% loss to follow-up at day-28.

Table 6.1: Planned schedule for recruitment of women and telephone calls, by study week

				Initial calls per week		
Study week	Recruits/day	Recruitment days/week	Recruits/week	Day 7	Day 28	Total
1	24	3	72	0	0	0
2	30	4	120	72	0	72
3	30	4	120	120	0	120
4	30	4	120	120	0	120
5	40	3	120	120	72	192
6	40	2	80	120	120	240
7	40	3	120	80	120	200
8	40	4	160	120	120	240
9	0		0	160	120	280
10	0		0	0	80	80
11	0		0	0	120	120
12	0		0	0	160	160
Total women eligible for contact			**912**			**1824**

Telephone schedule and protocol

A further two research nurses, stationed at IHI offices in Dar es Salaam, interviewed each woman by telephone in Kiswahili at 7 and 28 days after recruitment. Telephone interviews with women consisted of pre-coded closed questions on the history of specific symptoms of infection, day of symptom onset, care-seeking behaviour, and readmission to hospital. A card was created for each woman with her name, telephone number and scheduled interview dates, and filed under the planned day-7 interview.

Nurses were instructed to make four telephone call attempts to contact each woman per scheduled interview (day-7 or day-28); the second call a few hours after the first, the third the next day and the fourth after seven days. At each attempt, the nurses were expected to call each of the available woman's telephone numbers. If they reached a relative/friend, they were advised to ask for the best time and telephone number to call back in order to speak to the woman. The outcome of each call attempt was documented on the back of the woman's card and the card was moved to the next call-date in the filing system.

Data Collection

Data was entered on tablets with Open Data Kit (ODK), using unique identification (ID) numbers to maintain confidentiality. Data was extracted from maternal paper case-notes after hospital discharge, including woman's age and mode of delivery. Each telephone call attempt was entered into ODK with six possible outcomes of the call: 1) interview completed,

2) no answer, 3) incorrect number, 4) relative/friend answered, 5) woman left the study, 6) inconvenient time to speak. After an interview, the nurses documented whether they had used the first, second, or third telephone number provided by the woman. ODK was programmed to record the date and time a new entry was started and saved. The difference between these times was used to estimate the length of interview. Data was submitted weekly to SW in London who alerted the nurses to women missing the initial or final (after 7 days) attempted call for each scheduled interview.

Data management and statistical analysis

Data was cleaned and analysed using STATA 16. Duplicate ID numbers and data entry errors were corrected where possible using hospital case-notes or comparing with other study data. If uncertainty remained, data was regarded as missing. We describe the total calls made and the final outcome of the call attempts for each woman at day-7 and day-28. We explore how well the research nurses followed two areas of study protocol: the proportion of all calls made on the expected day (+/- one day) and the proportion of women not reached for interview who received four call attempts. The main study outcomes were 1) the proportion of women successfully contacted for each scheduled interview, 2) the proportion of interviewed women reached on the first call attempt and 3) the length of interview. Exposure factors were the scheduled interview day (day 7 or 28 post-recruitment), the nurse making the call, the study registration date, the time of day, the woman's age, the mode of delivery (caesarean section or vaginal birth) and whether the woman or baby were identified to have infection in hospital or at interview. We used generalised estimating equation (GEE) regression models with binomial distribution, logit link and unstructured covariance matrix to account for repeated calls (day 7 and 28) to each woman, to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between exposure factors and the chance of successfully contacting a woman (outcome 1). Variables showing association ($p<0.1$) were included in multivariable analysis. To assess the association with time of day, we included all call attempts and used logistic regression models with random effects to account for repeated attempts to each woman. Among women interviewed, we used a similar approach, with GEE regression models to assess associations with reaching them on the first call (outcome 2). We used GEE models with Poisson distribution, log link and unstructured covariance matrix to generate marginal mean interview lengths and explore differences in mean lengths between exposure groups (outcome 3). We tabulated the phone number used against exposure variables.

Ethics

The study was approved by the Tanzanian National Institute for Medical Research, IHI Institutional Research Board and LSHTM Research Ethics Committee. Written informed consent was obtained from women on the postnatal wards. Willingness to continue in the study was confirmed at the start of each telephone interview. There was no public or patient involvement in the study design or interpretation of results.

6.3.4 Results

Between 26th March and 14th June 2019, 2,896 attempted telephone calls were made to 879 recruited women (Fig. 6.1). Women were followed-up for a median of 29 days (range 7-43). Women were aged between 18 and 45 years with median age of 25 (Inter-quartile range (IQR) 22-30), and 164 (19%) delivered by caesarean section (Table 6.2). Nurse 1 made almost twice as many calls as Nurse 2. The majority of calls occurred in the second month of the study, and during the first half of the day. Overall, 85% of calls were made on the scheduled day (+/- 1 day). Compliance with the schedule improved over time, reaching 90% by the final study month.

Figure 6.1: Flow diagram

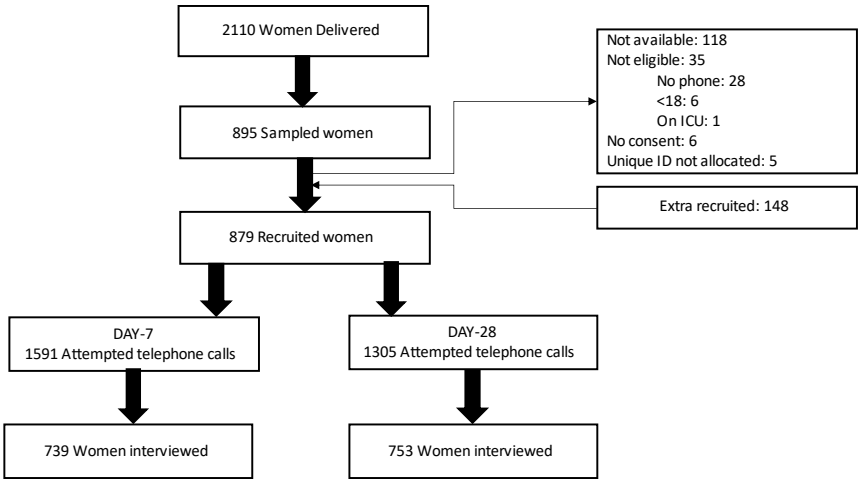

Table 6.2: Total call attempts and percentage call attempts on the expected day according to planned schedule

Factor		Total calls n (%)	Called on scheduled day (+/-1 day) n (%) (N=2862*)
Total		2896	2419 (84.5)
Interview Day	Day7	1591 (54.9)	1273 (81.3)
	Day28	1305 (45.1)	1147 (88.4)
Nurse	1	1836 (63.4)	1526 (84.3)
	2	1060 (36.6)	894 (85.0)
Date of call	26 Mar-21 Apr	814 (28.1)	644 (80.5)
	22 Apr-19 May	1546 (53.4)	1300 (84.9)
	20 May-14 Jun	536 (18.5)	476 (89.5)
Time of call	Before 9am	1019 (35.2)	
	9-11am	782 (27.0)	
	11am-1pm	561 (19.4)	
	1pm onwards	534 (18.4)	
Hospital	Amana	1461 (50.5)	1243 (85.6)
	Temeke	1435 (49.6)	1176 (83.4)

*Only includes the first 4 calls made to each woman

Overall, 791 (90%) women were interviewed at least once. A total of 1,492 interviews occurred: at day-7, 84% (739) of women were interviewed and at day-28, 86% (753) were interviewed (Table 6.3). The main reason why women were not interviewed is because they did not answer their telephones. Women interviewed at day-28 but not reached at day-7 commonly reported that their telephone batteries were not charged.

Table 6.3: Outcome of calls

Final outcome of call	Day 7 (N=879) n (%)	Day 28 (N=879) n (%)
Interviewed	739 (84.1)	753 (85.7)
No answer	88 (10.0)	77 (8.8)
Wrong number	24 (2.7)	12 (1.4)
Left study	2 (0.2)	0
Only reached relative	18 (2.1)	2 (0.2)
Not convenient	2 (0.2)	0
Not called	6 (0.7)	35* (4.0)

*Outcome at day 7 for 35 women not called at day 28: 19 wrong number, 2 left study, 1 not convenient, 3 no answer, 7 interviewed, 3 not called.

According to the study protocol, nurses were expected to make four attempted calls to reach each woman per scheduled interview, excluding those who left the study or had an incorrect telephone number. They complied with this aspect of the protocol in 52% (108) of the 207 expected instances. Compliance was similar between the two nurses, improved over time (test for trend $p<0.001$) and at the second (day-28) interview (Table 6.4).

Table 6.4: Proportion of women without an interview[a] who were called 4 times (as per protocol)

Factor		No scheduled interview	4+ calls n (%)	OR (95% CI) (using GEE[d])	p-value
	Total	207	108[c] (52.2)		
Interview Day	Day7	114	48 (42.1)	1	0.001
	Day28	93	60 (64.5)	2.5 (1.4-4.3)	
Nurse[b]	1	119	66 (55.5)	1	0.51
	2	68	42 (61.8)	1.2 (0.7-2.3	
Registration	18-31 Mar	61	19 (31.2)	1	<0.001
	1-14 Apr	56	26 (46.4)	1.9 (0.9-3.9)	
	15-28 Apr	38	25 (65.8)	4.1 (1.7-10.0)	
	29 Apr-10 May	52	38 (73.1)	5.9 (2.9-12.1)	

[a]Women who left the study and those identified to have provided an incorrect number were excluded.
[b]Excludes 20 women with no call as these cannot be attributed to a specific nurse
[c]99 (47.8%) women called <4 times: 20 (9.7%) not called, 10 (4.8%) 1 call, 23 (11.1%) 2 calls, 46 (22.2%) 3 calls
[d]GEE – generalised estimating equations

Women registered after the first two weeks in the study appeared slightly more likely to be reached for interview although evidence for an overall association with time was lacking (p=0.51). Success at contacting women was maintained at the second (day-28) interview. Both nurses were equally successful at reaching women, and none of the women's attributes (age, mode of delivery, hospital or date of registration) affected their chance of being interviewed (Table 6.5). The time of day of calls ranged from 05:19 to 21:37. 35% of calls were made before 09:00, 27% between 09:00 and 10:59, 19% between 11:00 and 12:59 and 18% from 13:00 onwards. In an analysis of all calls, after adjusting for interview day and date of registration, success at reaching women decreased progressively as calls occurred later in the day (test for trend p=0.005, full model not shown).

Table 6.5: Factors associated with successfully contacting women for interview (using GEE)

Factor		Scheduled interviews n (%)	Successfully contacted n (%)	OR (95% CI)	p-value (Wald test)
	Total	1758	1492 (84.9)		
Interview Day	Day7	879 (50.0)	739 (84.1)	1	
	Day28	879 (50.0)	753 (85.7)	1.1 (1.0-1.3)	0.14
Nurse[a]	1	1004 (58.4)	872 (86.9)	1	
	2	714 (41.6)	620 (86.8)	1.1 (0.9-1.4)	0.21
Registration	18-31 Mar	430 (24.5)	353 (82.1)	1	0.51
	1-14 Apr	472 (26.9)	405 (85.8)	1.3 (0.9-2.0)	
	15-28 Apr	382 (21.7)	327 (85.6)	1.3 (0.8-2.1)	
	29 Apr-10 May	474 (27.0)	407 (85.9)	1.3 (0.8-2.1)	
Age of woman[b]	<25	676 (41.1)	570 (84.3)	1	0.99
	25-29	470 (28.6)	397 (84.5)	1.0 (0.7-1.5)	
	30+	498 (30.3)	422 (84.7)	1.0 (0.7-1.6)	
	Missing	114			
Delivery mode	Vaginal	1430 (81.3)	1213 (84.8)	1	
	CS	328 (18.7)	279 (85.1)	1.0 (0.7-1.6)	0.93
Hospital	Amana	892 (50.7)	756 (84.8)	1	
	Temeke	866 (49.3)	736 (85.0)	1.0 (0.7-1.4)	0.91

[a]Missing 40 - no call made (therefore no nurse allocated)
[b]Missing 114 – age not provided in hospital records

Among 1,492 completed interviews, 71% (1,063) were reached at the first call attempt, 18% at the second, 8% at the third and 3% at the fourth attempt or later. Contact at the first attempt improved as the study progressed ($p<0.0001$). Nurse 2 was more successful at contacting women on the first attempt ($p<0.0001$). At day-7, 63% (465) of women were contacted on the first attempt versus 79% (598) of women on day-28, and the association remained after adjusting for nurse and registration date ($p<0.0001$) (Table 6.6).

Table 6.6: Factors associated with reaching women at the first call attempt among 1492 conducted interviews (using GEE)

		Conducted interviews	Reached at first call n (%)	OR (95% CI)	aOR* (95% CI)	p-value (Wald test)
	Total	1492	1063 (71.3)			
Interview Day	Day7	739	465 (62.9)	1	1	<0.0001
	Day28	753	598 (79.4)	2.3 (1.8-2.8)	2.2 (1.7-2.8)	
Nurse	1	872	583 (66.9)	1	1	0.0001
	2	620	480 (77.4)	1.7 (1.4-2.1)	1.6 (1.3-2.0)	
Registration	18-31 Mar	353	229 (64.9)	1	1	<0.0001
	1-14 Apr	405	267 (65.9)	1.0 (0.8-1.4)	1.1 (0.8-1.5)	
	15-28 Apr	327	257 (78.6)	2.0 (1.4-2.8)	2.1 (1.4-3.0)	
	29 Apr-10 May	407	310 (76.2)	1.7 (1.3-2.4)	1.9 (1.3-2.6)	
Age of woman	<25	570	392 (68.8)	1		
	25-29	397	282 (71.0)	1.1 (0.8-1.5)		
	30+	422	312 (73.9)	1.3 (1.0-1.7)		
Delivery mode	Vaginal	1213	857 (70.7)	1		
	CS	279	206 (73.8)	1.2 (0.9-1.6)		
Hospital	Amana	756	533 (70.5)	1		
	Temeke	736	530 (72.0)	1.1 (0.9-1.4)		
Infection	No	1358	970 (71.4)	1		
	Yes	134	93 (69.4)	0.9 (0.6-1.3)		

*Adjusted for interview day, nurse and registration date

Women were interviewed using their primary phone number on 89% of occasions and this increased as the study progressed; from 79% for women registered in the first fortnight to 94% for women registered in the final fortnight. A higher percentage of young women (age <25 years) were reached on their primary phone compared to older age groups (99% vs 87%). Women delivered by caesarean section were more likely to be reached on their primary phone than those who gave birth vaginally (93% vs 88%) (Table 6.7).

Table 6.7: Telephone number used for 1492 interviews

		Telephone used n (%)		
		Phone 1	Phone 2	Phone 3
	Total	1321 (88.5)	141 (9.5)	30 (2.0)
Number of calls	1	980 (92.2)	75 (7.1)	8 (0.8)
	>1	341 (79.5)	66 (15.4)	22 (5.1)
Interview Day	Day7	642 (86.9)	77 (10.4)	20 (2.7)
	Day28	679 (90.2)	64 (8.5)	10 (1.3)
Nurse	1	773 (88.7)	78 (8.9)	21 (2.4)
	2	548 (88.4)	63 (10.2)	9 (1.5)
Registration	18-31 Mar	279 (79.0)	53 (15.0)	21 (6.0)
	1-14 Apr	350 (86.4)	47 (11.6)	8 (2.0)
	15-28 Apr	310 (94.8)	16 (4.9)	1 (0.3)
	29 Apr-10 May	382 (93.9)	25 (6.1)	0
Age of woman	<25	510 (98.5)	44 (7.7)	16 (2.8)
	25-29	345 (86.9)	46 (11.6)	6 (1.5)
	30+	369 (87.4)	45 (10.7)	8 (1.9)
Delivery mode	Vaginal	1063 (87.6)	126 (10.4)	24 (2.0)
	CS	258 (92.5)	15 (5.4)	6 (2.2)
Hospital	Amana	670 (88.6)	73 (9.7)	13 (1.7)
	Temeke	651 (88.5)	68 (9.2)	17 (2.3)
Infection	No	1202 (88.5)	128 (9.4)	28 (2.1)
	Yes	119 (88.8)	13 (9.7)	2 (1.5)

Thirteen interviews were recorded to last for over one hour. These outliers were considered to be errors and these interview times were dropped from further analysis. The remaining 1485 interviews were on average six minutes long (range 1-59 minutes) but in cases of infection the interviews took longer, lasting on average 11 and a half minutes (range 3-59 minutes). Adjusted mean interview length fell by one minute 48 seconds between the first and second scheduled interviews and decreased throughout the study. One nurse was on average over two minutes quicker than the other (Table 6.8).

Among 429 (29%) interviews that were not conducted at the first call attempt, a friend or relative was initially reached in 28% (119) of instances. This fell from 40% (110/274) at the day-7 interview to 6% (9/155) at day-28 (Table 6.9). Overall, a call was documented with a friend or relative before 8.0% of all interviews.

Table 6.8: Factors associated with length of interview (using GEE)

		Conducted interviews	Mean length of interview in minutes and seconds (95% CI)	Change in mean interview length (95% CI), minutes and seconds	Adjusted change in mean interview length* (95% CI), minutes and seconds	p-value
	Total	1485	06:06 (03:49–06:24)			
Interview Day	Day7	734	07:23 (06:52–07:54)			
	Day28	751	04:53 (04:38–05:09)	⁻02:29 (⁻03:00–⁻01:57)	⁻01:48 (⁻02:19–⁻01:17)	<0.001
Nurse	1	868	07:06 (06:40–07:31)			
	2	617	04:45 (04:21–05:08)	⁻02:21 (⁻02:55–⁻01:47)	⁻02:21 (⁻02:52–⁻01:50)	<0.001
Registration	18-31 Mar	350	08:49 (00:08–09:39)			<0.001
	1-14 Apr	404	06:20 (05:48–06:52)	⁻02:29 (⁻03:28–⁻01:30)	⁻02:21 (⁻03:14–⁻01:28)	
	15-28 Apr	325	05:01 (04:35–05:27)	⁻03:49 (⁻04:44–⁻01:13)	⁻03:15 (⁻04:08–⁻02:23)	
	29 Apr-10 May	406	04:25 (04:05–04:45)	⁻04:25 (⁻05:18–⁻03:31)	⁻04:07 (⁻04:56–⁻⁻03:18)	
Age of woman	<25	567	05:53 (05:26–06:20)			
	25-29	395	06:20 (05:41–06:58)	00:27 (⁻00:19–01:13)		
	30+	421	06:23 (05:48–06:59)	00:30 (⁻00:14–01:15)		
	Missing	102				
Delivery mode	Vaginal	1208	05:58 (05:39–06:17)			
	CS	277	06:44 (05:56–07:32)	00:46 (⁻00:05–01:38)	00:41 (00:02–01:24)	0.06
Hospital	Amana	752	06:20 (05:53–06:47)			
	Temeke	733	05:53 (05:29–06:17)	⁻00:27 (⁻01:03–00:09)		
Infection	No		05:35 (05:18–05:51)			
	Yes		11:33 (10:04–13:02)	05:59 (04:28–07:29)	04:31 (03:16–05:46)	<0.001

*Adjusted for interview day, nurse, registration date, delivery mode and infection

Table 6.9: Percentage contact with friend/relative among interviewed women who were not reached at first call attempt

	Total interviewed	Not reached at first call attempt n (%)	Spoke to friend/relative before reaching woman for interview n (%)
Total	1492	429 (28.8)	119 (27.7)
Day 7	739	274 (37.1)	110 (40.2)
Day 28	753	155 (20.6)	9 (5.8)

6.3.5 Discussion

During this three-month study, two nurses made 1,897 attempted telephone calls and conducted 1,492 interviews. Scheduled interviews were successfully conducted in 85% of instances and there was no evidence that any of the characteristics we measured affected this. The nurses became more efficient through the study period, and between the day-7 and day-28 interview, reaching a higher proportion of women for interview at the first attempt, and taking less time on average to conduct each interview.

At least one interview was conducted with 90% of women in the study; a successful performance compared to an Indian postpartum call-centre (86%)[238], post-surgical infection surveillance studies in sub-Saharan Africa (79%[242] and 87%[243]) and post-caesarean infection surveillance in Baltimore (83%)[225]. This result was achieved using basic mobile telephones and a card-based filing system that could be easily duplicated in settings without consistent computer or internet access. Despite this clear potential for telephone contact, it is concerning that a global survey of maternal healthcare providers during the COVID-19 pandemic found only 25% of respondents in LICs were using any form of telemedicine[265] despite evidence of reduced facility attendance for delivery[267] and shortened facility stays after giving birth[265].

Only 71% of interviews were conducted at the first attempted call, 11% were conducted using the second or third telephone number, and an earlier call occurred with a friend or relative before 8% of interviews. These findings indicate that our success depended on multiple call attempts using more than one telephone number. Nurses' compliance with the call-protocol improved over time, supported by weekly data-sharing and feedback, however our success could have been greater if a larger proportion of women received the intended four calls. In most cases, when asked, women stated that they missed the day-7 interview because their telephone battery was not charged. Providing a specific day and time window for the initial call, and/or donating phone credit to call back after a missed call, may increase the success of future surveillance programs.

Retention in the study was maintained at the second (day-28) call which could be related to the rapport established during the first interview, satisfaction with the interview process and the perceived value of speaking with a nurse. Of note, the chance of successfully contacting a woman was not influenced by any other factor including the woman's age (it was equally possible to reach both older and younger women) mode of delivery, or delivery hospital – which could reflect different geographical areas and/or economic status. This indicates that

telephone surveillance is possible across a diverse population and is likely to generate representative data across several important maternal parameters. Further research is warranted to assess women's satisfaction with telephone interviews and explore their potential to form part of routine postnatal care.

Over the study period, the nurses became more efficient at reaching women on the first call attempt, which could reflect changes to the call time in response to their experience of when women answered, as well as suggesting improved counselling of women at recruitment. At day-28 compared to day-7, they reached more women on the first number called, suggesting that they followed protocol and confirmed the most appropriate number at day-7. These changes may partly explain why friends/relatives were spoken to less frequently at day-28 compared to day-7.

The average interview length of six minutes was longer than for telephone surveillance of post-caesarean SSI in Baltimore with median interview length of two minutes (range one to five minutes)[225]. This was most likely due to a difference in interview content; we covered other infections in addition to SSI and asked about the baby's health as well as the woman's. However, it may also reflect the women's desire to talk with a nurse during this period and the perceived limited opportunities to access health personnel in this setting.

Similar to the Baltimore study, the length of interview decreased over time as the nurses became more familiar and efficient with the process. Interview length also decreased by a substantial amount from day-7 to day-28, independently of other factors including infection, and despite additional questions on mood and function in the day-28 interview. This could reflect women's familiarity with the questions, a quicker process due to the rapport already established and/or fewer concerns and problems to talk about at this later point in the postnatal period.

Limitations

Our study was not designed to assess the validity of telephone surveillance methods to diagnose postnatal infection. However, other studies in the region have shown high specificity of telephone surveillance to diagnose caesarean SSI, and our risk of endometritis and possible severe newborn infection was consistent with other studies. Even in the absence of further validity studies, telephone methods could be used to screen for postnatal conditions including infection, with onward referral for clinical assessment, or to compare infection risk between facilities or regions and over time.

We recruited women delivered in hospital and excluded those without access to a mobile telephone. In Dar es Salaam 94% of women give birth in a health facility and among our initial sample of women only 3% did not have access to a telephone, therefore, our results are generalisable to the vast majority of the population of the city. However, this method of surveillance may be less feasible in rural populations with lower mobile telephone coverage.

Length of interview is calculated from the start and end time of entries on the tablet which may not correlate precisely with the time spent on the telephone. Hence, reductions in interview length could partly indicate improved familiarity with the tablet, rather than shorter interviews. Nonetheless, the shorter length still demonstrates improved efficiency in the surveillance process over time.

Nurses were expected to complete an ODK form for every call attempt, including those that did not result in interview. At the start of the study there was a discrepancy between the number of calls documented by the nurses and the number of calls logged on the tablets, indicating that this procedure was not always followed. Consistency improved significantly over time (data not shown). For our analysis we used the number of calls logged on the tablet, which could underestimate the number of call-attempts and the nurses' compliance with the protocol of 4 calls per interview, as well as potentially over-estimate the proportion of women reached at the first call.

Conclusions

Telephone surveillance proved an effective method to reach women for interview and could be useful for conducting routine infection surveillance, and for enhancing postnatal follow-up and care, in similar settings. Study nurses were able to survey a large number of women, and their efficiency improved over time. Our study demonstrates the contribution of using multiple telephone numbers, including those of friends/relatives, to enable successful contact, and in particular, the importance of calling multiple times over a number of days. It is possible that providing a specific day and time for the call, or credit to return a missed call, would further increase the proportion of women reached. In the current context of the COVID-19 pandemic when physical distancing is encouraged and many women choose not to access facility-based care[267], telephone calls should be considered as a means to maintain contact, encourage women to deliver in a facility and address issues during pregnancy and postnatal.

Chapter 7: Postnatal infection surveillance by telephone in Dar es Salaam, Tanzania. Incidence, risk factors and consequences of infection

7.1 Introduction

The second paper of results from the fieldwork conducted in Dar es Salaam addresses questions 5 and 6 of this PhD relating to the incidence of maternal postnatal infection and the risk factors and consequences of those infections.

My contribution to the overall design and implementation of the study has already been described. I wrote the analysis strategy and cleaned and analysed the data. I received statistical support from Andrea Rehman to conduct multiple imputation.

7.2 Cover sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	310061	**Title**	Dr
First Name(s)	Susannah		
Surname/Family Name	Woodd		
Thesis Title	Measurement, incidence and risk factors of Maternal Peripartum Infection		
Primary Supervisor	Professor Oona Campbell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS One		
When was the work published?	July 1st 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the initial concept and design for the study which I refined with help from other authors. I developed the questionnaires, programmed them in ODK and trained the research nurses to carry out the data collection. I conducted weekly remote supervision with the nurses and weekly data checks, and liaised with the local principle investigator and supervisor. I wrote the analysis strategy and cleaned and analysed the data. I received statistical support to conduct multiple imputation. I wrote the first draft of the paper and made revisions based on co-authors comments

SECTION E

Student Signature	[redacted]
Date	18/11/21

Supervisor Signature	[redacted]
Date	10/1/22

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7.3 Manuscript 3. Postnatal infection surveillance by telephone in Dar es Salaam, Tanzania: an observational cohort study

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Short title: Postnatal infection surveillance by telephone

7.3.1 Abstract

Introduction

Maternal and newborn infections are important causes of mortality but morbidity data from low- and middle-income countries is limited. We used telephone surveillance to estimate infection incidence and risk factors in women and newborns following hospital childbirth in Dar es Salaam.

Methods

We recruited postnatal women from two tertiary hospitals and conducted telephone interviews 7 and 28 days after delivery. Maternal infection (endometritis, caesarean or perineal wound, or urinary tract infection) and newborn infection (umbilical cord or possible severe bacterial infection) were identified using hospital case-notes at the time of birth and self-reported symptoms. Adjusted Cox regression models were used to assess the association between potential risk-factors and infection.

Results

We recruited 879 women and interviewed 791 (90%). From day 0–7, 67 per 1000 (49/791) women and 62 per 1000 (51/762) newborns developed infection. Using full follow-up data, the infection rate was higher in women with caesarean childbirth versus women with a vaginal delivery (aHR 1.93, 95%CI 1.11–3.36). Only 24% of women received pre-operative antibiotic prophylaxis before caesarean section. Infection was higher in newborns resuscitated at birth versus newborns who were not resuscitated (aHR 4.45, 95%CI 2.10–9.44). At interview, 66% (37/56) of women and 88% (72/82) of newborns with possible infection had sought health-facility care.

Conclusions

Telephone surveillance identified a substantial risk of postnatal infection, including cases likely to have been missed by hospital-based data-collection alone. Risk of maternal endometritis and newborn possible severe bacterial infection were consistent with other studies. Caesarean section was the most important risk-factor for maternal infection. Improved implementation of pre-operative antibiotic prophylaxis is urgently required to mitigate this risk.

7.3.2 Introduction

Preventing maternal and newborn infections is a high priority in the World Health Organization's (WHO) vision of good quality care for pregnant women and newborns[1]. Pregnancy-related sepsis is estimated to cause 11% of maternal mortality[7] and infection is responsible for 23% of newborn deaths[72] with the vast majority in low- and middle-income countries (LMICs). Increasing health-facility births in LMICs[268] presents an opportunity to reduce disease incidence through strengthened infection prevention initiatives.

Despite the importance of maternal and newborn infection, we have limited knowledge of the frequency in high-burden countries. A systematic review of maternal peripartum infection included only seven sub-Saharan Africa (SSA) studies (one from Tanzania[216]) and none were considered high quality[85]. From meta-analysis, the regional estimate for endometritis was 17 per 1000 and for wound infection was 34 per 1000. A systematic review of possible severe bacterial infection (pSBI) using the Young Infant Clinical Signs Study (YICSS) criteria[80] estimated 62 per 1000 newborns in SSA were affected (six studies, none from Tanzania). The case-fatality risk was 14.1%[75].

The majority of severe maternal infections occur postpartum, arising from the genito-urinary tract or wounds[5, 43], and presenting after the woman has been discharged home following childbirth[42]. The majority of newborn deaths from infection occur after the first week of life[72]. Community follow-up is therefore necessary to capture all cases of infection. Home visits are resource intensive, consequently many studies only report infection up to the time of hospital discharge following facility childbirth. Mobile telephone surveillance is a possible alternative, with emerging evidence of feasibility and validity to monitor surgical site infection (SSI) in SSA[243, 264], and postnatal outcomes in India[238].

Responding to the limited data on maternal newborn infection incidence in SSA our observational cohort study aimed to estimate the incidence and risk factors for infection in women and newborns in the four weeks following hospital childbirth in urban Tanzania, using hospital case-notes from the time of birth and telephone surveillance. We also assessed the feasibility of mobile telephone assessment for infection, described care-seeking behaviour following infection and explored possible consequences of infection; hospital readmission, depression and reduced maternal function.

7.3.3 Methods

This study was a collaboration between London School of Hygiene and Tropical Medicine (LSHTM) and Ifakara Health Institute (IHI) and based at two of the three public Regional Referral Hospitals in Dar es Salaam; Amana (Ilala district) and Temeke (Temeke district). Each hospital conducts approximately 1,000 births per month. It was a sub-study of a pilot evaluation of training in environmental cleaning[269].

Two research nurses per hospital recruited eligible women from postnatal wards every Monday to Thursday. They sampled from all women who gave birth in the previous 24 hours using a random number application[270] with probability proportional to delivery mode (caesarean or vaginal). Eligible women were aged 18 years or older with access to at least one mobile telephone and providing signed or witnessed thumbprint consent. Women admitted to the intensive care unit were ineligible. Women provided up to three mobile telephone numbers; one or two of their own and one for a relative or neighbour. Replacements were sampled in the same way when potential participants were unavailable or ineligible.

Two research nurses at IHI offices in Dar es Salaam interviewed each woman twice by telephone in Kiswahili, starting seven and 28 days after recruitment. Nurses made four telephone call attempts, over seven days, to reach each woman.

Outcomes and Exposures

The primary outcomes were 1) possible maternal postnatal infection (one or more of caesarean surgical site infection, urinary tract infection, perineal wound infection, or endometritis) and 2) possible newborn infection (either of pSBI or umbilical cord infection). Each outcome was measured as a rate, and as the day 7 (early infection) and day 8–28 cumulative risk. Infections were identified from women's hospital case-notes around the time of childbirth or from self-reported symptoms during telephone interview using standard definitions[80, 92, 259]. These definitions were adapted by the first author to include only symptoms and signs easily reported by the women (Table 7.1). Secondary outcomes were each individual infection listed above, plus mastitis.

Table 7.1: Syndromic infection definitions used

Infection	Questions to women	Definition	Standard definition adapted
Caesarean Section Surgical Site Infection (SSI)	At the site of your caesarean section (cut/operation on your abdomen) have you experienced: I. Pus discharge II. Pain III. Swelling IV. Redness V. Wound breakdown (wound edges separated) Have you experienced: VI. Fever VII. Abdominal pain VIII. Foul-smelling or pus vaginal discharge	Either I. OR, (V. AND one or more of II-IV.), OR two or more of VI-VIII	CDC[a]
Urinary Tract Infection (UTI)	Have you experienced: I. Pain passing urine II. Urinary frequency – passing urine more often III. Urinary urgency – need to pass urine quickly/difficulty in holding urine IV. Fever V. Abdominal pain	Either (I. and II.) OR, three or more of I-V.	SIGN[b]
Perineal wound infection	At the site of a perineal wound (cut or tear in the vagina) have you experienced: I. Pus discharge II. Pain III. Swelling IV. Wound breakdown (wound edges separated)	Either, I. OR, (IV AND one or both of II and III.)	CDC[a]
Endometritis	Have you experienced: I. Fever II. Abdominal pain III. Foul-smelling or pus vaginal discharge	Two or more of I-III where II is not explained by UTI and III is not explained by perineal wound infection. In women with caesarean section this was counted as an organ space SSI	CDC[a]

Mastitis	Have you experienced: I. Swollen, hard area of the breast II. Painful, red breast III. Fever	Either, I. OR, both II. and III.	CDC[a]
pSBI	Has your baby experienced: I. Fever II. Very cold (low temperature) III. Very fast breathing IV. Chest indrawing (sucking in the ribs when breathing) V. Convulsions/fits VI. Poor feeding/not feeding VII. Only moving when stimulated	One or more of I-VII.	YICSS[c]
Umbilical cord infection	Has your baby experienced: I. Redness around the umbilical cord stump II. Pus discharge from umbilical cord stump	One or both of I. and II.	CDC[a]

a)Centres for Disease Control[92] b) Scottish Intercollegiate Guidelines Network[259] c)Young Infants Clinical Signs Study[80]

Potential risk factors were extracted from hospital case-notes; maternal age, gestational age, parity, HIV, diabetes, hypertensive disorder, haemorrhage, prelabour rupture of membranes (PROM), induction of labour, delivery mode, postpartum haemorrhage (PPH) and infection during labour. Possible consequences of infection collected during telephone interview were self-reported readmission, depression assessed using a validated 5-question modified Edinburgh Postnatal Depression Scale (EPDS) and functionality according to five common postpartum activities (Appendix F: Questionnaire).

Data Collection

Data was entered on tablets with Open Data Kit (ODK), using unique identification (ID) numbers to maintain confidentiality. Data was extracted from maternal paper case-notes after hospital discharge, including demographics, pregnancy and childbirth history, infection diagnosed during admission and antibiotics prescribed (Appendix G: Extraction form). Telephone interviews with women consisted of pre-coded closed questions on the history of specific symptoms of infection, day of symptom onset, care-seeking behaviour, and readmission to hospital. At day-28, women were also asked questions on depression and function (Appendix F: Questionnaire). Women with infection symptoms were advised to attend a health-facility if they hadn't already. In cases of maternal depression or neonatal death, women were offered referral to social welfare liaison for counselling and support.

Research nurses received six days training in recruitment and data collection, including two days at the hospitals when they piloted the tools on 24 women. Telephone interview nurses additionally conducted pilot interviews with the same 24 women over two days.

Study size

With 900 women and an estimated 10% loss to follow-up at day-28, we would have 95% confidence to estimate a maternal infection risk of 30 per 1000 $\pm$ 12 per 1000, with 80% power. Our daily recruitment target was 12–20 women per hospital.

Data management

Data was cleaned and analysed using STATA 16. Gestational age was grouped as preterm (<37 weeks) or term (37–42 weeks). The depression score was grouped as no depression (0–5) or possible depression (6–30). Maternal function questions were analysed individually as "any" or "no difficulty" in performing the function.

Duplicate ID numbers and data entry errors were corrected where possible using hospital case-notes or comparing with other study data. Any remaining discordant data was dropped. There was inconsistency in the occurrence of stillbirths between data sources, therefore stillbirths were not analysed. Data on twin and triplet newborns was also inconsistent and in addition an error in ODK programming meant only data from the first baby was useable.

Statistical Analysis

Women's demographic and pregnancy data was described by delivery mode. Rates of infection were calculated from delivery until the day-28 telephone call using reported days from delivery to start of symptoms. Symptoms reported at both day-7 and day-28 were counted as distinct infection events if they started over 14 days apart, or if they met criteria for different infection types and started over seven days apart, or if initial symptoms had resolved by the day-7 interview. Date of death and infection data were not collected from babies who died before the day-7 interview, therefore these babies were excluded from infection outcome analyses. Babies who died after the day-7 interview contributed to infection analyses up to day 7. Using Cox regression with robust standard errors to account for clustering by person, we explored associations between potential risk factors and the rate of maternal postnatal infection or possible newborn infection. Proportional hazards assumptions were checked using tests based on Schoenfeld Residuals. Factors showing evidence of association in the crude analysis ($p<0.1$) were explored further in multivariable models. Maternal age and delivery hospital were considered *a priori* confounders for risk of

maternal postnatal infection. We restricted the parameters in the final models to 10% of the number of outcomes. For missing risk-factor data, we carried out multiple imputation using chained equations because most variables were categorical, creating 10 imputed datasets. Delivery mode and hospital were included as auxiliary variables. Women whose case-notes were missing were excluded from risk-factor analysis.

We report the highest level of care sought by women and newborns with possible infection and the percentage readmission to hospital for those with and without infection. We describe maternal depression and function at day-28 and explore associations with early postnatal infection using chi-squared tests and logistic regression.

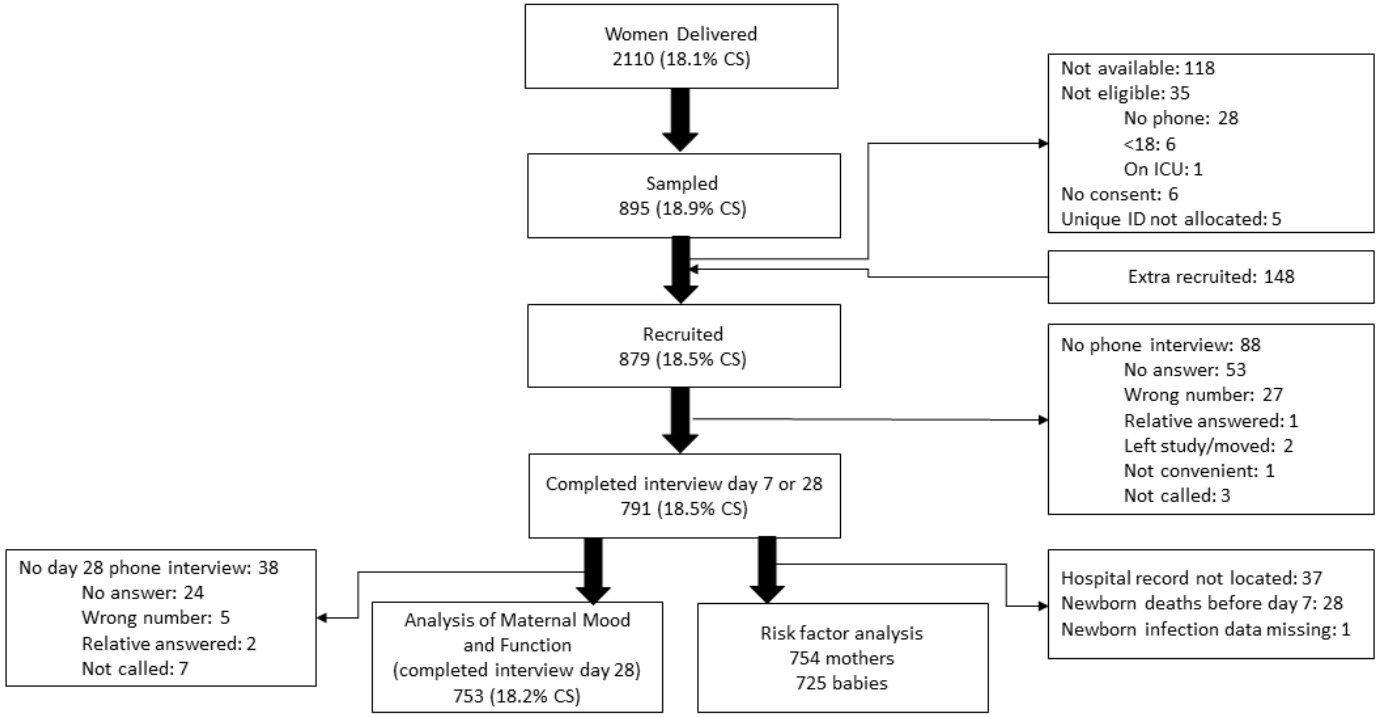
Ethics

The study was approved by the Tanzanian National Institute for Medical Research, IHI Institutional Research Board and LSHTM Research Ethics Committee. Written informed consent was obtained from women on the postnatal wards. Willingness to continue in the study was confirmed at the start of each telephone interview. There was no public or patient involvement in the study design or interpretation of results. The Soapbox Collaborative supported the study following external peer review of the study proposal.

7.3.4 Results

Between 15th March and 9th May 2018, research nurses recruited 879 women into the study, sampling from a total of 2,110 deliveries (18% caesarean section) (Fig 7.1). We interviewed 791 (90%) women at least once, providing data until day 7, and 753 (86%) completed the day-28 interview. Final interview occurred between 7 and 43 (median 29) days after delivery. Most women whose only interview was at day-28, reported that their telephone battery was not charged at day-7.

Figure 7.1: Flow Diagram



Case-notes were not located for 39 women. In the remaining 840, missing data was minimal except gestational age (39%). Mean age was 25 (range 18–45) years. Fewer than 3% of women were referred-in. Induction and augmentation of labour, including artificial rupture of membranes, were uncommon (each <3%) but occurred more frequently at Amana Hospital than Temeke Hospital (Additional Table 7.1). Among vaginal births (n=692), seven were breech and three were by vacuum extraction. Vaginal tears were experienced after 36% of vaginal deliveries and episiotomy was rare (Table 7.2). Among 829 liveborn babies, bag-and-mask resuscitation and admission were more common both following caesarean section and at Amana Hospital (Additional Table 7.1). Average length of stay after delivery was 0.8 days following vaginal delivery (range 0-8) and 2.4 days post-caesarean section (range 0-7).

Antenatally, 7.4% of women received antibiotics, primarily for prophylaxis before caesarean section or following PROM. Postnatally, 62% of all women were prescribed antibiotics: 94% of women undergoing caesarean section and 98% of all women giving birth at Amana hospital were prescribed antibiotics (Table 7.3).

Infection risk and rate

No postnatal maternal infections were documented in hospital case-notes at the time of birth and there were no maternal deaths. Among all 791 women with at least one telephone interview, 47 (59 per 1000) reported possible postnatal infection starting day 0–7. Symptoms of UTI affected 22 (28 per 1000) women and symptoms of endometritis affected 12 (15 per 1000). Among 146 women with caesarean section, 15 (103 per 1000) reported possible postnatal infection of whom 12 (82 per 1000) had symptoms of SSI (Table 7.4). From day 8–28, 9/753 (12 per 1000) developed possible postnatal infection. The rate of possible infection was 79.4 (95% CI 61.1–103.2) per 1000 women per month.

Table 7.2: Demographic, pregnancy and newborn factors by mode of delivery for 840 women and 829 liveborn babies with maternal hospital case-notes

	Vaginal Delivery n (%) (N=692)	**Caesarean Section n (%) (N=148)**	**Total N (%) (N=840)**
Maternal age in years			
18-24	288 (41.6)	50 (33.8)	338 (40.2)
25-29	193 (27.9)	42 (28.4)	235 (28.0)
30+	197 (28.5)	52 (36.1)	249 (29.6)
Missing	14 (2.0)	4 (2.7)	18 (2.1)
Parity			
Nulliparous	234 (33.8)	52 (35.1)	286 (34.1)
1	205 (29.6)	50 (33.8)	255 (30.4)
2	125 (18.1)	23 (15.5)	148 (17.6)
3+	106 (15.3)	19 (12.8)	125 (14.9)
Missing	22 (3.2)	4 (2.7)	26 (3.1)
Preterm birth (<37 weeks gestation)	59 (8.5)	22 (14.9)	81 (9.6)
Missing	287 (41.5)	42 (28.4)	329 (39.2)
Hypertensive disorders[a]	18 (2.6)	16 (10.8)	34 (4.1)
Missing	4 (0.6)	2 (1.4)	6 (0.7)
HIV	29 (4.2)	8 (5.4)	37 (4.4)
Missing/not available	14 (2.0)	1 (0.7)	15 (1.8)
PROM	25 (3.6)	4 (2.7)	29 (3.5)
Missing	2 (0.3)	1 (0.7)	3 (0.4)
Episiotomy	10 (1.5)	NA	10 (1.2)
Missing	14 (2.0)	NA	14 (1.7)
Perineal tear	250 (36.1)	NA	250 (29.8)
Missing	3 (0.4)	NA	3 (0.4)
PPH	7 (1.0)	2 (1.4)	9 (1.1)
Missing	2 (0.3)	0	2 (0.2)
Antibiotics in labour	26 (3.8)	36 (24.3)	62 (7.4)
Missing	5 (0.7)	1 (0.7)	6 (0.7)
Antibiotics postpartum	382 (55.2)	139 (93.9)	521 (62.0)
Missing	5 (0.7)	3 (2.0)	8 (1.0)
Newborn Factors	**Vaginal (N=681)**	**CS (N=148)**	**Total (N=829)**
Apgar Score at 5 minutes <7	5 (0.7)	5 (3.4)	10 (1.2)
Missing	2 (0.3	1. (0.7)	3 (0.4)
Bag and mask resuscitation	9 (1.3)	8 (5.4)	17 (2.1)
Missing	2 (0.3)	2 (1.4)	4 (0.5)
Admission	10 (1.5)	12 (8.1)	22 (2.7)
Missing	0	2 (1.4)	2 (0.2)

[a]Hypertensive disorders: 2 eclampsia, 19 pre-eclampsia, 17 pregnancy-induced hypertension

Table 7.3: Reason for antibiotics prescribed to women in hospital during labour and postpartum by delivery mode

	Vaginal Delivery n (%)	**Caesarean Section n (%)**	**Total**
Antibiotics in labour	**N=26**	**N=36**	**N=62**
Caesarean section prophylaxis	0	34 (94.4)	34 (54.8)
PROM	14 (53.9)	2 (5.6)	16 (25.8)
UTI	1 (3.9)	0	1 (1.6)
Other*	8 (30.8)	0	8 (12.9)
Unknown	3 (11.5)	0	3 (4.8)
Antibiotics postpartum	**N=382**	**N=139**	**N=521**
Caesarean section prophylaxis	0	131 (94.2)	131 (25.1)
PROM	2 (0.5)	0	2 (0.4)
Perineal suture	172 (45.0)	0	172 (33.1)
UTI	1 (0.3)	0	1 (0.2)
Routine	190 (49.7)	0	190 (36.5)
IUD	4 (1.1)	0	4 (0.8)
Unknown/not recorded	13 (3.4)	8 (5.8)	21 (4.0)

*Other reasons: Foetal distress 2, Meconium-stained liquor 4, Prolonged labour 1, Post-term and breech 1

Table 7.4: Maternal and newborn infections occurring up to 7 days after delivery

Maternal infection	**Vaginal delivery n (per 1000) N=645**	**Caesarean section n (per 1000) N=146**	**Total N (per 1000) N=791**
Postnatal infection	32 (50)	15 (103)	47 (59)
Endometritis	12 (19)	NA	12 (15)
SSI	NA	12 (82)	12 (15)
Perineal wound infection	7 (11)	0	7 (9)
UTI	15 (23)	7 (48)	22 (28)
Mastitis	13 (20)	3 (21)	16 (20)
Newborn infection	**N=621**	**N=141**	**N=762**
Possible newborn infection	40 (64)	11 (78)	51 (67)
pSBI	36 (58)	11 (78)	47 (62)
Umbilical cord infection	5 (8)	0	5 (07)

Before the first interview, 28 (3.5%) babies were stillborn or died and one was missing infection data. Of the remaining 762 babies, 51 (67 per 1000) developed possible newborn infection from day 0–7, almost entirely attributable to pSBI (47, 62 per 1000) (Table 4). From day 8–28, another six babies died, and 30/719 (43 per 1000) babies developed possible infection, one of whom had two episodes of infection. The rate of possible infection was 121.1 (95% CI 97.5–150.3) per 1000 babies per month. Three of these babies were diagnosed with sepsis in the maternal case-notes. For two of these three cases, no infection symptoms were reported by the mother at telephone interview.

Women sought care in a health facility following 37/56 (66%) episodes of possible postnatal infection: 24 (43%) at their delivery hospital, 8 (14%) at another hospital, and 5 (9%) at a lower level health facility. Babies were taken to a health facility following 72/82 (88%) episodes of possible infection: 38 (46%) to the delivery hospital, 25 (30%) to another hospital, and 9 (11%) to a lower level health facility.

Associations with infection

There was evidence that caesarean delivery doubled the rate of possible maternal postnatal infection compared to women who had a vaginal delivery, and this association remained after adjusting for maternal age and hospital (adjusted Hazard Ratio (aHR) 1.93, 95% CI 1.11–3.36, p=0.02). There was also weak evidence of an association between women's age-group and infection (p=0.06) with the highest infection rates occurring in women aged 25–29. (Table 7.5).

Table 7.5: Association between potential risk-factors and rate of possible maternal postnatal infection

Factor	Total women	Episodes of postnatal infection	Person-time (months)	Rate of infection per 1000 person months	Crude HR (95% CI) N=754[a]	Wald p-value	Adjusted HR (95% CI) N=754 [a]	Wald p-value
All women	791	56	705.3	79.4 (61.1-103.2)				
Delivery mode								
Vaginal	645	39	578.1	67.5	1	0.02	1	0.02
Caesarean section	146	17	127.3	133.6	1.95 (1.12-3.37)		1.93 (1.11-3.36)	
Maternal age (years)								
18-24	303	15	167.9	56.0	1	0.05	1	0.06
25-29	212	23	186.0	123.6	2.20 (1.15-4.28)		2.14 (1.12-4.09)	
30+	223	16	204.3	78.3	1.43 (0.72-2.84)		1.37 (0.69-2.70)	
Hospital								
Amana	403	28	362.0	77.4	1	0.87	1	0.98
Temeke	388	28	343.4	81.5	1.04 (0.62-1.75)		1.01 (0.60-1.70)	
Parity								
0	252	15	224.8	66.7	1	0.81		
1	233	19	206.9	91.8	1.33 (0.69-2.56)			
2	131	11	115.0	95.7	1.37 (0.65-2.89)			
3+	113	8	103.6	77.2	1.16 (0.48-2.81)			
Preterm birth (<37 weeks)								
No	392	30	346.5	86.6	1	0.89		
Yes	69	5	62.5	80.1	0.94 (0.37-2.35)			
Antibiotics in labour								
No	697	48	622.6	77.1	1	0.17		
Yes	51	6	43.7	137.3	1.75 (0.78-3.91)			
Postpartum antibiotics								
No	277	18	246.4	73.0	1	0.49		
Yes	469	37	417.9	88.5	1.22 (0.69-2.16)			

[a]Values imputed for variables with missing data, except for Preterm birth where the amount of missing data was considered too large to impute

Results shown if >2 infections in a single category. Full results in Additional Table 7.2

Bag-and-mask resuscitation at birth was strongly associated with possible newborn infection compared to babies who were not resuscitated (aHR 4.45, 95% CI 2.10–9.44, p<0.001), however this was a rare exposure (n=11 babies). There was weak evidence for increased possible newborn infection if the mother received antibiotics in labour compared to mothers who did not (Table 7.6).

In the first seven days postnatal 7/762 mother-baby pairs both experienced possible infection. Mothers with postnatal infection in the first 7 days had an increased risk of their baby suffering possible newborn infection during this time period, compared to mothers without infection (crude Odds Ratio 2.74, 95%CI 1.16–6.48, p=0.02).

Consequences of infection

At the day-7 interview, 5/43 (12%) women with possible postnatal infection reported they had been readmitted to hospital as compared with only 5/696 (0.7%) women without infection. All women readmitted with infection had given birth by caesarean section. Among 713 babies alive at the day-7 interview, 44% with possible infection had been readmitted to hospital compared with 1.8% of those without.

Depression scores ranged from 0–10/30 among 753 women at day-28 interview and 31 (4%) had possible depression (score >=6). Among 43 women with early postnatal infection (day 0–7), 4 (9.3%) developed possible depression versus 27 (3.8%) of those without infection (OR 2.1, 95% CI 0.64–6.89, p=0.22, adjusting for death of the baby).

At day-28 interview, 103/752 (13.7%) women reported difficulty with housework and 8/751 (1.1%) reported difficulty washing themselves. Among women with a living baby, 43/718 (6.0%) reported difficulty carrying or caring for their baby and 99.7% were exclusively breastfeeding. Difficulty with each activity was reported more frequently among women with possible early postnatal infection compared to those without infection, but statistical evidence was inconsistent. (Table 7.7).

Table 7.6: Association between potential risk factors and rate of possible newborn infection

Factor	Total newborns	Episodes of possible infection	Person-time (months)	Rate of infection per 1000 person months	Crude HR (95% CI) N=725[a]	Wald p-value	Adjusted HR (95% CI) N=725 [a]	Wald p-value
All babies	762	82	677.4	121.1 (97.5-150.3)				
Resuscitation (bag and mask)								
No	709	75	629.9	119.1	1	<0.001	1	<0.001
Yes	11	5	8.7	574.3	4.61 (2.35-9.04)		4.45 (2.10-9.44)	
Antibiotics in labour								
No	674	69	598.5	115.3	1	0.01	1	0.08
Yes	47	10	39.9	250.9	2.15 (1.18-3.91)		2.00 (0.93-4.30)	
Delivery mode								
Vaginal	621	64	552.2	115.9	1	0.35	1	0.95
Caesarean section	141	18	125.1	143.8	1.24 (0.74-2.09)		1.02 (0.55-1.91)	
PROM								
No	698	75	617.7	121.4	1	0.37	1	0.76
Yes	24	4	22.1	180.6	1.53 (0.61-3.84)		1.16 (0.45-2.99)	
Maternal age (years)								
18-24	291	29	256.9	112.9	1	0.51		
25-29	203	27	280.4	149.6	1.34 (0.79-2.28)			
30+	216	22	193.0	114.0	1.05 (0.60-1.84)			
Hospital								
Amana	388	41	347.1	118.1	1	0.94		
Temeke	374	41	330.3	124.1	1.04 (0.67-1.61)			
Preterm (<37 weeks gestation)								
No	376	38	330.6	114.9	1	0.65		
Yes	67	8	59.5	134.5	1.18 (0.57-2.44)			
Postpartum antibiotics								
No	266	21	236.8	88.7	1	0.07		
Yes	452	58	399.5	145.2	1.59 (0.96-2.62)			

[a]Values imputed for variables with missing data, except for Preterm birth where the amount of missing data was considered too large to impute

Results not shown if <3 infections in a single category. Full results in Additional Table 7.3

Table 7.7: Associations between early maternal postnatal infection (day 0-7) and maternal function at day 28

	Difficulty washing n/N (%)	Difficulty with housework n/N (%)	Difficulty carrying baby n/N (%)	Difficulty caring for baby n/N (%)
Postnatal infection				
No	6/709 (0.9)	94/709 (13.3)	39/679 (5.7)	38/679 (5.6)
Yes	2/42 (4.8)	9/43 (20.9)	4/39 (10.3)	5/39 (12.8)
Chi^2 p-value	0.02	0.16	0.25	0.06

7.3.5 Discussion

We conducted telephone interviews with 791 women at seven and/or 28 days after hospital childbirth in Dar es Salaam, Tanzania. We estimated a rate of 79.4 possible maternal and 121.1 possible newborn infections per 1000 person-months. Women with caesarean birth had twice the rate of infection. Newborns resuscitated at birth had over four times the rate of infection. Women and newborns with possible infection had substantially higher readmission rates compared with those without infection, and there was a trend towards increased depression risk following early infection. Telephone surveillance proved feasible: 97% of the initial sample had access to a mobile telephone and 90% of all recruited women were interviewed at least once.

Global incidence of pregnancy-related infection estimated by the Global Burden of Disease study 2017 equates to 82 per 1000 livebirths[19], and the recent Global Maternal Sepsis Study (GLOSS) reports prevalence of infection in hospitalised pregnant and postpartum women of 70.4 per 1000 livebirths[5]; however, their broader case definitions prevent direct comparison with our study. Our incidence of endometritis at day-7 (15 per 1000) is consistent with the 17 per 1000 (95% CI 14–21 per 1000) estimate for SSA from a recent meta-analysis[85]. However, we observed a caesarean surgical site infection risk of 82 per 1000, which is lower than the 156 per 1000 estimate from a systematic review for SSA[161]. Our incidence of pSBI (62 per 1000) was the same as the estimate for SSA from a meta-analysis of studies in which health or community workers applied YICSS criteria[22].

Caesarean section is an established risk factor for maternal infection and sepsis[4, 5, 43] and in our study carried a higher risk of both SSI and UTI than vaginal birth. Increasing rates of caesarean childbirth and evidence of antimicrobial resistance (AMR) in subsequent infections[60] demand enhanced infection prevention measures. Pre-operative prophylactic antibiotics are effective[271] and recommended in Tanzania[272], but were documented before only 24% of caesarean sections. Newborn infection could result from pathogens introduced

during resuscitation, explaining the strong association seen. Additionally, sick newborns requiring ventilation are at increased risk of infection, supporting calls to improve both intrapartum care and postnatal infection prevention[273].

Expected associations between prematurity, PROM, PPH, HIV, and either maternal or newborn infection were not evident, but these factors were reported less frequently than expected. Induction and augmentation of labour were similarly infrequent. This could reflect poor documentation at the hospitals or difficulties in extraction. Postpartum antibiotics were not associated with reduced infection incidence, providing no justification for universal prescribing observed at one study hospital. This practice is not recommended nationally or internationally[39], could be a driver of AMR and needs to be challenged. There was some evidence of a crude association between maternal and newborn infection, also found in a systematic review of maternal infection in labour[16], suggesting a shared aetiology for some infections and highlighting the importance of caring for the woman and newborn synergistically.

Depression prevalence (4.1%) was lower than other LMIC studies that also used EPDS at 4–8 weeks postnatal. However, these studies showed considerable heterogeneity (range 4.9–50.8%)[274]. Telephone follow-up could provide a valuable tool to screen for postnatal depression and warrants further validation. We did not power our study to assess associations between maternal infection and depression or functioning, but our results suggest a trend in that direction, compatible with previous studies of maternal morbidity[274-277].

In our study, 66% of women and 88% of newborns with possible infection had sought health-facility care when interviewed, revealing the important proportion of cases that would be missed by a purely hospital based study. Telephone diagnosis of caesarean site infection achieved high specificity in Kenya and Tanzania[243, 264]. Telephone surveillance detected more cases of SSI than using patient case-notes or written surveys in high-income settings[225, 278]. Mobile telephone access was high in our study sample (97%), and we reached a high proportion of recruited women (90%), supporting the feasibility of telephone surveillance in comparable LMIC settings.

Strengths and limitations

Our study benefited from collecting data on specific components of standard infection definitions during the interview that were used in diagnosis algorithms, rather than relying

on women's or data collectors' judgement. We collected data with a short recall period, reducing potential bias, and used symptom start dates to show infection distribution over time and estimate incidence rate. Although we recruited from two tertiary hospitals, we expect the population to be broadly representative of Dar es Salaam region where 94% of women are estimated to give birth in a facility and 17% by caesarean, similar to our study population.

The main limitation of this study is the unknown validity of the questionnaire to identify true cases of infection. We believe that the substantially increased rates of hospital readmission amongst women and newborns with telephone-based diagnosis of infections provide strong post-hoc support for the validity of our approach. Incidence of endometritis and pSBI and the association with caesarean childbirth are all closely consistent with other studies, lending further support to the results. However, we identified fewer cases of SSI than other studies, and we had two cases of neonatal sepsis extracted from hospital case-notes that were not subsequently reported at maternal interview. In addition, newborn deaths from infection were not captured, therefore true infection incidence may be higher than estimated. Furthermore, hospital case-notes were not located for 39 women, in some cases following admission of the baby, potentially reducing estimated infection incidence. It is possible that women who were unwell, or caring for a sick baby, were less likely to answer their telephones, also leading to an under-estimate of infection incidence. However, the use of a second telephone number belonging to a friend/relative, the repeated call attempts over seven days and the second interview at day-28 reduce this risk.

Conclusion

Our telephone surveillance study found a substantial and plausible rate of possible infection among mothers and newborns in urban Tanzania in the first month postnatal. Telephone interviews were feasible and identified cases that could be missed by hospital data collection alone. Results were consistent with previous studies, although further validation studies are needed. Therefore, this method of data collection shows promise for further use, both as a research tool and for routine medical practice. This could be of particular benefit during the current COVID pandemic, with concerns about reduced hospital attendance and the encouragement to work remotely. WHO does not recommend the use of routine postpartum antibiotics. Their use in this context showed no benefit and should be challenged. However, better implementation of pre-operative antibiotic prophylaxis for caesarean section is urgently required to mitigate the infection risk in mothers.

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7.3.6 Additional Tables of Results

Additional Table 7.1: Demographic, pregnancy and newborn factors by delivery hospital for 840 women and 829 liveborn babies with hospital record data by study hospital

	Amana n (%) (N=425)	Temeke n (%) (N=394)	Total n (%) (N=840)
Median maternal age in years (IQR)	25 (22-30)	26 (23-31)	25 (22-30)
Age grouped (years)			
18-24	184 (42.7)	154 (37.7)	338 (40.2)
25-29	121 (28.1)	114 (27.9)	235 (28.0)
30+	123 (28.5)	126 (30.8)	249 (29.6)
Missing	3 (0.7)	15 (3.7)	18 (2.1)
Parity grouped			
0	161 (37.4)	125 (30.6)	286 (34.1)
1	133 (30.9)	122 (29.8)	255 (30.4)
2	61 (14.2)	87 (21.3)	148 (17.6)
3+	67 (15.6)	58 (14.2)	125 (14.9)
Missing	9 (2.1)	17 (4.2)	26 (3.1)
Preterm birth (<37 weeks gestation)	37 (8.6)	44 (10.8)	81 (9.6)
Missing	184 (42.7)	145 (35.5)	329 (39.2)
Referred in	17 (3.9)	5 (1.2)	22 (2.6)
Missing	1 (0.2)	0	1 (0.1)
Diabetes/GDM	0	2 (0.5)	2 (0.2)
Missing	0	1 (0.2)	1 (0.1)
Hypertensive disorders	17 (3.9)	17 (4.2)	34 (4.1)
Missing	1 (0.2)	5 (1.2)	6 (0.7)
HIV	22 (5.1)	15 (3.7)	37 (4.4)
Missing/not available	8 (1.9)	7 (1.7)	15 (1.8)
PROM	18 (4.2)	11 (2.7)	29 (3.5)
Missing	1 (0.2)	2 (0.5)	3 (0.4)
Induction of labour	18 (4.2)	2 (0.5)	20 (2.4)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Artificial rupture of membranes	12 (2.8)	2 (0.5)	14 (1.7)
Missing	0	2 (0.5)	2 (0.2)
Augmentation of labour	22 (5.1)	2 (0.5)	24 (2.9)
Missing	0	3 (0.7)	3 (0.4)
Episiotomy	2 (0.5)	8 (2.0)	10 (1.2)
Missing	11 (2.6)	3 (0.7)	14 (1.7)
Perineal tear	168 (39.0)	82 (20.1)	250 (29.8)
Missing	1 (0.2)	2 (0.5)	3 (0.4)
Perineal suture (N=260 women with perineal trauma)	166/170 (97.7)	88/90 (97.8)	254 (97.7)
Missing	0	1 (1.1)	1 (0.4)
PPH	2 (0.5)	7 (1.7)	9 (1.1)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Antibiotics in labour	53 (12.3)	9 (2.2)	62 (7.4)

Missing	3 (0.7)	3 (0.7)	6 (0.7)
Antibiotics postpartum	425 (98.6)	96 (23.5)	521 (62.0)
Missing	1 (0.2)	7 (1.7)	8 (1.0)
Newborn Factors			**Total (N=829)**
Apgar Score at 5 minutes <7	5 (1.20)	5 (1.2)	10 (1.2)
Missing	2 (0.5)	1 (0.2)	3 (0.4)
Bag and mask	12 (2.9)	5 (1.2)	17 (2.1)
Missing	0	4 (1.1)	4 (0.5)
Admission	21 (5.0)	1 (0.2)	22 (2.7)
Missing	0	2 (0.5)	2 (0.2)

Additional Table 7.2: Associations between potential risk factors and possible maternal postnatal infection

Factor	Total women	Episodes of postnatal infection	Person-time (months)	Rate of infection per 1000 person months	Crude Rate ratio (95% CI) N=754[a]	Wald p-value
All women	791	56	705.3	79.4 (61.1-103.2)		
Delivery mode						
Vaginal	645	39	578.1	67.5	1	0.02
Caesarean section	146	17	127.3	133.6	1.95 (1.12-3.37)	
Maternal age (years)						
18-24	303	15	167.9	56.0	1	0.05
25-29	212	23	186.0	123.6	2.20 (1.15-4.28)	
30+	223	16	204.3	78.3	1.43 (0.72-2.84)	
Hospital						
Amana	403	28	362.0	77.4	1	0.87
Temeke	388	28	343.4	81.5	1.04 (0.62-1.75)	
Parity						
0	252	15	224.8	66.7	1	0.81
1	233	19	206.9	91.8	1.33 (0.69-2.56)	
2	131	11	115.0	95.7	1.37 (0.65-2.89)	
3+	113	8	103.6	77.2	1.16 (0.48-2.81)	
Preterm birth (<37 weeks)						
No	392	30	346.5	86.6	1	0.89
Yes	69	5	62.5	80.1	0.94 (0.37-2.35)	
HIV infection						
No	705	53	630.0	84.1	1	0.38
Yes	34	1	28.2	35.4	0.41 (0.06-2.91)	
Hypertensive disorders						
No	721	52	642.8	80.9	1	0.96
Yes	28	2	24.5	81.5	0.96 (0.25-3.75)	
PROM						
No	727	55	648.5	84.8		
Yes	24	0	21.6	0.00		
ARM						
No	738	55	657.6	83.6		
Yes	14	0	13.3	0.00		
PPH						
No	746	53	665.2	79.7	1	0.44
Yes	7	1	6.0	166.3	2.10 (0.33-13.49)	
Antibiotics in labour						
No	697	48	622.6	77.1	1	0.17
Yes	51	6	43.7	137.3	1.75 (0.78-3.91)	

Postpartum antibiotics						
No	277	18	246.4	73.0	1	0.49
Yes	469	37	417.9	88.5	1.22 (0.69-2.16)	

[a]Values imputed for variables with missing data except for preterm birth where a large amount of data was missing.

Additional Table 7.3: Associations between potential risk factors and possible newborn infection

Factor	Total newborns	Episodes of possible infection	Person-time (months)	Rate of infection per 1000 person months	Crude rate ratio (95% CI) N=725[a]	Wald p-value
All babies	762	82	677.4	121.1 (97.5-150.3)		
Resuscitation (bag and mask)						
No	709	75	629.9	119.1	1	<0.001
Yes	11	5	8.7	574.3	4.61 (2.35-9.04)	
Antibiotics in labour						
No	674	69	598.5	115.3	1	0.01
Yes	47	10	39.9	250.9	2.15 (1.18-3.91)	
Delivery mode						
Vaginal	621	64	552.2	115.9	1	0.35
Caesarean section	141	18	125.1	143.8	1.24 (0.74-2.09)	
PROM						
No	698	75	617.7	121.4	1	0.37
Yes	24	4	22.1	180.6	1.53 (0.61-3.84)	
Maternal age (years)						
18-24	291	29	256.9	112.9	1	0.51
25-29	203	27	280.4	149.6	1.34 (0.79-2.28)	
30+	216	22	193.0	114.0	1.05 (0.60-1.84)	
Hospital						
Amana	388	41	347.1	118.1	1	0.94
Temeke	374	41	330.3	124.1	1.04 (0.67-1.61)	
Preterm (<37 weeks gestation)						
No	376	38	330.6	114.9	1	0.65
Yes	67	8	59.5	134.5	1.18 (0.57-2.44)	
Postpartum antibiotics						
No	266	21	236.8	88.7	1	0.07
Yes	452	58	399.5	145.2	1.59 (0.96-2.62)	
HIV infection						
No	677	78	602.8	129.4	1	0.41
Yes	33	2	26.0	77.1	0.56 (0.14-2.20)	

Hypertensive disorders						
No	696	77	617.3	124.7	1	0.68
Yes	24	2	21.0	95.1	0.75 (0.19-2.94)	
Artificial rupture of membranes						
No	709	80	628.2	127.4		
Yes	14	0	12.6	0		
Postpartum haemorrhage						
No	717	78	635.9	122.7	1	0.82
Yes	7	1	6.7	149.2	1.24 (0.20-7.76)	

[a]values imputed for variables with missing data except for preterm birth which had a large amount of missing data

Chapter 8: Discussion

8.1 Key Findings

The aim of this thesis was to enhance understanding of the measurement and incidence of maternal peripartum infection. Incidence is the risk or rate of new cases occurring in a population, free of disease at the start of study, over a period of time. As stated at the beginning of this thesis, measurement of maternal peripartum infection incidence therefore requires a clear definition for peripartum infection, a defined population at risk i.e. all women giving birth, free of the infection at the start of labour, plus the ability to follow women and identify all cases until the end of the risk period, in this case 42 days postpartum.

My systematic review of studies measuring maternal peripartum infection and constituent components, highlighted challenges in all aspects of measurement. No studies set out to measure maternal peripartum infection, as defined by WHO. Few studies used a standard definition, and many did not follow women after their delivery admission.

Applying learning from the existing literature, I designed a study to measure peripartum infection in Tanzania. I demonstrate that standard definitions of constituent infections of maternal peripartum infection can be adapted for use in this population, and that postnatal follow-up is feasible using telephone interviews. Both the systematic review, and my Tanzanian study, reveal the ongoing importance of maternal peripartum infection as a complication.

8.2 Measurement of infection

8.2.1 Population

In the systematic review, we excluded 103 (7%) of 1432 articles because they lacked a suitable study population or appropriate denominator. Some of these studies presented infection as a proportion of all complications, rather than a proportion of women giving birth. Others presented infection as a ratio of livebirths, an approach that was also taken by the GLOSS study, published after the systematic review[5]. Logistically, there are advantages to this method, because large numbers of cases can be identified without the expense of recruiting and retaining a study cohort. However, it carries the risk of selection bias because it is not possible to guarantee that the population producing cases of infection is exactly the same as that of livebirths (e.g. women delivering at home may be missed in the denominator of hospital livebirths but still be counted as a case if they present to hospital with infection).

Selection bias was also possible in 31% of studies included in the review because they used poor or unclear strategies for sampling their population.

In my Tanzanian surveillance study, I attempted to reduce selection bias by randomly sampling from a population of women giving birth in two hospitals in Dar es Salam, and identifying infections within this cohort over time. Childbirth is a time when most women are in contact with health services and therefore easy to sample and recruit, as well as being a fixed point in the pregnancy continuum from which to start follow-up.

Generalizability can be affected by using facility-based rather that population-based identification of peripartum women, or by selecting a small number of facilities. In Dar es Salaam, 94% of women deliver in facilities, enhancing generalizability; however, the 2 hospitals may not reflect all facilities in the city.

8.2.2 Infection definition

As described in Chapter 1, there is no consensus on what comprises maternal infection, or how to define it. Global studies vary in the constituent infections measured, and often lack detailed criteria for these constituents, leading to estimates of frequency for broad groups of infection that are incomparable between studies, or over time. This thesis set out to measure maternal peripartum infections, but the systematic review did not identify a single study that precisely met that definition, or that measured all the constituent infections so that these could be combined. In addition, only 41% of studies used a standard definition for infection, leading to a risk of information bias. A substantial proportion of studies, accounting for half of endometritis and wound infection estimates, provided no clear definition at all. Sepsis estimates had the least risk of misclassification, with over half (and four out of five estimates of severe sepsis) meeting a standard definition. Studies using a broader or narrower definition of sepsis reported, on average, a higher or lower risk of disease respectively, demonstrating the importance of using a standard definition to avoid over- or under-estimating disease incidence.

One positive response to this measurement challenge was the development of the new definition of maternal sepsis[27]. This sets up a standard for measuring severe disease with organ dysfunction, although the criteria are not yet established. However, it does not provide a way forward for less severe infection.

In my Tanzanian study, I attempted to address the issue of studies measuring different, broad groups of infection by measuring the constituent infections before combining them as a

group. To reduce misclassification, I used definitions provided by CDC as my standard, adapting them to my study setting, and providing details of the adaptation process and the final criteria used.

8.2.3 Data collection and postnatal follow-up

In the review of methods presented in Chapter 3, half of studies only measured infection during the hospital admission for delivery, potentially leading to a large under-estimate of risk but failing to follow-up after discharge. In my study in Tanzania, only one case of maternal infection (UTI) was extracted from hospital records during the delivery admission, and therefore almost all infection (55 further cases) would have been missed without the further postnatal follow-up. In addition, as length of routine admission varies between countries[279], and discharge will be delayed for women with complications, this approach both affects generalisability and leads to selection bias. Postnatal follow-up, when it occurred, continued for different time periods (from 5-42 days), and used a variety of methods.

Hospital re-admission records were the most frequent source of postnatal data in studies of sepsis. This has logistical advantages over community-based methods and ensures a clinical diagnosis of infection. It is a reasonable approach for a severe condition requiring hospital care, especially in studies drawing on a representative sample of US hospital records, or in settings with universal access to health services. However, studies of re-admission are problematic for: milder disease, where there is the risk of cases being missed due to poor record-keeping (in smaller studies and in some low-resource settings), or if women are admitted to a non-obstetric ward, attend a different facility or fail to attend at all, or die at home before seeking care. The paucity of infection cases extracted from hospital records in my Tanzanian study may be partly a result of poor record-keeping.

Methods for postnatal follow-up, reviewed in Chapter 4, included passive surveillance via multiple, linked routine data sources. This showed potential to provide comprehensive and sustainable information in HICs, but it is less viable for many LMICs because of their weaker IT and data management systems. Active follow-up methods included: return clinic visits by women, home visits by researchers or health workers, postal questionnaires and telephone interviews. All methods had examples of poor retention, especially when employed as part of routine care as opposed to being a part of research, with high risk of selection bias. Requesting women to make return clinic visits in particular disadvantaged women with financial and geographical barriers to accessing healthcare.

Telephone interviews performed comparatively well, achieving coverage above 63% in all studies and over 80% in SSA and HIC studies. In my study in Dar es Salaam, 90% of recruited women were reached for interview at least once during the 28-day follow-up period, slightly higher than other SSA studies[243] and an Indian call-centre[238]. In my Tanzanian study, success at contacting women did not depend on their age, delivery mode or hospital. Among sampled women, 97% had access to a mobile phone, therefore, the study reached 87% of the desired population. It is the first study I am aware of to use telephone interviews to measure postpartum infection, not limited to SSI, and adds positive evidence to the small body of data demonstrating feasibility of telephone surveillance in a LMIC.

Telephone-based methods unavoidably rely on self-reported data. In the systematic review, incidence of endometritis was higher in studies using self-reported data, which could indicate misclassification and over-estimation. Two validation studies exist in SSA for measuring SSI by telephone, compared to subsequent clinical diagnosis of post-caesarean SSI. In one Tanzanian hospital, the telephone questionnaire had 72% sensitivity and 100% specificity[243]. A smaller study of all SSI at a Kenyan hospital produced similar results: 69.6% sensitivity and 100% specificity[264]. There was up to 48 hours delay between the telephone assessment and clinical review which may explain some of the cases in both studies that were missed by telephone. In the Tanzanian validation study, the infections identified by telephone were all superficial, whereas three of the seven infections missed at telephone interview were deep/organ space. In my telephone surveillance, I included symptoms for endometritis within my definition of SSI, which may have captured more of the deeper infections. However, further validity studies are required to support and optimise the use of telephone interviews to measure maternal postnatal infections.

8.3 Infection Incidence and risk factors

8.3.1 Maternal Peripartum Infection

No studies in the systematic review matched the exact WHO definition of maternal peripartum infection or included all the constituent infections. However, if a study used an ICD-9 or -10 code for major puerperal or other puerperal infection I considered it to use a standard definition for maternal peripartum infection. The pooled incidence from high-quality studies meeting this definition was 11 per 1000 (95% CI 3-24). There was no evidence of an association with region.

In my surveillance study, combined maternal postnatal infection, including UTI, was identified in a much higher proportion of women; 59 per 1000 at day 7. I did not report on

maternal peripartum infection in the paper presented in chapter 7, however, it can be calculated as combined chorioamnionitis (none reported in hospital records), wound infection and endometritis. This produces an incidence of 39 per 1000 at day 7, and 49 per 1000 at day 28, both of which are higher than the systematic review. The increase in the incidence risk by day 28 illustrates the importance of the length of follow-up.

There are no global estimates meeting the definition of MPI. The most recent results from the GBD study report an incidence of maternal infection that approximates 85 per 1000, but includes mastitis in the case definition[19]. The GLOSS study detected an incidence of 70.4 per 1000, but this includes infection throughout pregnancy and postpartum[5]. All these results highlight the important ongoing contribution of infection to maternal morbidity, but also illustrate the challenge of comparing results when studies use different definitions.

Greater comparability is possible within the results of constituent infections as described below. Delivery by caesarean section increased the rate of maternal postnatal infection in the Dar es Salaam surveillance study and is well documented as the most important risk factor for postnatal infection in other literature[4, 43, 49, 56, 66, 67]. Reducing this risk depends in part on providing prophylactic antibiotics. Two meta-analyses report a decreased risk of endometritis when this is done shortly before, compared to during or after surgery[271, 280]. One also showed evidence for a reduction in wound infection[271], although the other did not[280]. Timing of antibiotics did not effect UTI[271] or neonatal sepsis[280]. Data collected from hospital case-notes in my surveillance study in Tanzania indicated only 24% of women received pre-operative prophylaxis. A 2021 scoping review found even poorer performance in another Tanzanian study in 2016, with only 2.1% of women reporting pre-incision prophylaxis, and in a Nigerian study reporting optimal antibiotic timing in 16.5% of cases[281]. These findings indicate that there is huge potential to reduce infection by improving the timing of antibiotic prophylaxis.

Besides caesarean delivery, other documented risk factors for infection, including anaemia, diabetes, hypertensive disorders, prolonged rupture of membranes and postpartum haemorrhage[4, 49, 66], showed no evidence for an association in our Tanzanian cohort. However, many of these factors were reported very infrequently, which reduced our power to detect an association. The low prevalence of these conditions also raises questions about both their documentation in the women's case-notes and the quality of data extraction performed for the study. Misclassification of these potential exposures would have biased any estimate of effect towards the null.

8.3.2 Chorioamnionitis

The pooled incidence of chorioamnionitis from high-quality studies in the systematic review was 39 per 1000 (95% CI 18-68). This was the highest pooled incidence of any of the constituent infections in the review. Almost all studies were from North America and Europe. In my surveillance study, we did not collect data on chorioamnionitis from interviews with women, but we did extract data on infection in labour from hospital records. In marked contrast to the review, no cases were found. It is difficult to know if the lack of infection in Tanzania is a true finding, is a result of under-diagnosis by hospital staff, is due to poor documentation in hospital records, or stems from difficulties locating and extracting the data by research nurses.

There are no other global summaries of chorioamnionitis incidence to compare my results to. Earlier research of intra-amniotic infection reported a wide range of 5-100 per 1000 pregnancies, including histological and well as clinical disease and covering any time in pregnancy. The importance of the condition is demonstrated by a 2021 systematic review providing strong evidence for the risk of early and late-onset neonatal sepsis from both clinical and histologic chorioamnionitis, however, evidence for increased risk of maternal sepsis was inconclusive[282]. Given its importance, further studies of incidence using clear diagnostic criteria are required.

8.3.3 Endometritis

The pooled incidence of endometritis from high quality studies in the review was 16 per 1000 (95% CI 9-25). Four studies in SSA that followed women to a maximum of 7 days postnatal had a pooled incidence of 17 per 1000 (95% CI 14-21). Women in my surveillance study had a slightly higher incidence of 19 per 1000 at day 7 (including those with caesarean childbirth), and this increased to 27 per 1000 at day 28, emphasising the importance of longer follow-up. These results are higher than those from GLOSS (11 per 1000 livebirths)[5] and the WHO multi-country study (1 per 1000 puerperal endometritis)[21], both of which measured hospital admissions only, and would have missed infections managed in the community or at other health facilities.

8.3.4 Wound infection

In the systematic review, the incidence of wound infection was 12 per 1000 (95% CI 10-15) in one high-quality study and pooled incidence was 21 per 1000 (95% CI 12-32) from all included studies. Incidence varied with world region, was lowest in North America and

Europe (9 per 1000, 95% CI 3-18), and highest in East and South-East Asia (62 per 1000, 95% CI 24-116). In SSA the pooled incidence was 34 per 1000 (95% CI 1-110). I found a slightly lower incidence in my surveillance study of 28 per 1000 of women at day 28, but it fell within the wide confidence interval of the systematic review.

After caesarean childbirth, incidence of SSI in my study was 96 per 1000 at day 28. A review of caesarean complications in SSA reported a higher pooled incidence of 156 per 1000[161], however, it is difficult to interpret this result because the method used to pool estimates is not described and confidence intervals are not provided. The seven studies contributing data to the review had infection incidences ranging widely, from 73 to 482 per 1000, and five of them had a lower incidence than the pooled average, highlighting large heterogeneity in the results and uncertainty about any pooled average.

8.3.5 Sepsis

The pooled incidence from high-quality studies in the review was 0.5 per 1000 (95% CI 0.3-0.7) for all definitions of sepsis. There was weak evidence that incidence varied with world region, but few studies occurred outside North America and Europe. Sepsis was not specifically measured in my surveillance study. This was partly because definitions of sepsis rely largely on clinical signs that are difficult to measure through self-report. In addition, our questionnaire aimed to capture all cases of maternal peripartum infection, and therefore expected to include any that were further complicated by sepsis. GBD modelling of sepsis in 2017 reported an age-standardised incidence rate of 0.7 per 1000 (95% UI 0.4-1.2) for maternal disorders, which is very close to the results from the review, despite including disease throughout pregnancy and accounting for all world regions[283]. The WHO multi-country study and GLOSS reported much higher incidences, of 4 per 1000[21] and 10.9 per 1000[5] respectively. This may be partly explained by greater representation of LMICs, associated with a higher incidence of sepsis, as well as their use of tertiary hospitals where more sepsis cases will be managed. In addition, GLOSS measured a broader definition than sepsis, including all women meeting near-miss criteria who also had infection.

8.3.6 UTI

UTI was not measured in the systematic review as it is not included in the WHO definition of MPI. However, it is included in many definitions of puerperal infection, including ICD-9 and -10 codes, and shares risk factors with other postnatal infections, in particular caesarean delivery. Many studies of postpartum UTI focus on caesarean delivery and catheterisation.

Two studies in a systematic review both had 60 per 1000 cases of UTI among catheterised women, but much lower incidence in un-catheterised groups[284].

In my surveillance study, the incidence risk of UTI was 32 per 1000 at day 28, 26 per 1000 following vaginal delivery and 55 per 1000 after a caesarean section. Results from a Danish study were very similar to ours, reporting 31 cases per 1000 after vaginal delivery, and 54 per 1000 post-caesarean section[285]. Incidence in the GLOSS study was lower at 19.7 per 1000 livebirths despite including infection throughout pregnancy, however, only hospitalised women were included and most UTIs are mild infections, managed in the community[5].

8.4 Strengths

This thesis grappled with the important but complex, and often confused, topic of maternal infection. It is probably unsurprising that a systematic review of incidence has not been conducted before. Having initially set out to simply measure incidence and risk factors, the nature of the condition led to a more detailed exploration and consideration of measurement and definitions. The field work aimed to apply some of this learning and lead to improvements in future research in the area.

Throughout the thesis I have tried to be clear and transparent about the infections studied, the definitions and criteria applied, and the reason for the choices made. The WHO definition of peripartum infection was broken into its constituent parts and standard surveillance definitions (primarily from CDC) of each infection were adapted for use. These formed part of the quality assessment in the review, enabling only studies meeting the definitions to contribute to the pooled estimates from high-qualities studies. They also informed the comparison of measurement methods between studies. In the telephone surveillance study, the use of standard definitions reduced the risk of misclassification bias. In addition, these definitions allowed results to be compared between the review and the surveillance study, as well as creating opportunities to compare them with other published literature.

The systematic review benefited from a broad search in many databases and included articles in all languages. In throwing the search wide, and screening 31,528 studies, I hoped to avoid missing any relevant data, especially from LMICs. The approach ensured a significant minority (48%) of studies were from regions outside North America and Europe. Inclusion of sufficient data from LMICs is not only necessary to obtain valid regional and globally estimates of infection but contributes to the understanding of how infection is being measured in different geographical and socio-economic settings around the world.

The Tanzania surveillance study demonstrated the feasibility of following a cohort of postnatal women for a specified time period using telephone interviews. Over a short study period (3 months) and at low cost, nearly 900 women were recruited and 90% were followed to at least day-7. Utilising the constituent infection criteria, I attempted to minimise self-reporting bias by asking closed, symptom-specific questions and only classifying women with infection at the analysis stage.

8.5 Limitations

The choice of component infections changed during the course of the thesis. UTI was not measured in the systematic review because it is not part of the WHO definition of maternal peripartum infection. However, many other studies of postnatal infection, and ICD-10 codes for puerperal infection, include UTI, and the decision was made to measure it in the surveillance study. It could be argued that the systematic review would have been more informative if UTI was included because it is a frequent cause of postnatal infection, and the risk is increased by factors related to childbirth.

Chorioamnionitis, which was in the systematic review, and is part of WHO's MPI definition, was not specifically measured in the telephone surveillance, firstly because the study focussed on postnatal infection, and secondly because diagnosis of chorioamnionitis is based on physical signs which could not be measured by telephone interview. Given the high incidence of chorioamnionitis estimated in the systematic review, this omission could be important for an overall estimate of peripartum infection. However, data extracted from women's hospital records only recorded one case of infection (UTI) during pregnancy. Although the literature review and surveillance study did not measure exactly the same group of infections, the estimates for each component infection could still be compared.

While attempts were made to minimise bias in the Tanzanian surveillance study, there remained limitations. Selection bias could have occurred for a number of reasons. By default, the study excluded women without access to a telephone. Although this only accounted for 3% of women sampled, they are likely to have had a lower SES than the recruited women, and may have a higher risk of infection due to under-nutrition, or poorer access to water, sanitation and hygiene or healthcare services. However, women with higher SES may also carry higher risks of infection related to obesity and diabetes. At the request of the hospitals involved, women admitted to ICU were also excluded from the study, potentially leading to an under-estimate of infection because sepsis is a possible reason for admission. However, only one woman was excluded for this reason, so the effect on the results is negligible.

In the surveillance study, infection was determined by self-reported symptoms with the potential for information bias. I aimed to assess validity by comparing cases based on self-reported symptoms with hospital diagnoses. However, only one case of maternal infection was extracted from the hospital case-notes before discharge, and most women who attended a health facility postnatally were unable to tell us their clinical diagnosis, so this was not possible. Therefore, this method of surveillance still requires a proper validation study.

The study followed women to 28 days, rather than the full 42 days specified by the WHO definition of peripartum infection. This was for pragmatic reasons, as it allowed an assessment of newborn infection at the end of the neonatal period, and reduced the overall length of the study, thereby minimising costs. In addition, it is close to the 30-day cut-off for SSI. Moreover, the vast majority of maternal postnatal infections occur before 28 days, making it unlikely that many cases of infection were missed. However, ideally a further telephone call would be made at 42 days.

The population of Dar es Salaam has a higher SES and higher phone ownership than other regions of the country and tertiary hospitals are expected to provide the highest level of healthcare. Therefore, infection incidence risk may be lower than for the population overall. However, rates of caesarean delivery are higher in Dar es Salaam[84], and tertiary hospitals will also receive women with other medical complications, both of which can increase the risk of infection. It is therefore not possible to generalise either the infection incidence results or the feasibility of telephone interviews to the whole country or region. However, the findings are expected to be similar in other urban settings in the region.

The surveillance study was not powered for assessing risk factors or consequences occurring at a low frequency. However, no evidence of association was found for a number of expected risk factors, including diabetes, hypertensive disorders of pregnancy, premature rupture of membranes and postpartum haemorrhage[4, 49, 66]. A larger study would be beneficial to explore rare exposures and outcomes, and any effect of early infection on maternal mood and function.

8.6 How to improve measurement of maternal infection

8.6.1 What to measure

The results of this thesis raise the question of how to improve measurement of maternal infection, and specifically peripartum infection. In addressing this, it is important to

remember that infection is not one condition, but a range of diseases, and that measurement of infection is conducted for a variety of reasons which bring with them different priorities. The size of the study, the accuracy of measurement, and the infection studied will all differ, depending on the purpose.

If an estimate of infection burden is required for advocacy purposes, measurement will focus on reaching a wide population, and using a broad definition, for instance infection of any aetiology, occurring throughout pregnancy and postpartum. The alternative is to capture women with most severe disease, i.e. deaths, near-miss cases, or sepsis, to indicate the seriousness of the problem and the potential to make a big impact. Ease of measurement on a big scale is the priority, for example using existing medical records, or a hospital-based study, while accuracy of measurement and reducing risk of bias is of less consequence.

In contrast, if the aim is to understand trends and differentials in the frequency of infection and to determine risk factors of infection, then measurement accuracy and low risk of bias is the priority. Focusing on a single infection, or group of infections with shared risk factors, is beneficial. The same is true when comparing infection incidence between facilities or regions, or over time, in order to inform local health prioritisation, or provide feedback to practitioners to improve preventive behaviours. Studies should be large enough to test associations, but do not need to be extensive. Studying common infections, as opposed to rare disease such as sepsis, will make it easier to increase the power of the study. A cohort of women should be followed for a specified time, using a clear infection definition and community follow-up. Case-control designs can be used to assess risk factors for rare infections, but are not suited to estimating incidence risk.

Maternal peripartum infections, or postnatal infections in neonates, are both an important and useful group to study in relation to risk factors, and for comparing facilities and regions. Peripartum infections are common, they share risk factors including potential iatrogenic causes, and there are opportunities for infection prevention during birth, as well as facility birth providing an easy opening to recruit women to a cohort. Furthermore, the postnatal period is of prime importance to the newborn, and offers the chance to measure outcomes for both mother and baby and assess shared risk factors.

Based on the results of this thesis, I would argue that maternal peripartum infection should be broken into its constituent infections to both ensure standard criteria are used for measurement, and to allow comparability between studies that measure different

combinations of these constituents. Endometritis and caesarean SSI are the key infections to measure as both begin after birth, providing a clear start for follow-up, and their risk can be increased by the actions of birth attendants. Chorioamnionitis had the highest incidence of all constituent infections in my systematic review and therefore warrants inclusion, but requires different measurement methods because it occurs at a different time (during labour), diagnosis needs clinical and/or histological input, and risk factors are diverse. I would consider it a lower priority if research budgets were limited. UTI is not strictly a peripartum infection, or a direct maternal infection, however, it is easy to measure by self-report, occurs frequently, shares risk factors with the other peripartum infections, and can be iatrogenic. I would therefore advocate for its inclusion where possible.

8.6.2 Infection definitions

It is evident that improved measurement of maternal infection requires the use of standard definitions with clear criteria. I primarily used CDC definitions as my standard, however, these were developed for a high-income context, and some of the criteria, particularly the laboratory investigations, cannot be measured within many low-resource settings. My surveillance study provides an example of adapting these definitions to a LIC, creating a set of criteria that could be measured through telephone interviews with women. To improve infection measurement, validated surveillance definitions need to be produced for key constituent infections (endometritis, SSI, UTI and chorioamnionitis), which can be used across income-settings.

8.6.3 Postnatal follow-up

Maternal peripartum infection should be measured within a cohort of women over time, using beginning of labour as the start point. However, women are often not in contact with a health professional at the start of labour, so it can be difficult to determine the exact start-point and whether a woman presenting with chorioamnionitis has an MPI, or developed the infection before labour. Postnatal infection has the advantage of birth as a clear starting point, shared with the newborn. In both cases, community follow-up is necessary, preferably until 42 days postpartum.

In settings with good medical record-keeping, and systems to link data, postnatal infection data can be extracted from a variety of datasets that comprehensively cover women's contact with health providers. However, in most contexts, where this is not an option, direct contact needs to be made with the women. This thesis offers further evidence for the benefit of telephone interviews to conduct this follow-up. As access to mobile telephones continues

to rise globally, this method can be increasingly widely used. At least three contact points are needed: Day 7 or earlier to capture the highest-risk period; day 28-30 to mark the end of the neonatal period and the end of the measurement period for healthcare associated SSI; and the end of follow-up at day 42, the end of the post-partum period. To be most effective, there must be multiple attempted calls, at different times over several days, and women should be asked to provide more than one telephone number.

8.7 Future research Implications

8.7.1 Infection Measurement

As argued above, maternal peripartum infection, and specifically endometritis and caesarean SSI, are key maternal infections that should be measured in studies that compare maternal infection incidence between settings or over time. Even if a broader group of infections is studied, researchers need to measure and report separately on these constituent infections to allow comparability with other studies.

Research is needed to produce international, standard definitions and diagnostic criteria, prioritising endometritis and caesarean SSI, which can be used in low-resource settings without access to laboratory tests. Validation studies are required, comparing them with existing definitions, and examining them against key outcomes such as admission to hospital and severe complications including sepsis. Research funders and journal reviewers should request these standard definitions be applied to ensure their use.

In addition to validating infection definitions for LMICs, the measurement methods also need validating, including the use of self-report and telephone interviews. Two small SSA studies have tested the validity of telephone interviews to measure SSI, but larger studies including other peripartum infections are required. Qualitative research could also be valuable to improve the sensitivity of the questionnaire, for example by exploring the words women use themselves to describe symptoms, as well as their experience of postnatal symptoms such as abdominal pain and vaginal discharge and their understanding of when these are abnormal.

Telephone methods were successful in my Tanzanian study, but still only reached 85% of women at day 28, therefore, further effort is needed to improve coverage. Qualitative studies can explore telephone ownership, access and usage, as well as women's availability and barriers to telephone interviews. Women frequently reported that they missed calls because their telephone battery was not charged, and it is worth assessing simple actions to

address this, such as providing participants with a specific day and time-period for the interview, or giving telephone units to enable a participant to call back if they miss a call. Improving the coverage and usefulness of telephone methods has implications, not only for measuring postnatal infection but also for research into other postnatal complications such as postnatal depression or urinary incontinence, and more broadly for conducting simple surveys with a large population at relatively low-cost.

8.7.2 Infection Prevention

This thesis provides evidence of a high incidence of maternal peripartum infection and provides further evidence for the increased risk of postnatal infection associated with caesarean delivery. In addition, the study in Tanzania reported low rates of pre-operative antibiotics prophylaxis, one of the key interventions for reducing this risk. Implementation research to improve timing and duration of antibiotic prophylaxis has been conducted with mixed results[286-289]. A literature review suggests a multidisciplinary approach and individualised performance data can improve quality[290] however, more research is still required. This will include qualitative research to understand existing beliefs about effectiveness and barriers to implementation, as well as studies to explore behaviour change interventions.

As well as antibiotic prophylaxis, to reduce the risk from caesarean section the WHO recommends vaginal cleansing with povidone-iodine or chlorhexidine gluconate, and skin preparation with alcohol-based chlorhexidine gluconate[291]. Interestingly, a large trial in seven LMICs was recently published showing no benefit of alcohol chlorhexidine skin preparation compared to the cheaper povidone-iodine for all clean-contaminated surgical procedures, half of which were obstetric[292]. This demonstrates the importance of not assuming research findings can be generalised to different regions and settings, and highlights the need for further research into prevention of maternal infection to be conducted in LMICs.

The most common infection identified in the Tanzanian study was UTI and, similar to previous studies, this was associated with caesarean delivery[285]. Previous research has not shown a benefit from optimising timing of antibiotic prophylaxis[271], but there is some evidence from a systematic review that avoiding use of urinary catheter during caesarean section can reduce infection[284]. Larger, high-quality studies are required to support this finding, followed by implementation studies if a change in practice is recommended.

8.8 Practice and Policy implications

8.8.1 Routine Infection Surveillance

The feasibility of postnatal telephone surveillance is not only of benefit to researchers, but can be used at hospital and district level to conduct routine infection surveillance as a way to inform and improve local performance, and reduce infection rates. Previous studies have shown reduced infection over time with the implementation of routine surveillance[260, 261], and feedback is well-recognised as a tool within behaviour change strategies. I would encourage the introduction of regular, continuous or intermittent, telephone surveillance, following childbirth and/or after a surgical procedure, to inform clinical leaders and hospital mangers of the frequency of infection, how this is changing over time and how it compares to other facilities. Changes in policy to prevent infections can be easily monitored within this ongoing surveillance, including interventions to optimise antibiotic use.

8.8.2 Infection Prevention

As mentioned above, known infection prevention interventions are not being implemented universally. In addition to pre-incision prophylactic antibiotics for caesarean-delivery mentioned already, WHO also recommends antibiotic prophylaxis for operative vaginal delivery[291], pre-term prelabour rupture of membranes (PPROM), manual removal of the placenta, and following a third- or fourth-degree perineal tear[39]. In our Tanzanian study there were very few cases of operative vaginal delivery or PROM. We did not enquire about manual removal of the placenta or attempt to distinguish the degree of perineal tears. However, at one of the two study hospitals, postnatal antibiotic prophylaxis was given routinely to virtually all women. Antibiotic prophylaxis is not indicated for routine vaginal delivery[39].

Part of the answer to improving antibiotic stewardship and infection prevention is through implementation research, however, this is only beneficial if it informs policy and practice. National guidelines need to reflect the international recommendations and be disseminated to all stakeholders using methods that inform and engage. Change in practice should not rely on education alone, but use lessons from implementation research and behaviour-change studies. Routine infection surveillance, as described above, can expose the need for change, as well as providing feedback as part of a behaviour change strategy.

8.8.3 Postnatal Care

It was not the objective of this thesis to explore the use of telephone methods in the provision of routine postnatal care. However, the high coverage achieved by the telephone

surveillance study raises this possibility. Greater use of telemedicine in both ante-and post-natal care, including the use of video calls, has been of particular interest during the COVID pandemic. It was viewed by many care providers as an important alternative to in-person consultations, although concerns were raised about quality of care, elements of physical examination that will be missed, and the potential for widening inequalities[265]. However, current attendance for maternal postnatal review is low, ranging from 25% to 41% at one week in a study of four SSA countries[293]. Alternative or additional care models are worth exploring to support the large proportion of women who at present receive no postnatal care.

Telephone calls can be a means to assess women for signs of illness, including infection and depression. They can also offer an opportunity to address mothers' questions and concerns. A recent meta-synthesis of qualitative studies of postnatal women found women want guidance and advice from health professionals on a range of topics including baby development, vaccinations, practical care-giving, breastfeeding and hygiene[294]. A small Lebanese study reported on the feasibility of, and satisfaction with a postpartum telephone hotline. In the four months postpartum, 24% of women called at least once, the majority in the first four weeks, and primarily with questions about breastfeeding and routine infant care. Of the women who called, 60% did so more than once, reflecting satisfaction and confidence in the service.

8.9 Final Conclusions

Measurement of maternal infection requires greater consistency and accuracy. Maternal peripartum infections and postnatal infections are important and useful conditions to measure. This is best done by studying their constituent infections, especially endometritis and caesarean SSI. However, standard definitions and criteria that can be applied across income settings need to be agreed and validated. These infections should be measured within cohorts of women, recruited at the start of labour, or at birth, and followed until 42 days postpartum. Telephone methods offer a feasible and efficient means to conduct this community follow-up. Concurrent observation of the newborn should be encouraged.

Telephone methods warrant further research and use for routine infection surveillance, and in the provision of postnatal care.

Maternal peripartum infections remain unacceptably high, and greater efforts are needed, both by researchers and practitioners, to improve infection prevention behaviours, and particularly to implement optimal antibiotic prophylaxis before caesarean section.

References

1. Tunçalp Ö, Were W, MacLennan C, Oladapo O, Gülmezoglu A, Bahl R, et al. Quality of care for pregnant women and newborns—the WHO vision. BJOG. 2015;122(8):1045.
2. The Global Maternal and Neonatal Sepsis Initiative Working Group. The Global Maternal and Neonatal Sepsis Initiative: a call for collaboration and action by 2030. The Lancet Global Health. 2017;5(4):e390-e1.
3. Kramer H, Schutte JM, Zwart JJ, Schuitemaker NW, Steegers EA, Van Roosmalen J. Maternal mortality and severe morbidity from sepsis in the Netherlands. Acta obstetricia et gynecologica Scandinavica. 2009;88(6):647-53.
4. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLOS One. 2013;8(7):e67175.
5. Bonet M, Brizuela V, Abalos E, Cuesta C, Baguiya A, Chamillard M, et al. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. The Lancet Global Health. 2020;8(5):e661-e71.
6. Dolea C, Stein C. Global burden of maternal sepsis in the year 2000. Evidence and information for policy. Geneva: World Health Organisation; 2003.
7. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014;2(6):e323-e33.
8. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1736-88.
9. Graham W, Woodd S, Byass P, Filippi V, Gon G, Virgo S, et al. Diversity and divergence: the dynamic burden of poor maternal health. The Lancet. 2016;388(10056):2164-75.
10. Hensley MK, Bauer ME, Admon LK, Prescott HC. Incidence of maternal sepsis and sepsis-related maternal deaths in the United States. Jama. 2019;322(9):890-2.
11. Knight M BK, Tuffnell D, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2020.
12. Kassebaum NJ, Barber RM, Bhutta ZA, Dandona L, Gething PW, Hay SI, et al. Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1775.
13. Angus DC. The lingering consequences of sepsis: a hidden public health disaster? Jama. 2010;304(16):1833-4.
14. Hussein J, Walker L. Puerperal sepsis in low and middle income settings: past, present and future. Maternal and Infant Deaths: Chasing Millennium Development Goals. 2010;4:131-47.
15. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? The Lancet. 2005;365(9462):891-900.
16. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS medicine. 2013;10(8):e1001502.

17. Yokoe DS, Christiansen CL, Johnson R, Sands KE, Livingston J, Shtatland ES, et al. Epidemiology of and surveillance for postpartum infections. Emerging infectious diseases. 2001;7(5):837.
18. Hofmeyr GJ, Smaill FM. Antibiotic prophylaxis for cesarean section. Cochrane Database of systematic reviews. 2002;3.
19. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1789-858.
20. United Nations Department of Economic and Social Affairs. World Population Prospects 2019: United Nations; 2019 [cited 2021 21/07/2021]. Standard Projections, Fertility Data]. Available from: https://population.un.org/wpp/Download/Standard/Fertility/.
21. Souza JP, Gülmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. The Lancet. 2013;381(9879):1747-55.
22. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. The Lancet infectious diseases. 2009;9(7):428-38.
23. Prual A, Bouvier-Colle M-H, Bernis Ld, Breart G. Severe maternal morbidity from direct obstetric causes in West Africa: incidence and case fatality rates. Bulletin of the World Health Organization. 2000;78(5):593-602.
24. World Health Organization. The WHO application of ICD-10 to deaths during pregnancy, childbirth and puerperium: ICD MM. Geneva; 2012.
25. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Medicine. 2003;29(4):530-8.
26. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801-10.
27. Bonet M, Pileggi VN, Rijken MJ, Coomarasamy A, Lissauer D, Souza JP, et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health. 2017;14(1):67.
28. Abir G, Akdagli S, Butwick A, Carvalho B. Clinical and microbiological features of maternal sepsis: a retrospective study. International journal of obstetric anesthesia. 2017;29:26-33.
29. Bauer ME, Bauer ST, Rajala B, MacEachern MP, Polley LS, Childers D, et al. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and meta-analysis. Obstetrics & Gynecology. 2014;124(3):535-41.
30. Turner MJ. Maternal sepsis is an evolving challenge. International Journal of Gynecology & Obstetrics. 2019;146(1):39-42.
31. Aarvold AB, Ryan HM, Magee LA, Von Dadelszen P, Fjell C, Walley KR. Multiple organ dysfunction score is superior to the obstetric-specific sepsis in obstetrics score in predicting mortality in septic obstetric patients. Critical care medicine. 2017;45(1):e49.
32. Jain S, Guleria K, Suneja A, Vaid NB, Ahuja S. Use of the Sequential Organ Failure Assessment score for evaluating outcome among obstetric patients admitted to the intensive care unit. International Journal of Gynecology & Obstetrics. 2016;132(3):332-6.
33. Oliveira Neto AF, Parpinelli MA, Costa ML, Souza RT, Ribeiro do Valle C, Cecatti JG. Exploring epidemiological aspects, distribution of WHO maternal near Miss Criteria, and

organ dysfunction defined by SOFA in cases of severe maternal outcome admitted to obstetric ICU: a cross-sectional study. BioMed research international. 2018;2018.
34. Blauvelt CA, Nguyen KC, Gaw SL. 1117 Do severity scoring systems for sepsis predict obstetric and neonatal outcomes? American Journal of Obstetrics & Gynecology. 2021;224(2):S688.
35. Cagino SG, Burke A, Letner D, Leizer J, Zelig C. 59: qSOFA: Modifications for identifying sepsis in obstetrical patients. American Journal of Obstetrics & Gynecology. 2020;222(1):S50-S1.
36. World Health Organization. ICD-10-CM Official Guidelines for Coding and Reporting FY2019. 2018.
37. Puerperal sepsis. Collins Dictionary of Medicine2004, 2005.
38. World Health Organization. The prevention and management of puerperal infections: report of a technical working group. Geneva; 1992.
39. World Health Organization. WHO recommendations for prevention and treatment of maternal peripartum infections. Geneva; 2015.
40. Rothman KJ. Epidemiology: an introduction: Oxford university press; 2012.
41. Ps R, Verma S, Rai L, Kumar P, Pai MV, Shetty J. “Near miss” obstetric events and maternal deaths in a tertiary care hospital: an audit. Journal of pregnancy. 2013;2013.
42. Bianco A, Roccia S, Nobile CG, Pileggi C, Pavia M. Postdischarge surveillance following delivery: the incidence of infections and associated factors. American Journal of Infection Control. 2013;41(6):549-53.
43. Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M. Severe maternal sepsis in the UK, 2011–2012: a national case-control study. PLoS medicine. 2014;11(7):e1001672.
44. Meis JF, Muytjens HL, Van Den Berg PP, Voss A, Melchers WJ. Analysis of an outbreak of puerperal fever due to group A streptococci by random amplified polymorphic DNA fingerprinting. Infectious diseases in obstetrics and gynecology. 1997;5(3):232-6.
45. Thewessen E, Bontekoe-Hoornstra J, Smelting-Nagtzaam A, Bilkert-Mooiman M, Admiraal J. Een cluster van patiënten met kraamvrouwenkoorts in Gouda; een hernieuwde les van Semmelweis. Nederlands tijdschrift voor geneeskunde. 1999;143(33):1700-5.
46. Rottenstreich A, Benenson S, Levin G, Kleinstern G, Moses A, Amit S. Risk factors, clinical course and outcomes of pregnancy-related group A streptococcal infections: retrospective 13-year cohort study. Clinical Microbiology and Infection. 2019;25(2):251. e1-. e4.
47. Cannon JW, Bowen AC. An update on the burden of group A streptococcal diseases in Australia and vaccine development. The Medical Journal of Australia. 2021;215(1):27.
48. Wright CM, Moorin R, Pearson G, Dyer JR, Carapetis JR, Manning L. Increasing incidence of invasive group A streptococcal disease in Western Australia, particularly among Indigenous people. Medical Journal of Australia. 2021;215(1):36-41.
49. Foeller ME, Sie L, Foeller TM, Girsen AI, Carmichael SL, Lyell DJ, et al. Risk Factors for Maternal Readmission with Sepsis. American journal of perinatology. 2020;37(5):453.
50. Wilkie GL, Prabhu M, Ona S, Easter SR, Tuomala RE, Riley LE, et al. Microbiology and antibiotic resistance in peripartum bacteremia. Obstetrics & Gynecology. 2019;133(2):269-75.
51. Admas A, Gelaw B, Worku A, Melese A. Proportion of bacterial isolates, their antimicrobial susceptibility profile and factors associated with puerperal sepsis among post-partum/aborted women at a referral Hospital in Bahir Dar, Northwest Ethiopia. Antimicrobial Resistance & Infection Control. 2020;9(1):1-10.
52. Haldar T, Rit K, Pal N. A study of aerobic and anaerobic bacterial profile along with In vitro antibiotic susceptibility pattern in cases of puerperal, postabortion sepsis in a Tertiary Care Hospital. CHRISMED Journal of Health and Research. 2020;7(3):182.

53. Ifunanya NJ, Nobert OC, Chukwu IC, Chibuzor UD-P, Blessing O, Okwuchukwu OV. Pattern and determinants of puerperal pyrexia among postnatal women at the Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Southeast, Nigeria. Education. 2019;27(32):33-8.
54. Ingole KV, Shendre PP. Study of bacterial isolates in puerperal sepsis and its antibiotic sensitivity pattern. J Med Sci Clin Res. 2017;5:18563-8.
55. Kiponza R, Balandya B, Majigo MV, Matee M. Laboratory confirmed puerperal sepsis in a national referral hospital in Tanzania: etiological agents and their susceptibility to commonly prescribed antibiotics. BMC infectious diseases. 2019;19(1):1-7.
56. Maharaj D. Puerperal pyrexia: a review. Part I. Obstetrical & gynecological survey. 2007;62(6):393-9.
57. Eschenbach DA, Rosene K, Tompkins L, Watkins H, Gravett MG. Endometrial cultures obtained by a triple-lumen method from afebrile and febrile postpartum women. Journal of Infectious Diseases. 1986;153(6):1038-45.
58. Gibbs RS, O'Dell TN, MacGregor RR, Schwarz RH, Morton H. Puerperal endometritis: a prospective microbiologic study. American journal of obstetrics and gynecology. 1975;121(7):919-25.
59. Sherman D, Lurie S, Betzer M, Pinhasi Y, Arieli S, Boldur I. Uterine flora at cesarean and its relationship to postpartum endometritis. Obstetrics & Gynecology. 1999;94(5):787-91.
60. Bebell LM, Ngonzi J, Bazira J, Fajardo Y, Boatin AA, Siedner MJ, et al. Antimicrobial-resistant infections among postpartum women at a Ugandan referral hospital. PloS one. 2017;12(4):e0175456.
61. Ahmed S, Kawaguchiya M, Ghosh S, Paul SK, Urushibara N, Mahmud C, et al. Drug resistance and molecular epidemiology of aerobic bacteria isolated from puerperal infections in Bangladesh. Microbial Drug Resistance. 2015;21(3):297-306.
62. Sáez-López E, Guiral E, Fernández-Orth D, Villanueva S, Goncé A, López M, et al. Vaginal versus obstetric infection Escherichia coli isolates among pregnant women: antimicrobial resistance and genetic virulence profile. PloS one. 2016;11(1):e0146531.
63. United Nations. The sustainable development goals report 2021. United Nations, Department of Economic and Social Affairs; 2021.
64. Betrán AP, Ye J, Moller A-B, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PloS one. 2016;11(2):e0148343.
65. Mackeen AD, Packard RE, Ota E, Speer L. Antibiotic regimens for postpartum endometritis. Cochrane Database of Systematic Reviews. 2015(2).
66. Gravett CA, Gravett MG, Martin ET, Bernson JD, Khan S, Boyle DS, et al. Serious and life-threatening pregnancy-related infections: opportunities to reduce the global burden. PLoS Med. 2012;9(10):e1001324.
67. Dahlke JD, Mendez-Figueroa H, Rouse DJ, Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery: an updated systematic review. American journal of obstetrics and gynecology. 2013;209(4):294-306.
68. Elliyas S, Gaind R, Kanwal SK, Singh S, Arya S. Bacterial Colonization of Vagina in Indian Women During Labor and Its Association With Puerperal and Neonatal Sepsis: A Tertiary Hospital Study. Cureus. 2021;13(3).
69. Dare F, Bako A, Ezechi O. Puerperal sepsis: a preventable post-partum complication. Tropical Doctor. 1998;28(2):92-5.
70. Korang SK, Safi S, Nava C, Gordon A, Gupta M, Greisen G, et al. Antibiotic regimens for early-onset neonatal sepsis. Cochrane Database of Systematic Reviews. 2021(5).
71. Wang Q, Peng G, Gan L, Sun J, Wen D, Huang S, et al. Risk Factors of Early-Onset Neonatal Sepsis A Systematic Review and Meta-Analysis. 2021.

72. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bulletin of the World Health Organization. 2015;93(1):19-28.
73. Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Archives of Disease in Childhood. 2021.
74. Chaurasia S, Sivanandan S, Agarwal R, Ellis S, Sharland M, Sankar MJ. Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance. bmj. 2019;364.
75. Seale AC, Blencowe H, Manu AA, Nair H, Bahl R, Qazi SA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. The Lancet infectious diseases. 2014;14(8):731-41.
76. Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ global health. 2018;3(1):e000347.
77. Seale AC, Blencowe H, Zaidi A, Ganatra H, Syed S, Engmann C, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. Pediatric research. 2013;74(1):73-85.
78. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al. Every Newborn: progress, priorities, and potential beyond survival. The Lancet. 2014;384(9938):189-205.
79. McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. Pediatric research. 2020;88(1):14-26.
80. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. The Lancet. 2008;371(9607):135-42.
81. Zelellw DA, Dessie G, Worku Mengesha E, Balew Shiferaw M, Mela Merhaba M, Emishaw S. A Systemic Review and Meta-analysis of the Leading Pathogens Causing Neonatal Sepsis in Developing Countries. BioMed Research International. 2021;2021.
82. Okomo U, Akpalu EN, Le Doare K, Roca A, Cousens S, Jarde A, et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. The Lancet Infectious diseases. 2019;19(11):1219-34.
83. Sands K, Carvalho MJ, Portal E, Thomson K, Dyer C, Akpulu C, et al. Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. Nature microbiology. 2021;6(4):512-23.
84. Ministry of Health Community Development Gender Elderly Children - MoHCDGEC/Tanzania Mainland, Ministry of Health - MoH/Zanzibar, National Bureau of Statistics - NBS/Tanzania, Office of Chief Government Statistician - OCGS/Zanzibar, ICF. Tanzania Demographic and Health Survey and Malaria Indicator Survey 2015-2016. Dar es Salaam, Tanzania: MoHCDGEC, MoH, NBS, OCGS, and ICF; 2016.
85. Woodd SL, Montoya A, Barreix M, Pi L, Calvert C, Rehman AM, et al. Incidence of maternal peripartum infection: A systematic review and meta-analysis. PLoS Medicine. 2019;16(12).
86. Gon G, Leite A, Calvert C, Woodd S, Graham WJ, Filippi V. The frequency of maternal morbidity: A systematic review of systematic reviews. International Journal of Gynecology & Obstetrics. 2018;141:20-38.
87. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. International Journal of Evidence-based Healthcare. 2015;13(3):147-53.

88. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10.
89. Alkaline Software. ICD9Data.com: Alkaline Software; 2015 [Available from: http://www.icd9data.com/.
90. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision 2016 [Available from: https://icd.who.int/browse10/2016/en.
91. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clinics in Perinatology. 2010;37(2):339-54.
92. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control. 2008;36(5):309-32.
93. United Nations. SDG Indicators 2017 [Available from: https://unstats.un.org/sdgs/indicators/regional-groups/.
94. Schwarzer G. meta: An R package for meta-analysis. R News. 2007;7(3):40-5.
95. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010;36(3):1-48.
96. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics. 1950:607-11.
97. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013:jech-2013-203104.
98. Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? Journal of Statistical Planning and Inference. 2010;140(4):961-70.
99. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342:d549.
100. Chen L, Liu J, Kang Y, Liu J, Sufeng H. [Relationship between pre-pregnant body mass index and pregnancy growth with maternal and neonatal outcomes]. Chongqing Medicine. 2014;43(10):1178-80.
101. Dong L. [Management and Monitoring Measure of Nosocomial Infection in Cesarean Section, Normal Delivery, Domiciliary Delivery Integral Delivery Room]. Chinese Journal of Nosocomiology. 2009;19(16):39.
102. Dong L, Wang G. [Effect of hand washing method to maternity and infant]. Chinese Journal of Nosocomiology. 2010;20(15):2257-9.
103. Liu H, Cui Y. [Relationship between body mass index of pregnant women and postpartum incision infection]. Maternal and Child Health Care of China. 2010;25(18):2485-6.
104. Wang X, Yu X, Qian X. [Postpartum intrauterine infection: clinical features and preventive measures]. Chinese Journal of Nosocomiology. 2010;20(14):2050-1.
105. Jin Z, Chi X, Teng W, Wang X, Xu Q, Wang P, et al. [Sex hormone-binding globulin of gestational diabetes mellitus pregnant women with well-controlled glucose and pregnancy outcomes]. Zhonghua fu Chan ke za zhi. 2011;46(6):422-6.
106. Boccardo J, Manzur A, Duarte N, Yanzon C, Mazzanti A, Paparotti L, et al. [Puerperal endometritis in our setting]. Actual SIDA Infectol. 2013;21(80):48-52.
107. Okumura JA, Maticorena DA, Tejeda JE, Mayta-Tristán P. [Teenage pregnancy as a risk factor for obstetric and perinatal complications at a hospital in Lima, Peru]. Revista Brasileira de Saúde Materno Infantil. 2014;14(4):383-92.
108. Sanabria Fromherz ZE, Fernández Arenas C. [Pathologic behavior of puerperium] Revista Cubana de Obstetrícia y Ginecologia. 2011;37(3):330-40.

109. Sánchez JMB, Serrano YP, Soler JRM. [Advanced maternal age as a conducive element in obstetric complications and birth]. Revista de Ciencias Médicas de Pinar del Río. 2015;19(5):789-802.
110. Benincasa BC, Walker C, Cioba C, Rosa CCdS, Martins DE, Oliveira EDAd, et al. [Rates of infection related to cesarean and vaginal delivery at HCPA]. Revista HCPA Porto Alegre. 2012;32(1):5-9.
111. Luz AG, Tiago DB, Silva JCGd, Amaral E. [Severe maternal morbidity at a local reference university hospital in Campinas, São Paulo, Brazil]. Revista Brasileira de Ginecologia e Obstetrícia. 2008;30(6):281-6.
112. Péret FJA, Melo VH, Paula LBd, Andrade BAMd, Pinto JA. [Puerperal morbidity in HIV-infected and non-infected women]. Revista Brasileira de Ginecologia e Obstetricia. 2007;29(5):260-6.
113. Petter CE, Farret TCF, de Souza Scherer J, Antonello VS. [Factors related to surgical site infections after obstetric procedures]. Scientia Medica. 2013;23(1):5.
114. Ben SH, Khoudayer H, Ben HZ, Masmoudi A, Bouguerra B, Sfar R. [Severe maternal morbidity]. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction. 2007;36(7):694-8.
115. Mayi-Tsonga S, Meyé J-F, Tagne A, Ndombi I, Diallo T, Oksana L, et al. [Audit of the severe obstetrical morbidity (near miss) in Gabon]. Cahiers d'Etudes et de Recherches Francophones/Santé. 2007;17(2):111-5.
116. Saizonou J, Ouédraogo L, Paraiso MN, Ayélo P, Kpozèhouen A, Daraté R, et al. [Epidemiology and management of intrapartum infections in the maternity ward of Ouémé-Plateau county hospital in Benin]. The Pan African Medical Journal. 2014;17:89-.
117. Ivanov S, Tzvetkov K, Kovachev E, Staneva D, Nikolov D. [Puerperal infections after Cesarean section and after a natural childbirth]. Akusherstvo i Ginekologiia. 2014;53:25-8.
118. Marić T, Tomić V, Darko K. [Puerperal complications in nulliparous women delivered by section caesarean: pair study]. Medicinski Arhiv. 2006;60(4):246-50.
119. Dimitriu G. [Clinical statistical study on puerperal sepsis risk factors]. Revista Medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2010;114(1):195-8.
120. Abramovici A, Szychowski JM, Biggio JR, Sakawi Y, Andrews WW, Tita AT. Epidural use and clinical chorioamnionitis among women who delivered vaginally. American Journal of Perinatology. 2014;31(11):1009-14.
121. Jokhio AH, Winter HR, Cheng KK. An intervention involving traditional birth attendants and perinatal and maternal mortality in Pakistan. New England Journal of Medicine. 2005;352(20):2091-9.
122. Kovavisarach E, Jirasettasiri P. Randomised controlled trial of perineal shaving versus hair cutting in parturients on admission in labor. J Med Assoc Thai. 2005;88(9):1167.
123. Bakr AF, Karkour T. Effect of predelivery vaginal antisepsis on maternal and neonatal morbidity and mortality in Egypt. Journal of Women's Health. 2005;14(6):496-501.
124. Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A, Group MB. 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 & Gynaecology. 2005;112(1):89-96.
125. Chongsuvivatwong V, Bachtiar H, Chowdhury ME, Fernando S, Suwanrath C, Kor-anantakul O, et al. Maternal and fetal mortality and complications associated with cesarean section deliveries in teaching hospitals in Asia. Journal of Obstetrics and Gynaecology Research. 2010;36(1):45-51.
126. Harrison MS, Ali S, Pasha O, Saleem S, Althabe F, Berrueta M, et al. A prospective population-based study of maternal, fetal, and neonatal outcomes in the setting of prolonged labor, obstructed labor and failure to progress in low-and middle-income countries. Reproductive Health. 2015;12(2):S9.

127. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Bommarito K, Madden T, Olsen MA, et al. Maternal age and risk of labor and delivery complications. Maternal and Child Health Journal. 2015;19(6):1202-11.
128. Dumas A-M, Girard R, Ayzac L, Beaumont G, Caillat-Vallet E, Depaix F, et al. Effect of intrapartum antibiotic prophylaxis against group B streptococcal infection on comparisons of rates of endometritis and urinary tract infection in multicenter surveillance. Infection Control & Hospital Epidemiology. 2008;29(4):327-32.
129. Getahun D, Strickland D, Zeiger RS, Fassett MJ, Chen W, Rhoads GG, et al. Effect of chorioamnionitis on early childhood asthma. Archives of Pediatrics & Adolescent Medicine. 2010;164(2):187-92.
130. Kyser KL, Lu X, Santillan DA, Santillan MK, Hunter SK, Cahill AG, et al. The association between hospital obstetrical volume and maternal postpartum complications. American Journal of Obstetrics and Gynecology. 2012;207(1):42. e1-. e17.
131. Lyndon A, Lee HC, Gilbert WM, Gould JB, Lee KA. Maternal morbidity during childbirth hospitalization in California. The Journal of Maternal-Fetal & Neonatal Medicine. 2012;25(12):2529-35.
132. Malloy M. Chorioamnionitis: epidemiology of newborn management and outcome United States 2008. Journal of Perinatology. 2014;34(8):611.
133. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I^2 in assessing heterogeneity may mislead. BMC Medical Research Methodology. 2008;8(1):79.
134. Bleich AT, Alexander JM, McIntire DD, Leveno KJ. An analysis of second-stage labor beyond 3 hours in nulliparous women. American Journal of Perinatology. 2012;29(09):717-22.
135. Fronczak N, Antelman G, Moran A, Caulfield L, Baqui A. Delivery-related complications and early postpartum morbidity in Dhaka, Bangladesh. International Journal of Gynecology & Obstetrics. 2005;91(3):271-8.
136. Ghani N, Rukanuddin RJ, Ali TS. Prevalence and factors associated with postpartum vaginal infection in the Khyber agency federally administered tribal areas, Pakistan. Journal of Pakistan Medical Association. 2007;57(7):363.
137. Gözüm S, Kiliç D. Health problems related to early discharge of Turkish women. Midwifery. 2005;21(4):371-8.
138. Shriraam V, Shah P, Rani M, Palani G, Sathiyasekaran B. Postpartum morbidity and health seeking pattern in a rural community in South India–population based study. Indian Journal of Maternal and Child Health. 2012;14(3):10.
139. Andersson N, Omer K, Caldwell D, Dambam MM, Maikudi AY, Effiong B, et al. Male responsibility and maternal morbidity: a cross-sectional study in two Nigerian states. BMC Health Services Research. 2011;11(2):S7.
140. Suthee Panichkul M, Boonprasert K, Komolpis S, Panichkul P. The association between meconium-stained amniotic fluid and chorioamnionitis or endometritis. J Med Assoc Thai. 2007;90(3):442-7.
141. Al-Ostad G, Kezouh A, Spence AR, Abenhaim HA. Incidence and risk factors of sepsis mortality in labor, delivery and after birth: Population-based study in the USA. Journal of Obstetrics and Gynaecology Research. 2015;41(8):1201-6.
142. Dotters-Katz SK, Patel E, Grotegut CA, Heine RP. Acute infectious morbidity in multiple gestation. Infectious diseases in obstetrics and gynecology. 2015;2015.
143. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal and obstetric complications of pregnancy are associated with increasing gestational age at term. American Journal of Obstetrics and Gynecology. 2007;196(2):155. e1-. e6.
144. Braun D, Bromberger P, Ho NJ, Getahun D. Low rate of perinatal sepsis in term infants of mothers with chorioamnionitis. American Journal of Perinatology. 2016;33(02):143-50.

145. Edwards SE, Grobman WA, Lappen JR, Winter C, Fox R, Lenguerrand E, et al. Modified obstetric early warning scoring systems (MOEWS): validating the diagnostic performance for severe sepsis in women with chorioamnionitis. American Journal of Obstetrics and Gynecology. 2015;212(4):536. e1-. e8.
146. Cheng YW, Shaffer BL, Bryant AS, Caughey AB. Length of the first stage of labor and associated perinatal outcomes in nulliparous women. Obstetrics & Gynecology. 2010;116(5):1127-35.
147. Ayzac L, Caillat-Vallet E, Girard R, Chapuis C, Depaix F, Dumas A-M, et al. Decreased rates of nosocomial endometritis and urinary tract infection after vaginal delivery in a French surveillance network, 1997–2003. Infection Control & Hospital Epidemiology. 2008;29(6):487-95.
148. King JR, Korst LM, Miller DA, Ouzounian JG. Increased composite maternal and neonatal morbidity associated with ultrasonographically suspected fetal macrosomia. The Journal of Maternal-Fetal & Neonatal Medicine. 2012;25(10):1953-9.
149. Bauer ME, Bateman BT, Bauer ST, Shanks AM, Mhyre JM. Maternal sepsis mortality and morbidity during hospitalization for delivery: temporal trends and independent associations for severe sepsis. Anesthesia & Analgesia. 2013;117(4):944-50.
150. Tippawan Liabsuetrakul M, Suchonwanich Y. Birth rates and pregnancy complications in adolescent pregnant women giving birth in the hospitals of Thailand. J Med Assoc Thai. 2014;97(8):785-90.
151. Callaghan WM, MacKay AP, Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991-2003. American Journal of Obstetrics and Gynecology. 2008;199(2):133. e1-. e8.
152. Leth RA, Møller JK, Thomsen RW, Uldbjerg N, Nørgaard M. 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. 2009;88(9):976-83.
153. Knowles S, O'sullivan N, Meenan A, Hanniffy R, Robson M. Maternal sepsis incidence, aetiology and outcome for mother and fetus: a prospective study. BJOG: An International Journal of Obstetrics & Gynaecology. 2015;122(5):663-71.
154. Liu S, Liston RM, Joseph K, Heaman M, Sauve R, Kramer MS. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. CMAJ. 2007;176(4):455-60.
155. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Maternal and Child Health Journal. 2008;12(4):469-77.
156. Palmer WL, Bottle A, Aylin P. Association between day of delivery and obstetric outcomes: observational study. BMJ. 2015;351:h5774.
157. Guendelman S, Thornton D, Gould J, Hosang N. Obstetric complications during labor and delivery: assessing ethnic differences in California. Women's Health Issues. 2006;16(4):189-97.
158. Goff SL, Pekow PS, Avrunin J, Lagu T, Markenson G, Lindenauer PK. Patterns of obstetric infection rates in a large sample of US hospitals. American Journal of Obstetrics and Gynecology. 2013;208(6):456. e1-. e13.
159. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1545.
160. United Nations DESA/Population Division. World Population Prospects 2017 2017 [Available from: https://population.un.org/wpp/Download/Standard/Fertility/.

161. Sway A, Nthumba P, Solomkin J, Tarchini G, Gibbs R, Ren Y, et al. Burden of surgical site infection following cesarean section in sub-Saharan Africa: a narrative review. International Journal of Women's Health. 2019;11:309.
162. Sobhy S, Arroyo-Manzano D, Murugesu N, Karthikeyan G, Kumar V, Kaur I, et al. Maternal and perinatal mortality and complications associated with caesarean section in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet. 2019.
163. Admaty D, Benzing J, Burkhardt T, Lapaire O, Hegi L, Szinnai G, et al. Plasma midregional proadrenomedullin in newborn infants: impact of prematurity and perinatal infection. Pediatric Research. 2012;72(1):70.
164. Bear JJ, Wu YW. Maternal infections during pregnancy and cerebral palsy in the child. Pediatric Neurology. 2016;57:74-9.
165. Berg CJ, MacKay AP, Qin C, Callaghan WM. Overview of maternal morbidity during hospitalization for labor and delivery in the United States: 1993–1997 and 2001–2005. Obstetrics & Gynecology. 2009;113(5):1075-81.
166. Borders N, Lawton R, Martin SR. A clinical audit of the number of vaginal examinations in labor: A NOVEL Idea. Journal of Midwifery & Women's Health. 2012;57(2):139-44.
167. Cheng YW, Hopkins LM, Laros Jr RK, Caughey AB. Duration of the second stage of labor in multiparous women: maternal and neonatal outcomes. American Journal of Obstetrics and Gynecology. 2007;196(6):585. e1-. e6.
168. Danilack VA, Nunes AP, Phipps MG. Unexpected complications of low-risk pregnancies in the United States. American Journal of Obstetrics and Gynecology. 2015;212(6):809. e1-. e6.
169. Geller EJ, Wu JM, Jannelli ML, Nguyen TV, Visco AG. Maternal outcomes associated with planned vaginal versus planned primary cesarean delivery. American Journal of Perinatology. 2010;27(09):675-84.
170. Getahun D. Temporal trends in chorioamnionitis by maternal race/ethnicity and gestational age (1995–2010). International Journal of Reproductive Medicine. 2013;2013(Article ID 906467):6 pages.
171. Grotegut CA, Tatineni H, Dandolu V, Whiteman VE, Katari S, Geifman-Holtzman O. Obstetric outcomes with a false-positive one-hour glucose challenge test by the Carpenter-Coustan criteria. The Journal of Maternal-Fetal & Neonatal Medicine. 2008;21(5):315-20.
172. Magann EF, Doherty DA, Briery CM, Niederhauser A, Chauhan SP, Morrison JC. Obstetric characteristics for a prolonged third stage of labor and risk for postpartum hemorrhage. Gynecologic and obstetric investigation. 2008;65(3):201-5.
173. Matsuda Y, Kawamichi Y, Hayashi K, Shiozaki A, Satoh S, Saito S. Impact of maternal age on the incidence of obstetrical complications in Japan. Journal of Obstetrics and Gynaecology Research. 2011;37(10):1409-14.
174. Nelson DB, Lucke AM, McIntire DD, Sánchez PJ, Leveno KJ, Chalak LF. Obstetric antecedents to body-cooling treatment of the newborn infant. American Journal of Obstetrics and Gynecology. 2014;211(2):155. e1-. e6.
175. Osmundson S, Ou-Yang RJ, Grobman WA. Elective induction compared with expectant management in nulliparous women with an unfavorable cervix. Obstetrics & Gynecology. 2011;117(3):583-7.
176. Shah N, Rohra DK, Shuja S, Liaqat NF, Solangi NA, Kumar K, et al. Comparision of obstetric outcome among teenage and non-teenage mothers from three tertiary care hospitals of Sindh, Pakistan. JPMA-Journal of the Pakistan Medical Association. 2011;61(10):963.

177. The Healthcare Cost and Utilization Project (HCUP). Overview of the National (Nationwide) Inpatient Sample (NIS) 2016 [Available from: https://unstats.un.org/sdgs/indicators/regional-groups/.
178. Centers for Disease Control and Prevention. National Hospital Discharge Survey [Available from: https://www.cdc.gov/nchs/nhds/index.htm.
179. AHNFELDT-MOLLERUP P, Petersen LK, Kragstrup J, Christensen RD, Sørensen B. Postpartum infections: occurrence, healthcare contacts and association with breastfeeding. Acta obstetricia et gynecologica Scandinavica. 2012;91(12):1440-4.
180. Belfort MA, Clark SL, Saade GR, Kleja K, Dildy III GA, Van Veen TR, et al. Hospital readmission after delivery: evidence for an increased incidence of nonurogenital infection in the immediate postpartum period. American Journal of Obstetrics and Gynecology. 2010;202(1):35. e1-. e7.
181. Darmstadt GL, Hassan M, Balsara ZP, Winch PJ, Gipson R, Santosham M. Impact of clean delivery-kit use on newborn umbilical cord and maternal puerperal infections in Egypt. Journal of Health, Population, and Nutrition. 2009;27(6):746.
182. Ezugwu E, Onah H, Iyoke C, Ezugwu F. Obstetric outcome following free maternal care at Enugu State University Teaching Hospital (ESUTH), Parklane, Enugu, South-eastern Nigeria. Journal of Obstetrics and Gynaecology. 2011;31(5):409-12.
183. Guimarães EER, Chianca TCM, Oliveira ACd. [Puerperal infection from the perspective of humanized delivery care at a public maternity hospital]. Revista Latino-Americana de Enfermagem. 2007;15(4):536-42.
184. Iyengar K. Early postpartum maternal morbidity among rural women of Rajasthan, India: a community-based study. Journal of Health, Population, and Nutrition. 2012;30(2):213.
185. Magann EF, Doherty DA, Chauhan SP, Klimpel JM, Huff SD, Morrison JC. Pregnancy, obesity, gestational weight gain, and parity as predictors of peripartum complications. Archives of Gynecology and Obstetrics. 2011;284(4):827-36.
186. Ngoga E, Hall D, Mattheyse F, Grové D. Outcome of pregnancy in the morbidly obese woman. South African Family Practice. 2009;51(1).
187. Ramírez-Villalobos D, Hernández-Garduño A, Salinas A, González D, Walker D, Rojo-Herrera G, et al. [Early postpartum discharge and complications in the early puerperium]. Salud Pública de México. 2009;51(3):212-8.
188. Tabcharoen C, Pinjaroen S, Suwanrath C, Krisanapan O. Pregnancy outcome after age 40 and risk of low birth weight. Journal of Obstetrics and Gynaecology. 2009;29(5):378-83.
189. Winani S, Wood S, Coffey P, Chirwa T, Mosha F, Changalucha J. Use of a clean delivery kit and factors associated with cord infection and puerperal sepsis in Mwanza, Tanzania. Journal of midwifery & women's health. 2007;52(1):37-43.
190. Awan S, Bibi S, Makhdoom A, Farooq S, SM T, Qazi RA. Adverse fetomaternal outcome among pregnant overweight women. Pakistan Journal of Medical Sciences. 2015;31(2):383.
191. Bailit JL, Love TE, Dawson NV. Quality of obstetric care and risk-adjusted primary cesarean delivery rates. American Journal of Obstetrics and Gynecology. 2006;194(2):402-7.
192. Bodner K, Wierrani F, Grünberger W, Bodner-Adler B. Influence of the mode of delivery on maternal and neonatal outcomes: a comparison between elective cesarean section and planned vaginal delivery in a low-risk obstetric population. Archives of Gynecology and Obstetrics. 2011;283(6):1193-8.
193. Charrier L, Serafini P, Chiono V, Rebora M, Rabacchi G, Zotti CM. Clean and sterile delivery: two different approaches to infection control. Journal of Evaluation in Clinical Practice. 2010;16(4):771-5.

194. Danish N, Fawad A, Abbasi N. Assessment of pregnancy outcome in primigravida: comparison between booked and un-booked patients. Journal of Ayub Medical College Abbottabad. 2010;22(2):23-5.
195. Dasgupta A, Harichandrakumar K, Habeebullah S. Pregnancy outcome among obese Indians-a prospective cohort study in a tertiary Care Centre in South India. International Journal of Scientific Study. 2014;2(2):13-8.
196. Jaleel R. Impact of maternal obesity on pregnancy outcome. Journal of Surgery Pakistan (International). 2009;14(1).
197. Janssen PA, Saxell L, Page LA, Klein MC, Liston RM, Lee SK. Outcomes of planned home birth with registered midwife versus planned hospital birth with midwife or physician. CMAJ. 2009;181(6-7):377-83.
198. Latif T, Ali M, Majeed A, Nahar K, Noor Z. Labor outcome of primigravidae in Mymensingh Medical College Hospital. Mymensingh Medical Journal. 2013;22(3):432-7.
199. Oladapo OT, Lamina MA, SULE-ODU AO. Maternal morbidity and mortality associated with elective caesarean delivery at a university hospital in Nigeria. Australian and New Zealand journal of obstetrics and gynaecology. 2007;47(2):110-4.
200. Cape A, Tuomala RE, Taylor C, Puopolo KM. Peripartum bacteremia in the era of group B streptococcus prophylaxis. Obstetrics & Gynecology. 2013;121(4):812-8.
201. David K, Pricilla R, Venkatesan S, Rahman S, Sy G, Vijayaselvi R. Outcomes of deliveries in a midwife-run labour room located at an urban health centre: results of a 5-year retrospective study. The Natl Med J India. 2012;25:323-6.
202. Huda FA, Ahmed A, Dasgupta SK, Jahan M, Ferdous J, Koblinsky M, et al. Profile of maternal and foetal complications during labour and delivery among women giving birth in hospitals in Matlab and Chandpur, Bangladesh. Journal of Health, Population, and Nutrition. 2012;30(2):131.
203. Karolinski A, Mercer R, Micone P, Ocampo C, Mazzoni A, Fontana O, et al. The epidemiology of life-threatening complications associated with reproductive process in public hospitals in Argentina. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(13):1685-95.
204. Pallasmaa N, Ekblad U, Gissler M. Severe maternal morbidity and the mode of delivery. Acta obstetricia et gynecologica Scandinavica. 2008;87(6):662-8.
205. Pallasmaa N, Ekblad U, Gissler M, Alanen A. The impact of maternal obesity, age, pre-eclampsia and insulin dependent diabetes on severe maternal morbidity by mode of delivery—a register-based cohort study. Archives of Gynecology and Obstetrics. 2015;291(2):311-8.
206. Simoes E, Kunz S, Bosing-Schwenkglenks M, Schmahl F. Association between method of delivery and puerperal infectious complications in the perinatal database of Baden-Württemberg 1998–2001. Gynecologic and Obstetric Investigation. 2005;60(4):213-7.
207. Avcı ME, Şanlıkan F, Celik M, Avcı A, Kocaer M, Göçmen A. Effects of maternal obesity on antenatal, perinatal and neonatal outcomes. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;28(17):2080-3.
208. Bailit JL, Grobman WA, Rice MM, Spong CY, Wapner RJ, Varner MW, et al. Risk-adjusted models for adverse obstetric outcomes and variation in risk-adjusted outcomes across hospitals. American Journal of Obstetrics and Gynecology. 2013;209(5):446. e1-. e30.
209. Galyean A, Lagrew D, Bush M, Kurtzman J. Previous cesarean section and the risk of postpartum maternal complications and adverse neonatal outcomes in future pregnancies. Journal of Perinatology. 2009;29(11):726.

210. Gibson KS, Waters TP, Bailit JL. Maternal and neonatal outcomes in electively induced low-risk term pregnancies. American Journal of Obstetrics and Gynecology. 2014;211(3):249. e1-. e16.
211. Karlström A, Lindgren H, Hildingsson I. Maternal and infant outcome after caesarean section without recorded medical indication: findings from a Swedish case–control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(4):479-86.
212. Kovavisarach E, Chairaj S, Tosang K, Asavapiriyanont S, Chotigeat U. Outcome of teenage pregnancy in Rajavithi Hospital. J Med Assoc Thai. 2010;93(1):1.
213. Laws PJ, Xu F, Welsh A, Tracy SK, Sullivan EA. Maternal morbidity of women receiving birth center care in New South Wales: A matched-pair analysis using linked health data. Birth. 2014;41(3):268-75.
214. Mandal D, Manda S, Rakshi A, Dey R, Biswas S, Banerjee A. Maternal obesity and pregnancy outcome: a prospective analysis. The Journal of the Association of Physicians of India. 2011;59:486-9.
215. Ngoc NT, Sloan NL, Thach TS, Liem LK, Winikoff B. Incidence of postpartum infection after vaginal delivery in Viet Nam. Journal of Health, Population and Nutrition. 2005:121-30.
216. Winani S, Wood S, Coffey P, Chirwa T, Mosha F, Changalucha J. Use of a clean delivery kit and factors associated with cord infection and puerperal sepsis in Mwanza, Tanzania. Journal of Midwifery & Women's Health. 2007;52(1):37-43.
217. Ahnfeldt-Mollerup P, Petersen LK, Kragstrup J, Christensen RD, Sørensen B. Postpartum infections: occurrence, healthcare contacts and association with breastfeeding. Acta Obstetricia et Gynecologica Scandinavica. 2012;91(12):1440-4.
218. Dotters-Katz S, Patel E, Grotegut C, Heine R. Acute infectious morbidity in multiple gestation. Infectious Diseases in Obstetrics and Gynecology. 2015;2015:173261-.
219. Koek MB, Wille JC, Isken MR, Voss A, van Benthem BH. Post-discharge surveillance (PDS) for surgical site infections: a good method is more important than a long duration. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 2015;20(8):26.
220. European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010-2011. Stockholm: ECDC; 2013.
221. European Centre for Disease Prevention and Control. Healcare-associated infections: surgical site infections. In: ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2019.
222. Ahluwalia IB, Morrow B, D'Angelo D, Li R. Maternity care practices and breastfeeding experiences of women in different racial and ethnic groups: Pregnancy Risk Assessment and Monitoring System (PRAMS). Maternal & Child Health Journal.16(8):1672-8.
223. Hirshberg A, Downes K, Srinivas S. Comparing standard office-based follow-up with text-based remote monitoring in the management of postpartum hypertension: a randomised clinical trial. BMJ Quality & Safety.27(11):871-7.
224. Ng W, Brown A, Alexander D, Ho MF, Kerr B, Amato M, et al. A multifaceted prevention program to reduce infection after cesarean section: Interventions assessed using an intensive postdischarge surveillance system. American Journal of Infection Control.43(8):805-9.
225. Halwani MA, Turnbull AE, Harris M, Witter F, Perl TM. Postdischarge surveillance for infection following cesarean section: a prospective cohort study comparing methodologies. American journal of infection control. 2016;44(4):455-7.
226. Bjelland EK, Owe KM, Pingel R, Kristiansson P, Vangen S, Eberhard-Gran M. Pelvic pain after childbirth: a longitudinal population study. Pain.157(3):710-6.

227. Ferraro F, Piselli P, Pittalis S, Ruscitti LE, Cimaglia C, Ippolito G, et al. Surgical site infection after caesarean section: space for post-discharge surveillance improvements and reliable comparisons. New Microbiologica.39(2):134-8.
228. Løwer HL, Eriksen H-M, Aavitsland P, Skjeldestad FE. Methodology of the Norwegian Surveillance System for Healthcare-Associated Infections: the value of a mandatory system, automated data collection, and active postdischarge surveillance. American journal of infection control. 2013;41(7):591-6.
229. Troillet N, Aghayev E, Eisenring MC, Widmer AF, Swissnoso. First Results of the Swiss National Surgical Site Infection Surveillance Program: Who Seeks Shall Find. Infection Control & Hospital Epidemiology.38(6):697-704.
230. Williams A, Herron-Marx S, Knibb R. The prevalence of enduring postnatal perineal morbidity and its relationship to type of birth and birth risk factors. Journal of Clinical Nursing.16(3):549-61.
231. Zejnullahu VA, Isjanovska R, Sejfija Z, Zejnullahu VA. Surgical site infections after cesarean sections at the University Clinical Center of Kosovo: rates, microbiological profile and risk factors. BMC Infectious Diseases.19(1):752.
232. Axelsson D, Blomberg M. Prevalence of postpartum infections: a population-based observational study. Acta obstetricia et gynecologica Scandinavica. 2014;93(10):1065-8.
233. Ward V, Charlett A, Fagan J, Crawshaw S. Enhanced surgical site infection surveillance following caesarean section: experience of a multicentre collaborative post-discharge system. Journal of Hospital Infection. 2008;70(2):166-73.
234. Lima JL, de Aguiar RA, Leite HV, Silva HH, de Oliveira WM, Sacramento JP, et al. Surveillance of surgical site infection after cesarean section and time of notification. American Journal of Infection Control.44(3):273-7.
235. Mosquera PS, Lourenco BH, Gimeno SGA, Malta MB, Castro MC, Cardoso MA, et al. Factors affecting exclusive breastfeeding in the first month of life among Amazonian children. PLoS ONE [Electronic Resource].14(7):e0219801.
236. Darmstadt GL, El Arifeen S, Choi Y, Bari S, Rahman SM, Mannan I, et al. Household surveillance of severe neonatal illness by community health workers in Mirzapur, Bangladesh: coverage and compliance with referral. Health Policy & Planning.25(2):112-24.
237. Surkan PJ, Sakyi KS, Christian P, Mehra S, Labrique A, Ali H, et al. Risk of Depressive Symptoms Associated with Morbidity in Postpartum Women in Rural Bangladesh. Maternal & Child Health Journal.21(10):1890-900.
238. Gass Jr JD, Semrau K, Sana F, Mankar A, Singh VP, Fisher-Bowman J, et al. Evaluation of a call center to assess post-discharge maternal and early neonatal outcomes of facility-based childbirth in Uttar Pradesh, India. PloS One. 2018;13(11):e0207987.
239. Callaghan-Koru JA, Nonyane BA, Guenther T, Sitrin D, Ligowe R, Chimbalanga E, et al. Contribution of community-based newborn health promotion to reducing inequities in healthy newborn care practices and knowledge: evidence of improvement from a three-district pilot program in Malawi. BMC Public Health.13:1052.
240. Creanga AA, Odhiambo GA, Odera B, Odhiambo FO, Desai M, Goodwin M, et al. Pregnant Women's Intentions and Subsequent Behaviors Regarding Maternal and Neonatal Service Utilization: Results from a Cohort Study in Nyanza Province, Kenya. PLoS ONE [Electronic Resource].11(9):e0162017.
241. Kirkwood BR, Manu A, ten Asbroek AH, Soremekun S, Weobong B, Gyan T, et al. Effect of the Newhints home-visits intervention on neonatal mortality rate and care practices in Ghana: a cluster randomised controlled trial. Lancet.381(9884):2184-92.
242. Elbur AI, Yousif M, ElSayed AS, Abdel-Rahman ME. Post-discharge surveillance of wound infections by telephone calls method in a Sudanese Teaching Hospital. Journal of infection and public health. 2013;6(5):339-46.

243. Nguhuni B, De Nardo P, Gentilotti E, Chaula Z, Damian C, Mencarini P, et al. Reliability and validity of using telephone calls for post-discharge surveillance of surgical site infection following caesarean section at a tertiary hospital in Tanzania. Antimicrobial Resistance & Infection Control. 2017;6(1):43.
244. Nthumba P, Stepita-Poenaru E, Poenaru D, Bird P, Allegranzi B, Pittet D, et al. Cluster-randomized, crossover trial of the efficacy of plain soap and water versus alcohol-based rub for surgical hand preparation in a rural hospital in Kenya. British journal of surgery. 2010;97(11):1621-8.
245. Yugbare Belemsaga D, Goujon A, Bado A, Kouanda S, Duysburgh E, Temmerman M, et al. Integration of postpartum care into child health and immunization services in Burkina Faso: findings from a cross-sectional study. Reproductive Health.15(1):171.
246. Goudar SS, Carlo WA, McClure EM, Pasha O, Patel A, Esamai F, et al. The maternal and newborn health registry study of the global network for women's and children's health research. International Journal of Gynecology & Obstetrics. 2012;118(3):190-3.
247. Madhi SA, Rivera LM, Saez-Llorens X, Menendez C, Carrim-Ganey N, Cotton MF, et al. Factors influencing access of pregnant women and their infants to their local healthcare system: a prospective, multi-centre, observational study. BMC Pregnancy & Childbirth.18(1):29.
248. Aftab F, Ahmed I, Ahmed S, Ali SM, Amenga-Etego S, Ariff S, et al. Direct maternal morbidity and the risk of pregnancy-related deaths, stillbirths, and neonatal deaths in South Asia and sub-Saharan Africa: A population-based prospective cohort study in 8 countries. PLoS Medicine / Public Library of Science. 2021;18(6):e1003644.
249. Shulman HB, D'Angelo DV, Harrison L, Smith RA, Warner L. The pregnancy risk assessment monitoring system (PRAMS): overview of design and methodology. American journal of public health. 2018;108(10):1305-13.
250. Aziz A, Zork N, Aubey JJ, Baptiste CD, D'Alton ME, Emeruwa UN, et al. Telehealth for High-Risk Pregnancies in the Setting of the COVID-19 Pandemic. American Journal of Perinatology.37(8):800-8.
251. Reforma LG, Duffy C, Collier AY, Wylie BJ, Shainker SA, Golen TH, et al. A multidisciplinary telemedicine model for management of coronavirus disease 2019 (COVID-19) in obstetrical patients. American Journal of Obstetrics & Gynecology MFM.2(4):100180.
252. Fawsitt CG, Meaney S, Greene RA, Corcoran P. Surgical Site Infection after Caesarean Section? There Is an App for That: Results from a Feasibility Study On Costs and Benefits. Irish Medical Journal.110(9):635.
253. Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C. Cohort profile: the Norwegian mother and child cohort study (MoBa). International journal of epidemiology. 2006;35(5):1146-50.
254. Kanotra S, D'Angelo D, Phares TM, Morrow B, Barfield WD, Lansky A. Challenges faced by new mothers in the early postpartum period: an analysis of comment data from the 2000 Pregnancy Risk Assessment Monitoring System (PRAMS) survey. Maternal & Child Health Journal.11(6):549-58.
255. Woodward BM, Zadoroznyj M, Benoit C. Beyond birth: Women's concerns about post-birth care in an Australian urban community. Women & Birth: Journal of the Australian College of Midwives.29(2):153-9.
256. Greco G, Daviaud E, Owen H, Ligowe R, Chimbalanga E, Guenther T, et al. Malawi three district evaluation: Community-based maternal and newborn care economic analysis. Health Policy & Planning.32(suppl_1):i64-i74.
257. Rochat TJ, Tomlinson M, Newell M-L, Stein A. Detection of antenatal depression in rural HIV-affected populations with short and ultrashort versions of the Edinburgh Postnatal Depression Scale (EPDS). Archives of women's mental health. 2013;16(5):401-10.

258. Cresswell JA, Barbour KD, Chou D, McCaw-Binns A, Filippi V, Cecatti JG, et al. Measurement of maternal functioning during pregnancy and postpartum: findings from the cross-sectional WHO pilot study in Jamaica, Kenya, and Malawi. BMC pregnancy and childbirth. 2020;20(1):1-11.
259. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. In: Health Improvement Scotland, editor. Edinburgh: SIGN88; 2012.
260. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn vP, et al. The efficacy oe infection surveillance and control programs in preventing nosocomial infections in US hospitals. American Journal of Epidemiology. 1985;121(2):182-205.
261. Geubbels EL, Nagelkerke NJ, Mintjes-De Groot AJ, Vandenbroucke-Grauls CM, Grobbee DE, De Boer AS. Reduced risk of surgical site infections through surveillance in a network. International Journal for Quality in Health Care. 2006;18(2):127-33.
262. Petherick ES, Dalton JE, Moore PJ, Cullum N. Methods for identifying surgical wound infection after discharge from hospital: a systematic review. BMC infectious diseases. 2006;6(1):170.
263. Eriksen H-M, Sæther AR, Løwer HL, Vangen S, Hjetland R, Lundmark H, et al. Infections after caesarean sections. Tidsskrift for Den norske legeforening. 2009.
264. Aiken A, Wanyoro A, Mwangi J, Mulingwa P, Wanjohi J, Njoroge J, et al. Evaluation of surveillance for surgical site infections in Thika Hospital, Kenya. Journal of hospital infection. 2013;83(2):140-5.
265. Galle A, Semaan A, Huysmans E, Audet C, Asefa A, Delvaux T, et al. A double-edged sword—telemedicine for maternal care during COVID-19: findings from a global mixed-methods study of healthcare providers. BMJ Global Health. 2021;6(2):e004575.
266. Woodd SL, Kabanywanyi AM, Rehman AM, Campbell OM, Kagambo A, Martiasi W, et al. Postnatal infection surveillance by telephone in Dar es Salaam, Tanzania: An observational cohort study. PloS one. 2021;16(7):e0254131.
267. Ashish K, Gurung R, Kinney MV, Sunny AK, Moinuddin M, Basnet O, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. The Lancet Global Health. 2020;8(10):e1273-e81.
268. Campbell OM, Calvert C, Testa A, Strehlow M, Benova L, Keyes E, et al. The scale, scope, coverage, and capability of childbirth care. The Lancet. 2016;388(10056):2193-208.
269. Gon G, Kabanywanyi AM, Blinkhoff P, Cousens S, Dancer SJ, Graham WJ, et al. The Clean pilot study: evaluation of an environmental hygiene intervention bundle in three Tanzanian hospitals. Antimicrobial Resistance & Infection Control. 2021;10(1):1-14.
270. RandomAppsInc. Randum Number Generator Plus. In: Chiou A, editor.: https://github.com/Gear61/Random-Number-Generator; 2015. p. Android 4.0.
271. Bollig C, Nothacker M, Lehane C, Motschall E, Lang B, Meerpohl JJ, et al. Prophylactic antibiotics before cord clamping in cesarean delivery: a systematic review. Acta Obstetricia et Gynecologica Scandinavica. 2018;97(5):521-35.
272. Ministry of Health and Social Welfare - The United Republic of Tanzania. Standard Treatment Guidelines and Essential Medicines List. Fourth ed2013.
273. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? The Lancet. 2014;384(9940):347-70.
274. Norhayati M, Hazlina NN, Asrenee A, Emilin WW. Magnitude and risk factors for postpartum symptoms: a literature review. Journal of affective Disorders. 2015;175:34-52.
275. Filippi V, Ganaba R, Baggaley RF, Marshall T, Storeng KT, Sombié I, et al. Health of women after severe obstetric complications in Burkina Faso: a longitudinal study. The Lancet. 2007;370(9595):1329-37.

276. Guida JP, Costa ML, Parpinelli MA, Pacagnella RC, Ferreira EC, Mayrink J, et al. The impact of hypertension, hemorrhage, and other maternal morbidities on functioning in the postpartum period as assessed by the WHODAS 2.0 36-item tool. International Journal of Gynecology & Obstetrics. 2018;141:55-60.
277. Machiyama K, Hirose A, Cresswell JA, Barreix M, Chou D, Kostanjsek N, et al. Consequences of maternal morbidity on health-related functioning: a systematic scoping review. BMJ open. 2017;7(6):e013903.
278. Petrosillo N, Drapeau CM, Nicastri E, Martini L, Ippolito G, Moro ML. Surgical site infections in Italian hospitals: a prospective multicenter study. BMC Infectious Diseases. 2008;8(1):34.
279. Campbell OM, Cegolon L, Macleod D, Benova L. Length of stay after childbirth in 92 countries and associated factors in 30 low-and middle-income countries: compilation of reported data and a cross-sectional analysis from nationally representative surveys. PLoS medicine. 2016;13(3):e1001972.
280. Baaqeel H, Baaqeel R. Timing of administration of prophylactic antibiotics for caesarean section: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(6):661-9.
281. Jury I, Thompson K, Hirst JE. A scoping review of maternal antibiotic prophylaxis in low-and middle-income countries: Comparison to WHO recommendations for prevention and treatment of maternal peripartum infection. International Journal of Gynecology & Obstetrics. 2021.
282. Beck C, Gallagher K, Taylor LA, Goldstein JA, Mithal LB, Gernand AD. Chorioamnionitis and Risk for Maternal and Neonatal Sepsis: A Systematic Review and Meta-analysis. Obstetrics & Gynecology. 2021;137(6):1007-22.
283. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395(10219):200-11.
284. Li L, Wen J, Wang L, Li Y, Li Y. Is routine indwelling catheterisation of the bladder for caesarean section necessary? A systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2011;118(4):400-9.
285. Gundersen TD, Krebs L, Loekkegaard ECL, Rasmussen SC, Glavind J, Clausen TD. Postpartum urinary tract infection by mode of delivery: a Danish nationwide cohort study. BMJ open. 2018;8(3):e018479.
286. Abubakar U, Syed Sulaiman SA, Adesiyun AG. Impact of pharmacist-led antibiotic stewardship interventions on compliance with surgical antibiotic prophylaxis in obstetric and gynecologic surgeries in Nigeria. PloS one. 2019;14(3):e0213395.
287. Aiken AM, Wanyoro AK, Mwangi J, Juma F, Mugoya IK, Scott JAG. Changing use of surgical antibiotic prophylaxis in Thika Hospital, Kenya: a quality improvement intervention with an interrupted time series design. PloS one. 2013;8(11):e78942.
288. Kilan R, Moran D, Eid I, Okeahialam C, Quinn C, Binsaddiq W, et al. Improving antibiotic prophylaxis in gastrointestinal surgery patients: A quality improvement project. Annals of medicine and surgery. 2017;20:6-12.
289. Putnam LR, Chang CM, Rogers NB, Podolnick JM, Sakhuja S, Matusczcak M, et al. Adherence to surgical antibiotic prophylaxis remains a challenge despite multifaceted interventions. Surgery. 2015;158(2):413-9.
290. Gagliardi AR, Fenech D, Eskicioglu C, Nathens AB, McLeod R. Factors influencing antibiotic prophylaxis for surgical site infection prevention in general surgery: a review of the literature. Canadian Journal of Surgery. 2009;52(6):481.
291. AlignMNH. New Guidance: Updated WHO Recommendations on the Prevention and Treatment of Maternal Peripartum Infections. June 2021.

292. Ademuyiwa AO, Hardy P, Runigamugabo E, Sodonougbo P, Behanzin H, Kangni S, et al. Reducing surgical site infections in low-income and middle-income countries (FALCON): a pragmatic, multicentre, stratified, randomised controlled trial. The Lancet. 2021.
293. Duysburgh E, Kerstens B, Kouanda S, Kaboré CP, Yugbare DB, Gichangi P, et al. Opportunities to improve postpartum care for mothers and infants: design of context-specific packages of postpartum interventions in rural districts in four sub-Saharan African countries. BMC pregnancy and childbirth. 2015;15(1):1-11.
294. Finlayson K, Crossland N, Bonet M, Downe S. What matters to women in the postnatal period: a meta-synthesis of qualitative studies. PLoS One. 2020;15(4):e0231415.

Appendices

Appendix A: Published version of manuscript 1

PLOS MEDICINE

RESEARCH ARTICLE

Incidence of maternal peripartum infection: A systematic review and meta-analysis

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Abstract

Background

Infection is an important, preventable cause of maternal morbidity, and pregnancy-related sepsis accounts for 11% of maternal deaths. However, frequency of maternal infection is poorly described, and, to our knowledge, it remains the one major cause of maternal mortality without a systematic review of incidence. Our objective was to estimate the average global incidence of maternal peripartum infection.

Methods and findings

We searched Medline, EMBASE, Global Health, and five other databases from January 2005 to June 2016 (PROSPERO: CRD42017074591). Specific outcomes comprised chorioamnionitis in labour, puerperal endometritis, wound infection following cesarean section or perineal trauma, and sepsis occurring from onset of labour until 42 days postpartum. We assessed studies irrespective of language or study design. We excluded conference abstracts, studies of high-risk women, and data collected before 1990. Three reviewers independently selected studies, extracted data, and appraised quality. Quality criteria for incidence/prevalence studies were adapted from the Joanna Briggs Institute. We used random-effects models to obtain weighted pooled estimates of incidence risk for each outcome and metaregression to identify study-level characteristics affecting incidence. From 31,528 potentially relevant articles, we included 111 studies of infection in women in labour or postpartum from 46 countries. Four studies were randomised controlled trials, two were before–after intervention studies, and the remainder were observational cohort or cross-sectional studies. The pooled incidence in high-quality studies was 3.9% (95% Confidence Interval [CI] 1.8%–6.8%) for chorioamnionitis, 1.6% (95% CI 0.9%–2.5%) for endometritis, 1.2% (95% CI 1.0%–1.5%) for wound infection, 0.05% (95% CI 0.03%–0.07%) for sepsis, and 1.1% (95% CI 0.3%–2.4%) for maternal peripartum infection. 19% of studies met all quality criteria. There were few data from developing countries and marked heterogeneity in study designs and infection definitions, limiting the interpretation of these estimates as measures

Data Availability Statement: Files of study characteristics and outcomes for all included studies are available from LSHTM data compass (https://doi.org/10.17037/DATA.00001411).

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Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CI, Confidence Interval; GBD, Global Burden of Disease; KPMP, Kaiser Permanente Medical Program; LILACS, Latin American and Caribbean Health Science Information; LMICs, low- and middle-income countries; LSHTM, London School of Hygiene and Tropical Medicine; NHDS, National Hospital Discharge Survey; NHS, National Health Service; NIS, National Inpatient Sample; OR, odds ratio; SDG, sustainable development goal; SIRS, systemic inflammatory response syndrome; SSI, surgical site infection; WCC, white cell count; WHO, World Health Organization.

of global infection incidence. A limitation of this review is the inclusion of studies that were facility-based or restricted to low-risk groups of women.

Conclusions

In this study, we observed pooled infection estimates of almost 4% in labour and between 1%–2% of each infection outcome postpartum. This indicates maternal peripartum infection is an important complication of childbirth and that preventive efforts should be increased in light of antimicrobial resistance. Incidence risk appears lower than modelled global estimates, although differences in definitions limit comparability. Better-quality research, using standard definitions, is required to improve comparability between study settings and to demonstrate the influence of risk factors and protective interventions.

Author summary

Why was this study done?

- Maternal infections during pregnancy and childbirth are a leading cause of preventable death in both the mother and child.
- It is unknown how frequently maternal infections occur because existing studies have not been summarised previously, to our knowledge.
- It is important for decision makers and clinical staff to know how common these infections are so that efforts are made to prevent them.
- One key reason it is difficult to summarise data on maternal infections is that the research community has used a wide variety of differing criteria to classify women as having an infection.

What did the researchers do and find?

- We screened 31,528 research articles and included 111 in a systematic review of maternal peripartum infection, defined by the World Health Organization as infection of the genital tract and surrounding tissues during labour and up to 42 days after birth. We included articles published in all languages that would provide an estimate of the frequency of infection and found data from 46 countries.
- Using meta-analysis to combine the estimates of infection and account for variability between studies, we found that for 1,000 women giving birth, we estimated averages of 39 women with chorioamnionitis, 16 women with endometritis, 12 women with wound infection, and 0.5 women with sepsis.
- Estimates of infection varied considerably between different studies, partly explained by world region, the study design, and the criteria used to determine infection.

What do these findings mean?

- Infection is an important complication for many women at and after giving birth, and infection prevention should be a priority for clinicians and policymakers. However, our study found less infection than has been previously estimated.
- Representative data from all world regions were not available, highlighting knowledge gaps.
- Future research will benefit from the use of standardised infection definitions and good-quality study methods.

Introduction

Infection is an important preventable cause of maternal morbidity and mortality, with pregnancy-related sepsis accounting for approximately 11% (95% uncertainty interval 5.9%–18.6%) of maternal deaths globally [1]. Infection also contributes significantly to deaths from other causes [2] and leads to serious consequences, including chronic pelvic inflammatory disease, ectopic pregnancy, and infertility [3]. Intrapartum fever also increases the risk of perinatal death [4]. Improved understanding of maternal infection is key to achieving the sustainable development goals (SDGs) and executing the strategies toward ending preventable maternal and neonatal mortality. However, the frequency of infection in pregnancy is poorly understood; a review of maternal morbidity identified no published systematic literature review of infection incidence, making it the one major direct cause of maternal morbidity without such a review to our knowledge [5]. A commonly cited estimate of 4% for puerperal sepsis, modelled for the 2000 Global Burden of Disease (GBD), is based on a single-centre United States (US) study, two African studies comparing home and hospital, and a Cochrane review on antibiotic prophylaxis for cesarean section comprising 66 studies [6]. Recent 2017 GBD data estimate 12.1 million incident cases of maternal sepsis and other maternal infections, including mastitis [7].

A challenge in quantifying the incidence of pregnancy-related infection is the variety of terms, definitions, time periods, sites, and severity of infections used, partly reflecting the breadth of infectious disease in this period. A commonly used term such as puerperal sepsis can range from localised symptoms and signs of genital tract infection [8] to more disseminated disease, including peritonitis, pyaemia, and sepsis [9], and with time periods that can vary from 10 days [10] to 42 days postpartum [9] and sometimes include sepsis in labour [8]. In partial response to this quantification challenge, a new definition for maternal sepsis was published in early 2018 [2]. However, the challenges remain in relation to less severe disease.

This review focusses on recent epidemiological evidence for the incidence of 'maternal peripartum infection', defined by the World Health Organization (WHO) in 2015 to encompass infections of the genital tract and surrounding tissues from onset of labour or rupture of membranes until 42 days postpartum [11]. At a time of increased global attention on maternal sepsis, this group of infections was chosen as being notable for causing over half the cases of severe maternal sepsis in the UK. In addition, the direct association of maternal peripartum infection with the process of giving birth presents key opportunities for prevention and for protecting the efficacy of antibiotics, amidst growing concerns about antimicrobial resistance

[11]. To aid prioritisation by decision makers and guide future research, we set out to estimate the average global incidence of maternal peripartum infection.

Methods

The review was registered with PROSPERO [CRD42017074591] and conducted according to PRISMA guidelines (S1 PRISMA Checklist).

Search strategy

We searched Medline, EMBASE, Global Health, Popline, CINAHL, the Latin American and Caribbean Health Science Information (LILACS) database, Africa-Wide Information, and regional WHO online databases using Global Index Medicus from January 2005 to June 2016. Search strategies were customised to each electronic database's individual subject headings and searching structure (S1 Text). The approach was to include articles if their abstract, title, or keywords contained a maternal term, an infection term, and a term for incidence/prevalence.

Exclusion criteria

All identified studies were systematically assessed, irrespective of language or study design. For clinical trials in which the infection risk differed between study arms ($p < 0.05$), we used the control arm or the arm most similar to usual care. There were no case-control studies in which incidence/prevalence could be estimated.

Studies were excluded if their titles or abstracts indicated they had any of the following:

- No data on maternal peripartum infection
- A composite outcome from which it was not possible to extract data on maternal peripartum infection alone
- Only a subgroup of women at higher risk of infection than the general population of peripartum women (e.g., only cesarean section deliveries or only women with diabetes)
- No quantitative data
- No numerator
- No denominator for the total population of women
- Fewer than 30 participants
- Data collected before 1990, because of potential decreases in incidence over time. If a study spanned 1990 but disaggregated by year, data from 1990 onwards were used
- Conference and poster abstracts
- No primary data, except for reviews, which were hand-searched for additional primary studies.

We sought the full text for all remaining studies, including those for which the abstract had insufficient information to decide. The same exclusion criteria applied to full texts.

Outcome definitions

WHO defines maternal peripartum infection as 'a bacterial infection of the genital tract or surrounding tissues occurring at any time between the onset of rupture of membranes or labour

and the 42nd day postpartum' [11]. We considered this to encompass specific constituent infections, namely chorioamnionitis in labour, puerperal endometritis, and wound infection following cesarean section, perineal tear, or episiotomy. We included sepsis occurring within the defined time period, restricted to sepsis of genital tract or wound origin when possible. We included a fifth category, 'maternal peripartum infection', for studies with a composite outcome of two or more of the above infection types or those that used a broader or unspecified definition of infection within the peripartum period.

Measures of frequency

We aimed to estimate the incidence risk of infection in the peripartum period, defined as cases of infection emerging until 42 days postpartum among women who were infection-free at the start of labour. Because the starting point is clear (labour) and the follow-up period is short (42 days), we considered most studies to have approximated a measure of incidence risk (rather than a rate or period prevalence) and report the results as such.

Screening and data extraction

We used the Institute of Education software, Eppi-Reviewer 4, to store citations and full-text articles, to detect duplicates, and to code screening and data extraction. SLW and AM double-screened 300 (approximately 1%) title and abstracts to ensure consistency; the rest were single-screened. Full-text screening and extraction was conducted by SLW, AM, and MB, with approximately 8% of articles double-screened and extracted to ensure consistency. AM extracted Spanish papers, and MB extracted Portuguese papers. LP screened over 40 Chinese-language papers and extracted from the included studies. Queries were resolved through discussion and, when necessary, with input from a third reviewer (OMRC). Nine authors were contacted to clarify study eligibility.

Data extracted included language, location and dates of study, study population, study design, sampling, outcome definition, denominator, time period for observing infection, data source, diagnosis, and incidence of infection (S2 Text).

Critical appraisal of studies

We appraised the quality of each study outcome according to criteria in Table 1, adapted from Joanna Briggs Institute criteria for assessing incidence/prevalence studies [12]. For each criterion, estimates were classified as having met the criteria or not or of providing insufficient information to judge. Estimates meeting all five criteria were considered high-quality.

Table 1. Quality assessment criteria.

	Quality Assessment Criteria	
1	Were study participants representative of the study target population? (appropriate recruitment strategy and sampling)	Selection bias
2	Was data analysis conducted with sufficient coverage of the identified sample? (refusals and loss are small [<15%] and unlikely to be related to the outcome)	Attrition/missing data
3	Was a clear, standard definition used for maternal infection?	Measurement bias
4	Was infection measured reliably using trained/educated data collectors, appropriate/reliable diagnostic procedures, or reliable forms of retrospective data (clinical records meeting standard definitions)?	Measurement bias
5	Were study subjects and setting described in sufficient detail to determine whether results are comparable with other studies?	Poor characterisation of study population

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To determine whether a standard definition was used (criterion 3), we compared the study definition to internationally recognised definitions for each infection (Table 2). The most recent definition of sepsis (Sepsis-3) agreed upon in early 2016 [13] and the related definition for maternal sepsis [2] proposed by WHO and JHPIEGO in 2017 were not used because these supersede our included studies; however, these revised definitions are similar to the definition for severe sepsis.

Table 2. Standard definitions for infection outcomes.

	Subgroup	Definition	Additional Comments
Chorioamnionitis [14]		Fever (>38˚C) plus one of	Studies of histological chorioamnionitis and microbial invasion of the amniotic fluid were excluded from the review.
		a) maternal tachycardia,	
		b) foetal tachycardia,	
		c) uterine tenderness, or	
		d) foul-smelling vaginal discharge during labour	
Endometritis [15]		At least two of the following:	
		a) fever (>38˚C),	
		b) abdominal pain with no other recognised cause,	
		c) uterine tenderness with no other recognised cause, or	
		d) purulent drainage from uterus	
Wound infection [15]	Superficial	One of	
		a) purulent drainage,	
		b) organisms cultured,	
		c) incision deliberately opened AND at least one of pain, tenderness, swelling, erythema, or heat, or	
		d) diagnosis by attending doctor	
	Deep	Involves fascia and muscle and one of	
		a) purulent drainage,	
		b) spontaneous dehiscence or reopening AND organisms identified AND symptoms similar to superficial infection, or	
		c) abscess	
	Organ/space	Deeper than fascia and meets criterion for a specific organ/space infection, e.g., endometritis, and one of	
		a) purulent drainage from a drain,	
		b) organisms, or	
		c) abscess	
Sepsis [16]	Infection plus SIRS	At least two of	We also accepted slightly different ranges (e.g., heart rate >100/minute, WCC >17,000/mm^3) because of uncertainty regarding appropriate values for pregnant and postpartum women.
		a) temperature >38˚C or <36˚C,	
		b) heart rate >90/minute,	
		c) respiratory rate >20/minute or PaCO2 <32 mm Hg, and/or	
		d) WCC >12,000/mm^3 or <4,000/mm^3 or >10% immature bands	
	Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Abnormalities included, but were not limited to, lactic acidosis, oliguria, or an acute alteration in mental status	Studies that used management indicators of severe disease such as ICU admission or prolonged hospital stay were also accepted.
	Blood stream infection	Positive blood culture	
Maternal peripartum infection		Two or more of the above definitions, presented as a composite outcome	

Abbreviations: SIRS, systemic inflammatory response syndrome; WCC, white cell count.

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If all study cases fell within these definitions, the criterion was met, even if the study definition was more restrictive and may have consequently underestimated infection incidence. Reference to national guidelines or obstetric textbooks met the criteria, as did clearly specified and appropriate ICD-9/10 codes (S1 Table). No codes exactly match the WHO definition of maternal peripartum infection, but we classified studies using ICD-9 670 (major puerperal infection, including endometritis and puerperal sepsis) [17] and ICD-10 O86 (other puerperal infection, including endometritis and wound infection) [18] as having measured maternal peripartum infection.

Data management and analysis

We analysed infection incidence estimates separately for chorioamnionitis, endometritis, wound infection, sepsis, and maternal peripartum infection.

We exported and managed data in Microsoft Excel and STATA 15.1. We extracted information on study characteristics with potential to influence the risk of infection for use in metaregression. We categorised geographical location using SDG world regions [19]. We created a variable named 'study extent' to reflect how nationally representative the study population might be: national level (total population or representative sample), state/regional level, health facility network (e.g., surveillance network or insurance scheme), two or more facilities or field sites, and single facility or field site. Data collection was coded as routine or specific to the study. We coded diagnostic method as clinical or based on reported symptoms, except for chorioamnionitis, for which we compared the use of ICD codes with specified clinical signs. We grouped total follow-up time as being until hospital discharge, 7 days, 30 days, or 42 days postpartum. We grouped studies as only including low-risk women (e.g., low obstetric/medical risk, live birth, vaginal delivery, singleton pregnancy, or term birth) versus including all women who delivered.

We conducted meta-analyses in R version 3.5.0 using the meta [20] and metafor packages [21] to obtain a weighted pooled estimate of incidence of each infection outcome 1) for all studies, 2) for high-quality studies, and 3) stratified by world region. The pooled estimate of sepsis was also stratified by three levels of severity. When studies using nationally representative databases measured the same infection outcome over the same dates, we kept the study with the longest time period.

Infection incidence risk (as a proportion) was transformed using the Freeman–Tukey transformation to approximate a normal distribution and stabilise the variance [22, 23]. Because study designs and outcome definitions varied, we used random effects to combine study estimates [12]. The tau^2 measure of between-study heterogeneity was estimated using restricted maximum likelihood [24]. The pooled estimates were backtransformed, and results were presented as proportions. We generated prediction intervals to provide a predicted range for the true incidence in any individual study [25]. As sensitivity analyses, we calculated standardised residuals, removed outliers with $p > 0.05$ (based on the t distribution), and noted changes in heterogeneity and prediction intervals.

We used metaregression and reported odds ratios (ORs), 95% Confidence Intervals (CIs), and p-values from Wald-type tests to explore whether world region or study characteristics influenced infection incidence. Infection risk was log-transformed, and univariate random-effects models were used to explore associations between each variable and odds of infection. World region and variables with evidence of association ($p < 0.1$) were included in multivariable models unless data were sparse or closely correlated.

Results

Fig 1 shows the 31,528 potentially relevant articles identified, of which 1,543 were eligible for full-text review after title and abstract screening. We could not find two full texts. Of the

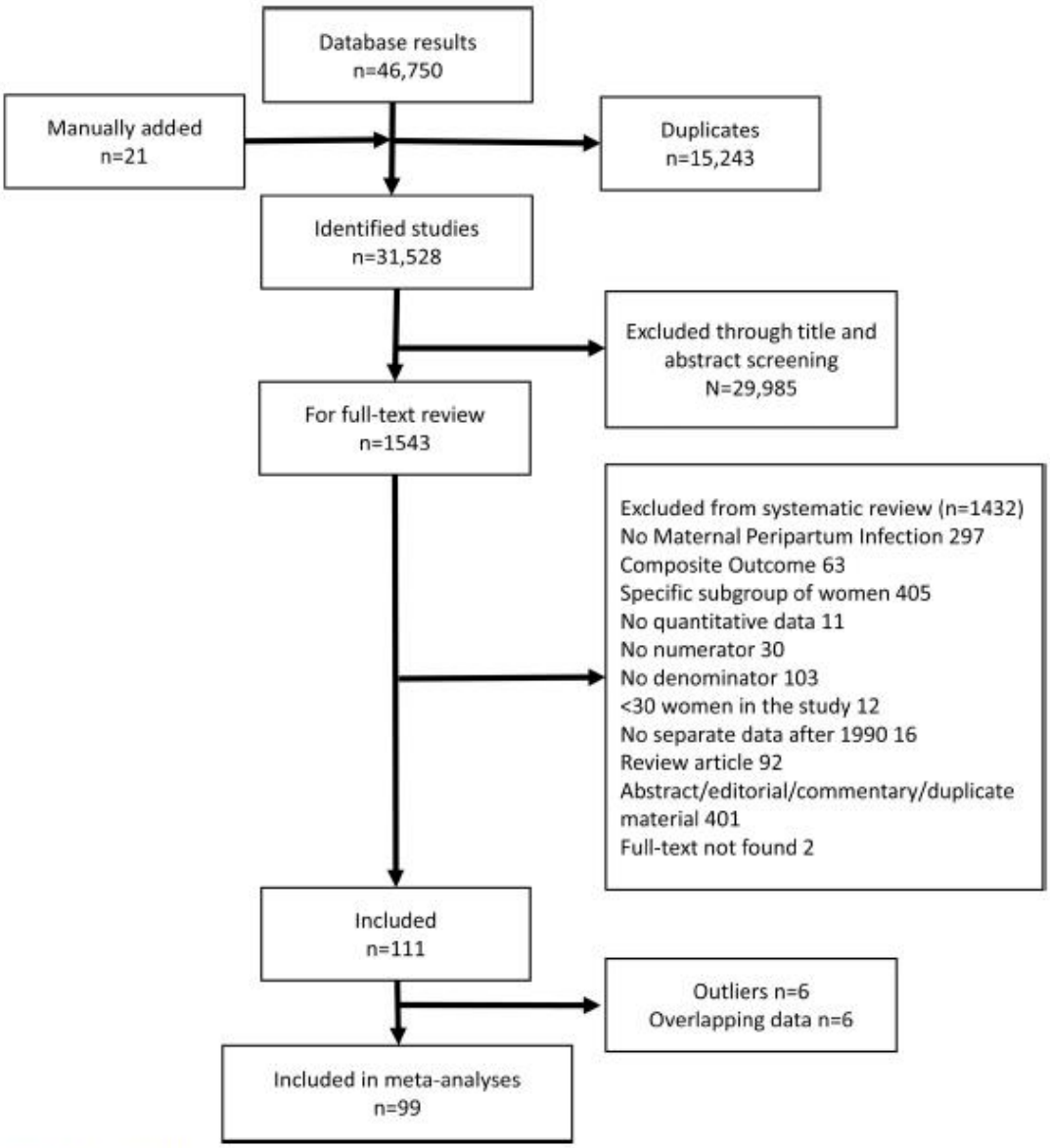

Fig 1. Flow diagram of studies.

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remaining 1,541 full texts screened, 111 were included. Common reasons for exclusions were ineligible types of publication (N = 493) or for which the study involved only a subgroup of high-risk women (N = 405), e.g., cesarean deliveries only. Most included papers were in English, with six in Chinese [26–31], four in Spanish [32–35], four in Portuguese [36–39], three in French [40–42], and one each in Bulgarian [43], Bosnian [44], and Romanian [45]. Twenty-seven studies reported chorioamnionitis, 38 reported endometritis, 28 reported wound infection, 27 reported sepsis, and 28 reported maternal peripartum infection (S2 Table–S6 Table).

Description of study populations

The 111 studies included data from 46 countries. Four studies were randomised controlled trials [28, 46–48], two were before–after intervention studies [27, 49], and the remainder were observational cohort or cross-sectional studies. Three studies had multiple countries: one covered nine European countries, a second involved nine Asian countries, and the third had sites in South Asia, Latin America, and sub-Saharan Africa. Of the remaining studies, 57 occurred in North America and Europe, of which 38 were in the US. There were 14 in Central and South Asia, 12 in East and Southeast Asia, 11 in Latin America, seven in sub-Saharan Africa, six in Western Asia and North Africa, and one in Australia. Nearly half the studies were conducted in one hospital, but many studies also attempted to capture all births in a country or a representative sample of them using birth certificate data or national hospital databases. In the regions/countries using such hospital databases (North America, Europe, Japan, and Thailand), over 95% of all births are in hospital facilities. In low- and middle-income countries (LMICs), only nine studies (in 10 countries: Tanzania, Nigeria, Egypt, Bangladesh, India, Pakistan, Argentina, Guatemala, Kenya, and Zambia) sought to capture population-level data.

Study quality

Quality scores for the studies are available in S7 Table. When studies had multiple infection outcomes, the lowest score is presented. Of 111 studies, 19% met all five quality criteria, 37% met four, 22% met three, 14% met two, 7% met one, and 2% did not meet any. Only 41% of studies used a standard definition for infection, and 37% also measured infection reliably, thereby meeting both measurement criteria. In 13% of studies, there was attrition or missing data in >15% of observations, and 31% of studies had a risk of selection bias. Women or study sites were poorly characterised in 25% of studies.

Incidence of infection

Incidence results are presented separately for the five infection outcomes (Table 3). Six studies contributed no data to the meta-analyses because of overlapping populations and dates [50–55]. Heterogeneity was high, as measured by I^2 (>99% for all pooled estimates), but tau^2 values were small and are probably more meaningful for these data since they measure actual between-study variance [56]. We identified six outlier estimates, all with high infection incidence, described below. One single-facility US study of chorioamnionitis in low-risk pregnancies provided no infection definition [57]. Three studies classified as endometritis from Bangladesh, Pakistan, and Turkey relied on self-reported symptoms of pelvic or vaginal infection [58–60]. An Indian study gave no definition for their measure of self-reported puerperal sepsis, collected up to six months after delivery [61], and similarly, a Nigerian study gave no definition for their measure of self-reported postpartum infection collected up to three years after giving birth [62]. Removal of these outliers did not change I^2 but led to important

Table 3. Summary estimates for all infection outcomes.

	All Studies		Meta-Analyses of All Studies (Excluding Outliers)			High-Quality Studies		Meta-Analysis of High-Quality Studies		
Infection Type	N	Range %	N	Pooled Incidence % (95% CI)	95% PI	N	Range %	N	Pooled Incidence % (95% CI)	95% PI
Chorioamnionitis	28	0.6–19.7	21	4.1 (2.5–6.2)	0–18.0	8	0.9–12.6	7	3.9 (1.8–6.8)	0–17.9
Endometritis	41	0–16.2	36	1.4 (0.9–1.9)	0–5.9	6	0.3–2.5	6	1.6 (0.9–2.5)	0–6.0
Wound infection	30	0–10.9	30	2.1 (1.2–3.2)	0–11.2	1	1.2	1	1.2 (1.0–1.5)	–
Sepsis	31	0–3.8	26	0.11 (0.04–0.21)	0–0.6	13	0.02–0.13	11	0.05 (0.03–0.07)	0–0.18
Maternal peripartum infection	30	0.1–18.1	26	1.9 (1.3–2.8)	0–7.9	7	0.2–5.8	7	1.1 (0.3–2.4)	0–8.3

Abbreviations: CI, Confidence Interval; PI, Prediction Interval.

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reductions in both tau^2 and prediction intervals; therefore, meta-analyses results are presented after removing these outliers.

Chorioamnionitis

Chorioamnionitis incidence ranged from 0.6% to 19.7%, with a pooled incidence of 4.1% (95% CI 2.5%–6.2%) (Table 3). The prediction interval was wide, suggesting the incidence in any future study could lie between 0% and 18%. In North America and Europe, the pooled incidence was 4.9% (Fig 2). Only three studies were conducted in other regions. In the univariate metaregression (Table 4), study extent explained 38% of the heterogeneity, with the highest incidence seen in single-hospital studies. Studies including only singleton deliveries or only term pregnancies also had higher incidence, but almost all of these studies were conducted at single facilities.

Seven high-quality studies (meeting all five quality criteria) had a pooled infection incidence of 3.9%. The lowest incidence (0.9%) was reported in low-risk women delivering at a hospital in Bangkok, Thailand [63]. The other six estimates were from the US. Two used the US National Inpatient Sample (NIS) database and recorded a chorioamnionitis ICD-9 code in 1.7% of women in 1998–2008 [64] and 2.6% in 2008–2010 [65]. Two studies from Kaiser Permanente Medical Program (KPMP) hospitals in California also used ICD-9 codes and recorded 3.5% of women in 1995–1999 [66] and 4.0% in 2010 [67]. The highest incidences were reported in studies at single tertiary hospitals: 6.1% in Chicago [68] and 12.6% in California (among women delivering a live, single, term baby) [69].

Endometritis. Endometritis incidence ranged from 0%–16.2% with a pooled incidence of 1.4% (95% CI 0.9%–1.9%) (Table 3). The prediction interval suggests a true incidence of up to 6% in future studies. Pooled incidence was similar across most world regions, ranging from 1.3%–1.9%. However, it was much lower in studies from Eastern Asia and Southeastern Asia at 0.3% (Fig 3). In univariate metaregression, no variables were associated with incidence (Table 5).

Six high-quality studies had a pooled incidence of 1.6%. The lowest incidence (0.3%) was in women delivering vaginally at 66 hospitals in a surveillance network in France [70] with follow-up to 30 days postpartum. The other five studies only reported infections until hospital discharge after childbirth. Endometritis ICD-9 codes were recorded for 1.4% of women in the NIS database [65] and 1.2% of low-risk deliveries at Kaiser Permanente hospitals in California [66]. Higher infection incidence (2.4%–2.5%) was reported in three single-centre studies: two in the US [69, 71] and one in Argentina [32].

Wound infection. Wound infection incidence ranged from 0%–10.9%, with a pooled incidence of 2.1% (95% CI 1.2%–3.2%) (Table 3). The prediction intervals suggest the

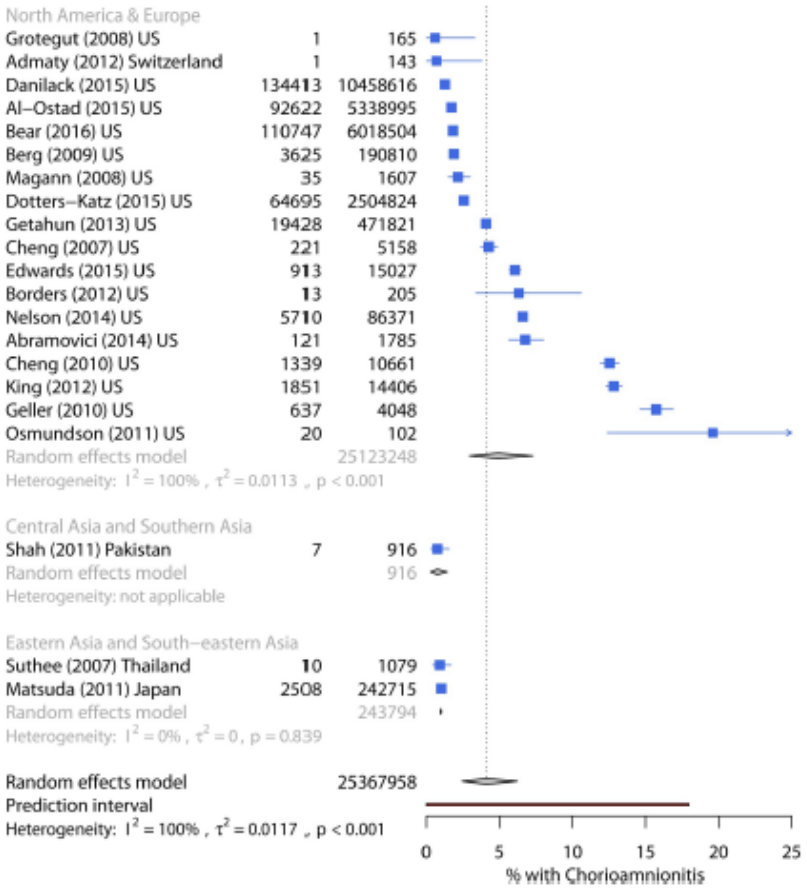

Fig 2. Forest plot of chorioamnionitis incidence by world region. CI, Confidence Interval.

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incidence could be as high as 11.2% in future studies. Pooled incidence was highest in Eastern Asia and Southeastern Asia (6.2%) and lowest in the US and Europe (0.9%) (Fig 4). In univariate metaregression, single-site studies were associated with higher infection incidence. Unexpectedly, six studies that only included vaginal deliveries had higher pooled incidence than studies that included all delivery methods. A substantial proportion (44%) of between-study heterogeneity was explained by world region and study extent in multivariable metaregression (Table 6).

Only one study met all five quality criteria and identified 1.2% of women with cesarean or episiotomy wound infection from medical records at a single Brazilian hospital [39].

Sepsis. Incidence of sepsis—combining systemic inflammatory response syndrome (SIRS), severe sepsis, and blood stream infection—ranged from 0%–3.8%, with pooled

Table 4. Chorioamnionitis univariate metaregression.

Factor		No. of Studies	OR	95% CI	p-Value	R^2 (%)
Region	North America and Europe	18	1			
	Central Asia and South Asia	1	0.17	0.02–1.26		
	East Asia and Southeast Asia	2	0.22	0.05–0.87	0.03	23.7
Study extent	Single site	12	1			
	2+ sites	2	0.11	0.02–0.54		
	Network	2	0.32	0.09–1.14		
	State	1	0.29	0.05–1.58		
	National	4	0.28	0.11–0.74	0.007	37.6
Number of foetuses	All pregnancies	8	1			
	Singleton only	13	2.64	1.07–6.53	0.04	13.9
Delivery mode	All deliveries	18	1			
	Vaginal only	3	1.41	0.37–5.43	0.61	0
Gestational age	All gestations	12	1			
	Term only	9	3.36	1.56–7.24	0.002	35.3
Live birth	All deliveries	12	1			
	Live birth only	9	1.16	0.44–3.04	0.77	0
Low risk	All women	16	1			
	Low-risk pregnancy only	5	1.56	0.52–4.69	0.43	0
Diagnosis	ICD9/10	6	1			
	Fever and other signs	7	0.85	0.25–2.95		
	Fever only	8	1.47	0.46–4.74	0.63	0
Data collection	Routine	14	1			
	Study	5	1.62	0.51–5.19		
	Unclear	2	1.29	0.25–6.52	0.71	0

Abbreviations: CI, Confidence Interval; OR, odds ratio.

https://doi.org/10.1371/journal.pmed.1002984.t004

incidence 0.10% (95% CI 0.04%–0.21%) (Table 3). The prediction interval suggests the incidence could be up to 0.6% in future studies. Pooled incidence was 0.11% for SIRS, 0.08% for severe sepsis, and 0.10% for blood stream infection (S1 Fig). The majority of estimates came from the US and Europe, with a pooled incidence of 0.10%. Latin America had a similar incidence of 0.08%, whilst Central and South Asia had slightly more infection (0.27%) (Fig 5). In univariate analysis, there was weak evidence for an association with world region, no evidence for an association with severity, but increased incidence of sepsis with longer follow-up. Women with singleton pregnancies had higher infection incidence, but the two studies involved also had longer follow-up periods. Data were too sparse to investigate other factors or conduct multivariable metaregression (Table 7).

Eleven high-quality estimates produced a pooled incidence of 0.05%. Four high-quality estimates of SIRS used data from the delivery admission: NIS (0.03%) [72], all Californian hospitals (0.10%) [73], all hospitals in Thailand (0.13%) [74], and one reference hospital in São Paolo, Brazil (0.04%) [37]. Incidence of severe sepsis with organ dysfunction was low: NIS (0.01%) [72], Californian hospitals (0.05%) [73], and no cases in a near-miss study at one hospital in Gabon [41]. US data from NIS and the National Hospital Discharge Survey (NHDS) estimated blood stream infection at 0.02% [65] and 0.07% [75]. One region in Denmark and two hospitals in Ireland followed women until 30 and 42 days postpartum and identified blood stream infection in 0.06% [76] and 0.11% [77], respectively.

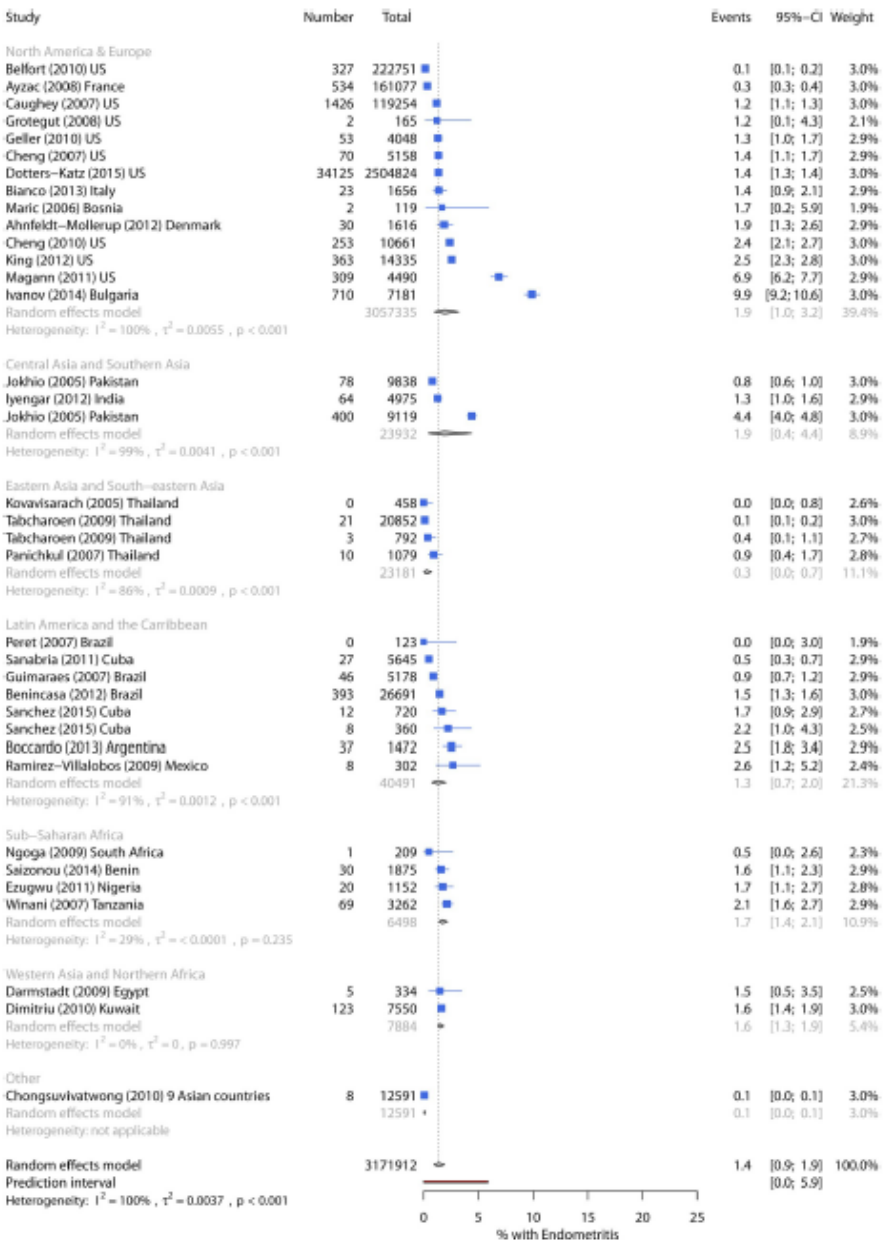

Fig 3. Forest plot of endometritis incidence by world region. CI, Confidence Interval.

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Table 5. Endometritis metaregression.

Factor		No. of Studies	OR	95% CI	p-Value	R^2 (%)
Region	North America and Europe	14	1			
	Central Asia and South Asia	3	1.09	0.35–3.46		
	East Asia and Southeast Asia	4	0.18	0.06–0.59		
	Latin America & Caribbean	8	0.91	0.39–2.11		
	Sub-Saharan Africa	4	0.99	0.33–2.97		
	West Asia and North Africa	2	1.03	0.25–4.29	0.12	8.0
Study extent	Single site	25	1			
	2+ sites	4	1.82	0.66–4.99		
	Network	2	0.48	0.13–1.81		
	State	2	1.44	0.38–5.51		
	National	2	0.34	0.09–1.29	0.20	6.9
Number of foetuses	All pregnancies	23	1			
	Singleton only	12	1.52	0.75–3.07	0.24	2.6
Delivery mode	All deliveries	31	1			
	Vaginal only	4	0.60	0.19–1.93	0.39	0
Gestational age	All gestations	27	1			
	Term only	8	1.17	0.52–2.64	0.70	0
Live birth	All deliveries	30	1			
	Live birth only	5	1.41	0.55–3.63	0.47	0
Low risk	All women	28	1			
	Low-risk pregnancy only	7	0.72	0.28–1.84	0.49	0
Diagnosis	Clinical	30	1			
	Self-report	5	1.58	0.62–4.02	0.34	0
Data collection	Routine	25	1			
	Study	10	1.25	0.58–2.68	0.57	0
Follow-up*	Hospital discharge	20	1			
	7 days	5	1.13	0.39–3.25		
	8–42 days	9	0.87	0.38–1.96	0.90	0

*Length of follow-up was missing for one study. **Abbreviations:** CI, Confidence Interval; OR, odds ratio.

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Maternal peripartum infection. Incidence of maternal peripartum infection ranged from 0.1%–18.1%, with pooled incidence of 1.9% (95% CI 1.3%–2.8%) (Table 3). The prediction intervals suggest the incidence could be up to 8% in future studies. Pooled incidence in the US and Europe was 1.9%, and in East Asia, it was 2.6%. Other regions contained only one or two studies (Fig 6), and there was no evidence that world region was associated with incidence. In univariate analysis, study extent was strongly associated with incidence. Studies with only low-risk pregnancies or vaginal deliveries also showed some evidence of association, although this was lost after adjusting for study extent (Table 8); many of these studies used either broad or poorly described definitions of infection.

Pooled incidence in seven high-quality studies was 1.1%. The highest incidence of 5.8% was from a single-facility study in China, using Ministry of Health standard diagnosis of genital tract and cesarean section incision infection [30]. All the other estimates extracted ICD-9 or 10 codes for major/other puerperal infection from state or nationally representative hospital databases with incidences of 0.2% in Canada and Thailand [74, 78], 0.5% using NIS data [79], 0.8% in all National Health Service (NHS) hospital deliveries in the UK with follow-up to 42 days

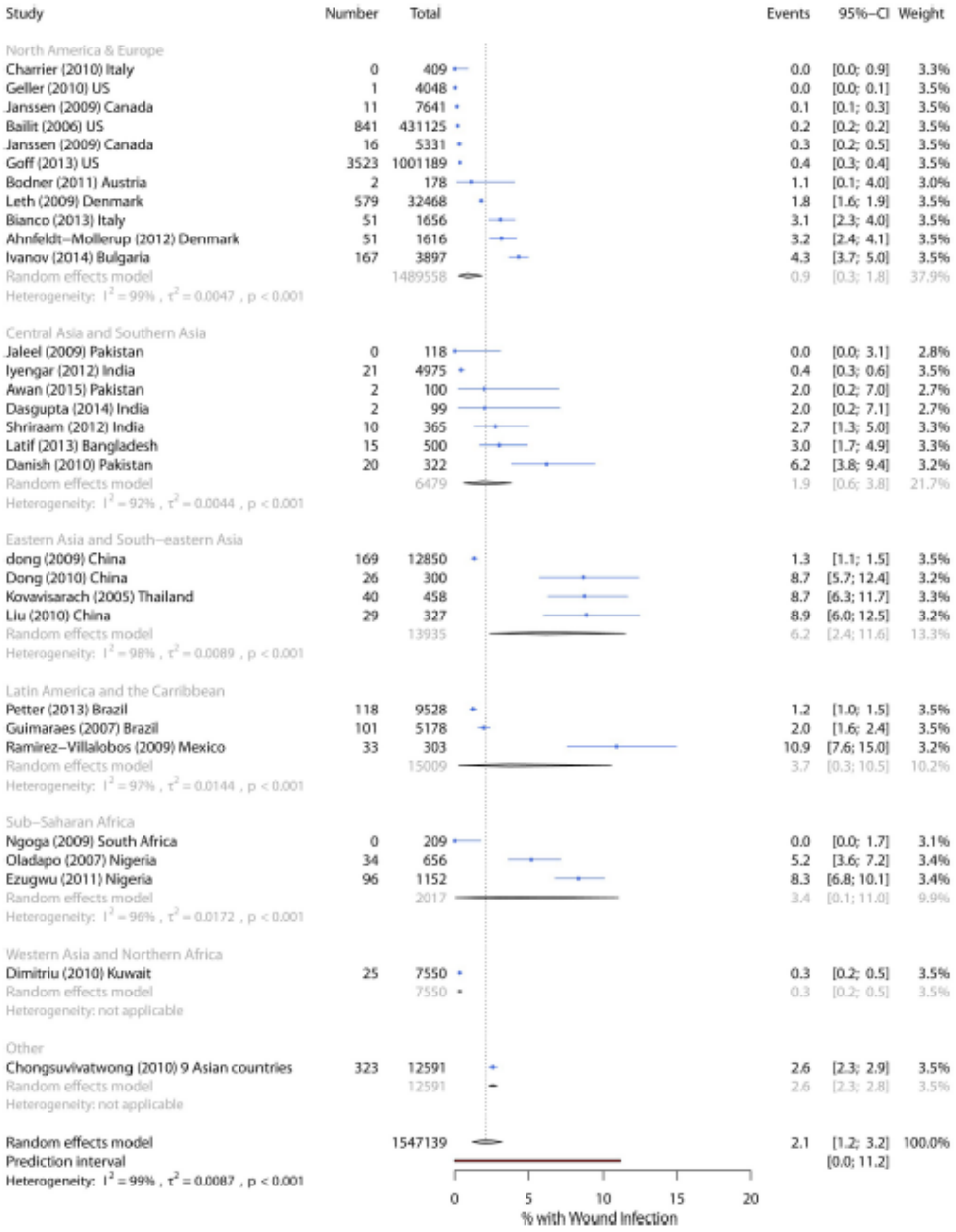

Fig 4. Forest plot of wound infection incidence by world region. CI, Confidence Interval.

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Table 6. Wound metaregression.

Factor		No. of Studies	OR	95% CI	*p*-Value	R2 (%)	Adj. OR	95% CI
							R^2 = 43.78%	
Region	North America and Europe	11	1		0.02	25.2	1	
	Central Asia and South Asia	7	3	0.83–10.82			1.84	0.48–7.12
	East Asia and Southeast Asia	4	9.1	2.11–39.20			3.85	0.89–16.72
	Latin America and the Caribbean	3	4.85	0.96–24.52			2.06	0.42–10.06
	Sub-Saharan Africa	3	5.98	1.03–34.69			2.75	0.50–15.22
	Western Asia and Northern Africa	1	0.52				0.22	0.02–2.37
Study extent	Single site	22	1		0.002	37.9		
	2+ sites	2	0.11	0.02–0.80			0.13	0.02–0.94
	State	4	0.13	0.04–0.46			0.24	0.05–1.04
	National	1	0.13	0.01–1.30			0.23	0.02–2.44
Number of foetuses	All pregnancies	21	1					
	Singleton only	8	1.95	0.56–6.75	0.29	3.5		
Delivery mode	All deliveries	24	1					
	Vaginal only	5	4.64	1.21–17.76	0.02	17.8		
Gestational age	All gestations	24	1					
	Term only	5	0.85	0.18–4.08	0.84	0		
Live birth	All deliveries	26	1					
	Live birth only	3	1.31	0.22–7.76	0.76	0		
Low risk	All women	21	1					
	Low-risk pregnancy only	8	0.60	0.17–2.14	0.43	0		
Diagnosis	Clinical	25	1					
	Self-report	4	1.58	0.62–4.02	0.33	0		
Data collection	Routine	16	1					
	Study	8	2.99	0.87–10.25				
	Unclear	5	1.92	0.40–9.19	0.21	5.9		
Follow-up*	Discharge	17	1					
	Day 7	2	3.57	0.42–30.25				
	8–42 days	8	1.26	0.38–4.22	0.50	0		

*Length of follow-up was missing from two studies. **Abbreviations:** Adj., adjusted; CI, Confidence Interval; OR, odds ratio.

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[80], and 0.9% using birth certificate data in California [81]. One large US study also included chorioamnionitis and reported 2.0% of women with infection [82].

Discussion

We systematically reviewed the incidence of maternal peripartum infection and identified 111 studies from 46 countries, representing all world regions, from among 31,528 potential studies. Pooled infection incidence in high-quality studies was 3.9% (95% CI 1.8%–6.8%) for chorioamnionitis, 1.6% (95% CI 0.9%–2.5%) for endometritis, 1.2% (95% CI 1.0%–1.5%) for wound infection (one study), and 1.1% (95% CI 0.3%–2.4%) for maternal peripartum infection. Pooled incidence of sepsis was 0.05% (95% CI 0.03%–0.07%). Studies of composite outcomes had, on average, a lower incidence than obtained by summing other infection outcomes (1.1% versus 6.7%), probably because they rarely included chorioamnionitis (3.9%) but also because coinfections can occur.

Comparing our results to other global estimates is complicated by the different definitions used. The recent 2017 GBD global incidence of maternal infection of 12.1 million women [83]

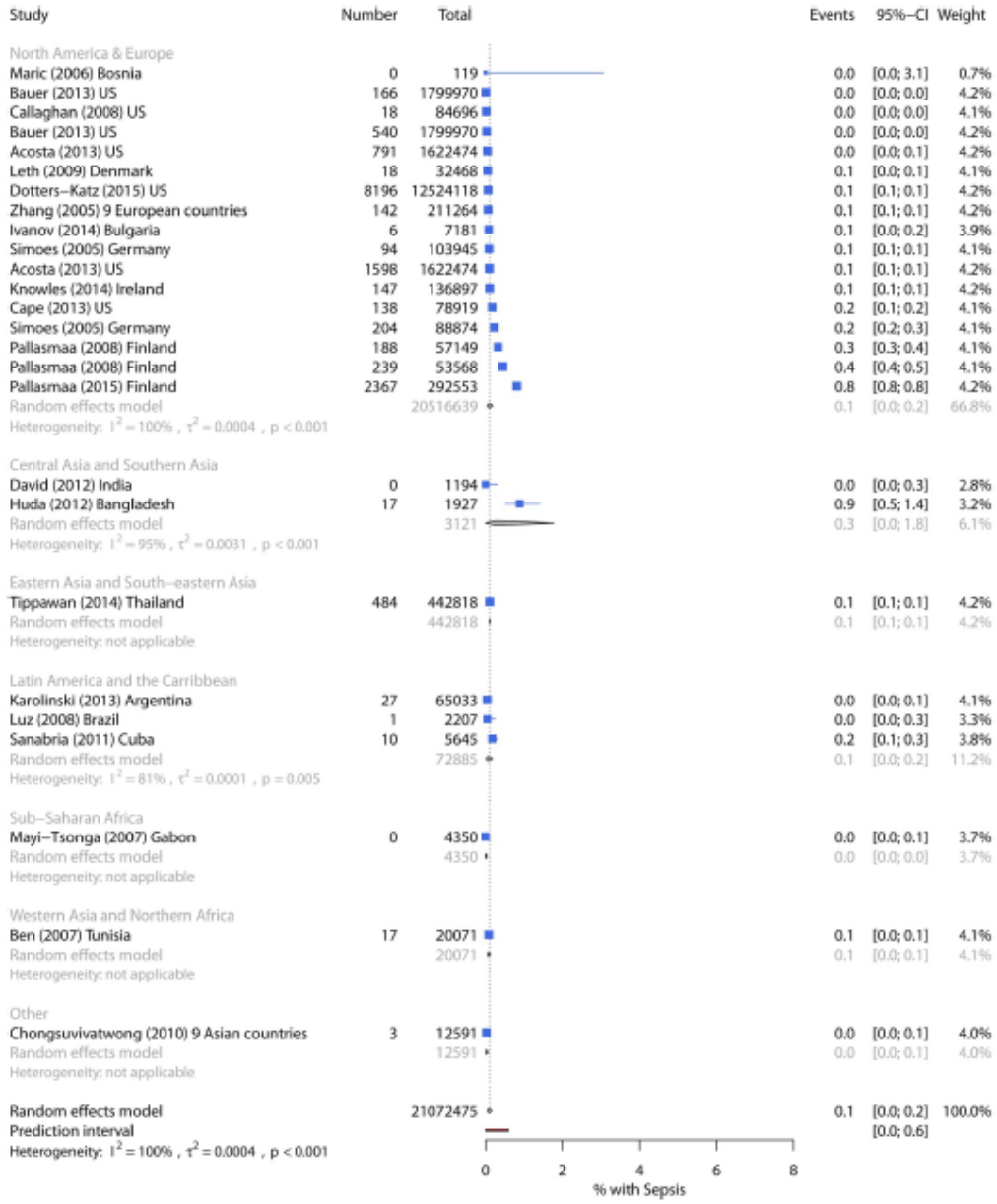

Fig 5. Forest plot of sepsis incidence by world region. CI, Confidence Interval.

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Table 7. Sepsis metaregression.

Factor		No. of Studies	OR	95% CI	*p* Value	R^2 (%)
Severity	SIRS*	13	1			
	Severe sepsis	5	0.32	0.08–1.35		
	Septicaemia/peritonitis	7	0.52	0.15–1.78	0.25	2.6
Region	North America and Europe	16	1			
	Central Asia and South Asia	3	11.00	2.25–53.75		
	East Asia and Southeast Asia	1	1.23	0.12–12.50		
	Latin America and the Caribbean	3	0.83	0.18–3.84		
	Sub-Saharan Africa	1	0.13	0.004–4.79		
	West Asia and North Africa	1	0.96	0.09–10.15	0.06	25.1
Study extent	Single site	8	1			
	2+ sites	2	6.84	0.83–56.64		
	Network	2	2.06	0.25–17.12		
	State	6	0.92	0.21–4.08		
	National	7	0.83	0.20–3.50	0.32	2.5
Number of foetuses	All deliveries	23	1			
	Singleton only	2	6.64	1.11–39.63	0.04	13.5
Delivery mode	All deliveries	23	1			
	Vaginal only	2	1.24	0.08–19.58	0.88	0
Gestational age	All gestations	25	–			
	Term only	0				
Live birth	All deliveries	24	1			
	Live birth only	1	0.37	0.02–5.54	0.47	0
Low risk	All women	24	1			
	Low-risk pregnancy only	1	0.42	0.01–14.91	0.64	0
Diagnosis	Clinical	25				
	Self-report	0				
Data collection	Routine	24	1			
	Study	1	2.99	0.87–10.25		
	Unclear	1	1.92	0.40–9.19	0.21	5.9
Follow-up*	Discharge/day 7	13	1			
	Day 8–42	10	3.57	1.55–8.22	0.003	27.2

*Length of follow-up was missing for two studies. **Abbreviations:** CI, Confidence Interval; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

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translates to an estimated 8.2% of live births [84] but includes mastitis, so it is not comparable with ours. Dolea and Stein's older figure of 4% for puerperal sepsis [6] excludes surgical site infection (SSI) but includes urinary tract infection. Our average estimates of endometritis, maternal peripartum infection, and sepsis are all substantially lower, which may reflect our exclusion of urinary tract infection or a reduction in infection since 2000. Our identification of source estimates is vastly more comprehensive than either GBD or Dolea and Stein, and we do not rely on modelling. A recently published review of infection following cesarean section in sub-Saharan Africa reports an SSI rate of 15.6% that, at their reported cesarean section rate of 12.4%, corresponds to 1.9% for the total population of women giving birth [85]. This is a little lower than the average incidence (3.4%) in our three fairly small, poor-quality African studies but does not include perineal wound infection and does lie within our prediction interval.

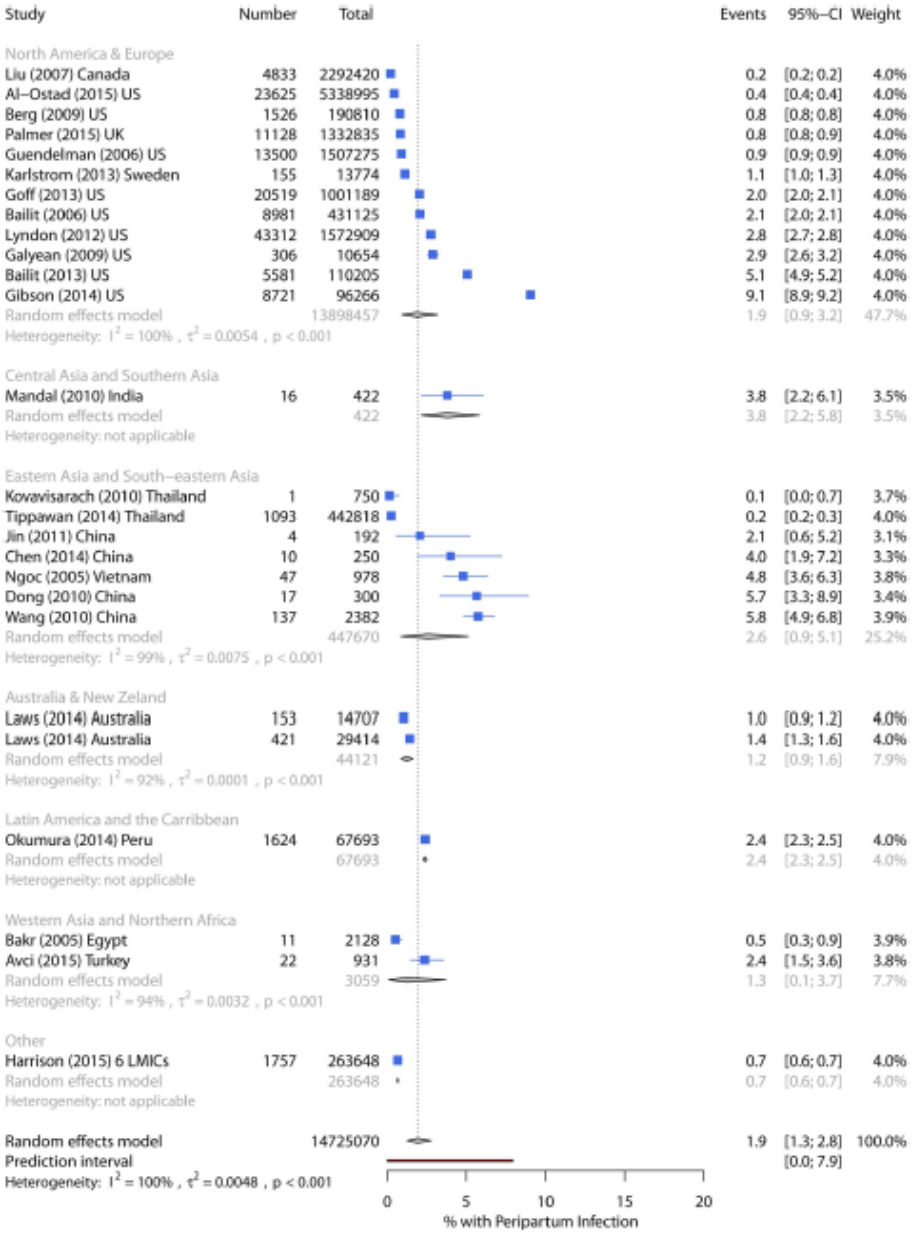

Fig 6. Forest plot of maternal peripartum infection incidence by world region. CI, Confidence Interval; LMICs, low- and middle-income countries.

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Table 8. Maternal peripartum infection metaregression.

Factor		No. of Studies	OR	95% CI	*p*-Value	R^2 (%)	Adj. OR	95% CI
							R^2 = 35.7%	
Region	North America and Europe	12	1					
	Central Asia and South Asia	1	2.63	0.24–28.80				
	East Asia and Southeast Asia	7	1.37	0.45–4.16				
	Australia and New Zealand	2	0.82	0.15–4.61				
	Latin America and the Caribbean	1	1.64	0.16–17.05				
	West Asia and North Africa	2	0.76	0.13–4.38	0.93	0		
Study extent	Single site	9	1				1	
	2+ sites	5	1.22	0.47–3.17			1.32	0.50–3.48
	Network	1	2.20	0.38–12.80			1.54	0.24–9.87
	State	3	0.72	0.23–2.24			0.88	0.27–2.85
	National	7	0.26	0.10–0.61	0.005	35.6	0.29	0.12–0.70
Number of foetuses	All deliveries	14	1					
	Singleton only	11	1.66	0.71–3.87	0.24	0.7		
Delivery mode	All deliveries	22	1					
	Vaginal only	3	3.83	1.16–12.67	0.03	14.3		
Gestational age	All gestations	17	1					
	Term only	8	0.89	0.36–2.23	0.81	0		
Live birth	All deliveries	20	1					
	Liver birth only	5	1.61	0.57–4.59	0.37	0		
Low risk	All women	19	1				1	
	Low-risk pregnancy only	6	2.34	0.90–6.04	0.08	7.3	1.74	0.71–4.27
Diagnosis	Clinical	24	–					
	Unclear	1						
Data collection	Routine	18	1					
	Study	3	2.67	0.71–10.10				
	Unclear	4	0.74	0.22–2.52	0.28	1.5		
Follow-up	Discharge	20	1					
	Until day 42	5	1.17	0.40–3.41	0.77	0		

Abbreviations: Adj., adjusted; CI, Confidence Interval; OR, odds ratio.

https://doi.org/10.1371/journal.pmed.1002984.t008

Limitations of included studies

The quality of many studies was poor, with potential for bias. Measurement bias was possible in 63% of studies, primarily because the infection was not defined, or the definition used was too broad and risked overestimating incidence. This explains part of the between-study heterogeneity observed. Attrition was minimal because most studies were cross-sectional or had short follow-up periods. There was potential selection bias in nearly one-third of studies: most trials did not describe initial selection methods, and pair-matched studies produced nonrandom control groups; however, it is unclear whether and how this might have affected infection incidence. Restricting the results to high-quality studies made little difference to the pooled estimates for chorioamnionitis or endometritis but produced lower pooled incidence for the other outcomes, although with similar prediction intervals. This lower incidence may be an underestimate of infection because some high-quality studies had narrower outcome definitions than the standards. In addition, only one lower-middle–income and four upper-middle–income countries contributed to high-quality estimates, reducing their generalisability to LMICs.

We explored and quantified the importance of world region and study characteristics on infection risk using metaregression to explain heterogeneity and better compare study estimates. Unfortunately, our analyses were limited by data sparsity. Beyond North America and Europe, data were scarce, especially from sub-Saharan Africa and Western Asia and North Africa. We found some evidence for increased wound infection outside North America and Europe but saw a mixed picture for endometritis, with surprisingly low incidence in East and Southeast Asia. In common with other studies, we found a higher incidence of SSI in LMICs, which could reflect differences in surgical and infection control practices [86]. However, studies outside North America and Europe were also more likely to be at single facilities, use self-reported symptoms, and collect data specifically for the study—all features that relate to higher incidence.

For chorioamnionitis, wound infection, and maternal peripartum infection, there was evidence that study extent was associated with infection risk. Pooled incidence was up to five times higher in single-facility studies compared to estimates using nationally representative databases, although the association was less clear with state-level studies. Large databases relying on routine medical records risk underestimating incidence because of missing or misclassified data. Conversely, studies at single tertiary-level hospitals may represent higher risk populations, especially in LMICs with low facility delivery rates, producing overestimates of population-level incidence. We excluded studies of high-risk women from this review but chose to retain single-facility studies and regress the effect of study extent on infection because omitting single facilities would lead to extensive loss of data, especially from LMICs.

Longer follow-up (risk) period was unsurprisingly associated with higher sepsis incidence, and a similar trend was observed with wound infection but lacked statistical evidence. This supports the findings of one included study in which the majority of infections occurred after hospital discharge [87]. Unfortunately, the majority of studies only collected data during hospital admission and may therefore have missed many cases.

Expected low-risk groups, including live, term, singleton, and vaginal births, did not have a lower infection risk compared to studies of all deliveries. This was surprising, but because the majority of deliveries, even in population-level studies, are also low-risk, it is difficult to show evidence of a difference. Occasionally, there was evidence of higher infection incidence in the studies of low-risk groups, but numbers were often small, and results were confounded by other study design factors.

Strengths and limitations of review

This review's strengths include the very extensive search conducted and the inclusion of articles in all languages identified. However, studies published after June 2016 have not contributed to the findings. Our review adopted the 2015 WHO definition of maternal peripartum infections and used international standard definitions among its quality criteria. It could be criticised for not restricting included studies to those meeting the full WHO definition, including the specified time period from onset of labour until 42 days postpartum. However, it is telling that none of the studies measured this exact outcome, and very few of those investigating postpartum infection continued until 42 days.

The review reported infection outcomes as an incident risk. This assumes all women were at risk (i.e., free of the infections under consideration) at the start of follow-up: onset of labour or immediately postpartum. However, some studies were unable or did not seek to exclude women with existing infections, potentially overestimating the incidence. Some studies only assessed or interviewed women at one time point after delivery; however, follow-up periods were short, so the chance of missing infections is small. We excluded studies that only assessed

high-risk subgroups of women; however, we did not limit our review to population-level studies, potentially overestimating infection incidence, as discussed above. Conversely, we did include groups of low-risk women, and so our pooled estimates may be an underestimate.

There are arguments against pooling estimates in the presence of extensive heterogeneity. Although I^2 was very high, this is driven by the substantial number of large, precise studies [56]. Tau^2 is a more relevant measure of heterogeneity in this case, and values were small. Moreover, we believe that within our outcome groups, each study was attempting to measure the same outcome, and therefore, the average estimates remain useful, although they should be treated cautiously and not overinterpreted as measures of global incidence.

Conclusion

To our knowledge, this is the first global systematic review of maternal peripartum infection incidence. It demonstrates that infection is an important complication of childbirth. Moreover, we found that a large proportion of these infections occurred in labour, with implications for the baby and the mother. Postpartum infection incidence appears lower than modelled global estimates, although the difference in definition limits comparability, and the proportion of women affected is still considerable. At a time of growing concern about antimicrobial resistance, these findings highlight the importance for clinicians and policymakers to focus efforts on improved infection prevention practices to reduce this preventable cause of maternal morbidity. Our study provides useful estimates to guide sample-size calculations for future intervention research. However, we also highlight the paucity of data from LMICs and the heterogeneity in study designs, quality, and infection definitions. Better-quality research, using standard definitions and follow-up after hospital discharge, is required to improve comparability between different study settings and to demonstrate the influence of risk factors and protective interventions.

Supporting information

S1 Checklist. PRISMA checklist. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
(DOC)

S1 Text. Search strategy.
(DOCX)

S2 Text. Data extraction form.
(DOCX)

S1 Table. ICD codes for infection outcomes.
(DOCX)

S2 Table. Studies of chorioamnionitis.
(DOCX)

S3 Table. Studies of endometritis.
(DOCX)

S4 Table. Studies of wound infection.
(DOCX)

S5 Table. Studies of sepsis.
(DOCX)

S6 Table. Studies of maternal peripartum infection.
(DOCX)

S7 Table. Quality of 111 included studies.
(DOCX)

S1 Fig. Forest plot of sepsis incidence by severity.
(TIF)

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Writing – review & editing: Susannah L. Woodd, Ana Montoya, Maria Barreix, Li Pi, Clara Calvert, Andrea M. Rehman, Doris Chou, Oona M. R. Campbell.

References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014; 2(6):e323–e333. https://doi.org/10.1016/S2214-109X(14)70227-X PMID: 25103301

2. Bonet M, Pileggi VN, Rijken MJ, Coomarasamy A, Lissauer D, Souza JP, et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health. 2017; 14(1):67. https://doi.org/10.1186/s12978-017-0321-6 PMID: 28558733
3. Hussein J, Walker L. Puerperal sepsis in low and middle income settings: past, present and future. Maternal and Infant Deaths: Chasing Millennium Development Goals. 2010; 4:131–147.
4. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? The Lancet. 2005; 365(9462):891–900.
5. Gon G, Leite A, Calvert C, Woodd S, Graham WJ, Filippi V. The frequency of maternal morbidity: A systematic review of systematic reviews. International Journal of Gynecology & Obstetrics. 2018; 141:20–38.
6. Dolea C, Stein C. Global burden of maternal sepsis in the year 2000. Evidence and information for policy. Geneva: World Health Organisation; 2003.
7. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018; 392(10159):1789–1858.
8. WHO. The prevention and management of puerperal infections: report of a technical working group. Geneva: 1992.
9. Centers for Medicare Medicaid Services. ICD-10-CM Official Guidelines for Coding and Reporting FY2019. 2018. [cited 2018 Aug 28]. Available from: https://www.cms.gov/Medicare/Coding/ICD10/Downloads/2019-ICD10-Coding-Guidelines-.pdf.
10. Collins Dictionary of Medicine 2004, 2005 [Internet]. S.v. "puerperal sepsis." [cited 2018 Dec 11]. Available from: https://medical-dictionary.thefreedictionary.com/puerperal+sepsis.
11. WHO. WHO recommendations for prevention and treatment of maternal peripartum infections. Geneva: WHO; 2015.
12. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. International Journal of Evidence-based Healthcare. 2015; 13(3):147–153. https://doi.org/10.1097/XEB.0000000000000054 PMID: 26317388
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315(8):801–810. https://doi.org/10.1001/jama.2016.0287 PMID: 26903338
14. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clinics in Perinatology. 2010; 37(2):339–354. https://doi.org/10.1016/j.clp.2010.02.003 PMID: 20569811
15. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control. 2008; 36(5):309–332. https://doi.org/10.1016/j.ajic.2008.03.002 PMID: 18538699
16. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Medicine. 2003; 29(4):530–538. https://doi.org/10.1007/s00134-003-1662-x PMID: 12664219
17. Alkaline Software. ICD9Data.com: Alkaline Software; 2015 [cited 2018 Aug 28]. Available from: http://www.icd9data.com/.
18. WHO. International Statistical Classification of Diseases and Related Health Problems 10th Revision 2016 [cited 2018 Aug 28]. Available from: https://icd.who.int/browse10/2016/en.
19. United Nations. [Internet.] SDG Indicators 2017 [cited 2018 Nov 5]. Available from: https://unstats.un.org/sdgs/indicators/regional-groups/.
20. Schwarzer G. meta: An R package for meta-analysis. R News. 2007; 7(3):40–45.
21. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010; 36(3):1–48.
22. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics. 1950:607–611.
23. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013; 67:974–978. https://doi.org/10.1136/jech-2013-203104 PMID: 23963506
24. Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? Journal of Statistical Planning and Inference. 2010; 140(4):961–970.
25. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011; 342:d549. https://doi.org/10.1136/bmj.d549 PMID: 21310794

26. Chen L, Liu J, Kang Y, Liu J, Sufeng H. [Relationship between pre-pregnant body mass index and pregnancy growth with maternal and neonatal outcomes]. Chongqing Medicine. 2014; 43(10):1178–1180.

27. Dong L. [Management and Monitoring Measure of Nosocomial Infection in Cesarean Section, Normal Delivery, Domiciliary Delivery Integral Delivery Room]. Chinese Journal of Nosocomiology. 2009; 19 (16):39.

28. Dong L, Wang G. [Effect of hand washing method to maternity and infant]. Chinese Journal of Nosocomiology. 2010; 20(15):2257–2259.

29. Liu H, Cui Y. [Relationship between body mass index of pregnant women and postpartum incision infection]. Maternal and Child Health Care of China. 2010; 25(18):2485–2486.

30. Wang X, Yu X, Qian X. [Postpartum intrauterine infection: clinical features and preventive measures]. Chinese Journal of Nosocomiology. 2010; 20(14):2050–2051.

31. Jin Z, Chi X, Teng W, Wang X, Xu Q, Wang P, et al. [Sex hormone-binding globulin of gestational diabetes mellitus pregnant women with well-controlled glucose and pregnancy outcomes]. Zhonghua fu Chan ke za zhi. 2011; 46(6):422–426. PMID: 21781582

32. Boccardo J, Manzur A, Duarte N, Yanzon C, Mazzanti A, Paparotti L, et al. [Puerperal endometritis in our setting]. Actual SIDA Infectol. 2013; 21(80):48–52.

33. Okumura JA, Maticorena DA, Tejeda JE, Mayta-Tristán P. [Teenage pregnancy as a risk factor for obstetric and perinatal complications at a hospital in Lima, Peru]. Revista Brasileira de Saúde Materno Infantil. 2014; 14(4):383–392.

34. Sanabria Fromherz ZE, Fernández Arenas C. [Pathologic behavior of puerperium] Revista Cubana de Obstetricia y Ginecologia. 2011; 37(3):330–340.

35. Sánchez JMB, Serrano YP, Soler JRM. [Advanced maternal age as a conducive element in obstetric complications and birth]. Revista de Ciencias Médicas de Pinar del Rio. 2015; 19(5):789–802.

36. Benincasa BC, Walker C, Cioba C, Rosa CCdS, Martins DE, Oliveira EDAd, et al. [Rates of infection related to cesarean and vaginal delivery at HCPA]. Revista HCPA Porto Alegre. 2012; 32(1):5–9.

37. Luz AG, Tiago DB, Silva JCGd, Amaral E. [Severe maternal morbidity at a local reference university hospital in Campinas, São Paulo, Brazil]. Revista Brasileira de Ginecologia e Obstetrícia. 2008; 30 (6):281–286. https://doi.org/10.1590/s0100-72032008000600003 PMID: 19142505

38. Péret FJA, Melo VH, Paula LBd, Andrade BAMd, Pinto JA. [Puerperal morbidity in HIV-infected and non-infected women]. Revista Brasileira de Ginecologia e Obstetrícia. 2007; 29(5):260–266.

39. Petter CE, Farret TCF, de Souza Scherer J, Antonello VS. [Factors related to surgical site infections after obstetric procedures]. Scientia Medica. 2013; 23(1):5.

40. Ben SH, Khoudayer H, Ben HZ, Masmoudi A, Bouguerra B, Sfar R. [Severe maternal morbidity]. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction. 2007; 36(7):694–698. https://doi.org/10.1016/j.jgyn.2007.05.006 PMID: 17574775

41. Mayi-Tsonga S, Meyé J-F, Tagne A, Ndombi I, Diallo T, Oksana L, et al. [Audit of the severe obstetrical morbidity (near miss) in Gabon]. Cahiers d'Etudes et de Recherches Francophones/Santé. 2007; 17 (2):111–115.

42. Salzonou J, Ouédraogo L, Paraiso MN, Ayélo P, Kpozèhouen A, Darsalé R, et al. [Epidemiology and management of intrapartum infections in the maternity ward of Ouémé-Plateau county hospital in Benin]. The Pan African Medical Journal. 2014; 17:89. https://doi.org/10.11604/pamj.2014.17.89.2857 PMID: 25120854

43. Ivanov S, Tzvetkov K, Kovachev E, Staneva D, Nikolov D. [Puerperal infections after Cesarean section and after a natural childbirth]. Akusherstvo i Ginekologiia. 2014; 53:25–28.

44. Marić T, Tomić V, Darko K. [Puerperal complications in nulliparous women delivered by section caesarean: pair study]. Medicinski Arhiv. 2006; 60(4):246–250. PMID: 16761520

45. Dimitriu G. [Clinical statistical study on puerperal sepsis risk factors]. Revista Medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2010; 114(1):195–198. PMID: 20509301

46. Abramovici A, Szychowski JM, Biggio JR, Sakawi Y, Andrews WW, Tita AT. Epidural use and clinical chorioamnionitis among women who delivered vaginally. American Journal of Perinatology. 2014; 31 (11):1009–1014. https://doi.org/10.1055/s-0034-1371357 PMID: 24705965

47. Jokhio AH, Winter HR, Cheng KK. An intervention involving traditional birth attendants and perinatal and maternal mortality in Pakistan. New England Journal of Medicine. 2005; 352(20):2091–2099. https://doi.org/10.1056/NEJMsa042830 PMID: 15901862

48. Kovavisarach E, Jiraseftasiri P. Randomised controlled trial of perineal shaving versus hair cutting in parturients on admission in labor. J Med Assoc Thai. 2005; 88(9):1167. PMID: 16536100

49. Bakr AF, Karkour T. Effect of predelivery vaginal antisepsis on maternal and neonatal morbidity and mortality in Egypt. Journal of Women's Health. 2005; 14(6):496–501. https://doi.org/10.1089/jwh.2005.14.496 PMID: 16115003

50. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Bommarito K, Madden T, Olsen MA, et al. Maternal age and risk of labor and delivery complications. Maternal and Child Health Journal. 2015; 19(6):1202–1211. https://doi.org/10.1007/s10995-014-1624-7 PMID: 25366100

51. Dumas A-M, Girard R, Ayzac L, Beaumont G, Caillat-Vallet E, Depaix F, et al. Effect of intrapartum antibiotic prophylaxis against group B streptococcal infection on comparisons of rates of endometritis and urinary tract infection in multicenter surveillance. Infection Control & Hospital Epidemiology. 2008; 29(4):327–332.

52. Getahun D, Strickland D, Zeiger RS, Fassett MJ, Chen W, Rhoads GG, et al. Effect of chorioamnionitis on early childhood asthma. Archives of Pediatrics & Adolescent Medicine. 2010; 164(2):187–192.

53. Kyser KL, Lu X, Santillan DA, Santillan MK, Hunter SK, Cahill AG, et al. The association between hospital obstetrical volume and maternal postpartum complications. American Journal of Obstetrics and Gynecology. 2012; 207(1):42.e1–17.

54. Lyndon A, Lee HC, Gilbert WM, Gould JB, Lee KA. Maternal morbidity during childbirth hospitalization in California. The Journal of Maternal-Fetal & Neonatal Medicine. 2012; 25(12):2529–2535.

55. Malloy M. Chorioamnionitis: epidemiology of newborn management and outcome United States 2008. Journal of Perinatology. 2014; 34(8):611. https://doi.org/10.1038/jp.2014.81 PMID: 24786381

56. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I^2 in assessing heterogeneity may mislead. BMC Medical Research Methodology. 2008; 8(1):79.

57. Bleich AT, Alexander JM, McIntire DD, Leveno KJ. An analysis of second-stage labor beyond 3 hours in nulliparous women. American Journal of Perinatology. 2012; 29(09):717–722.

58. Fronczak N, Anteman G, Moran A, Caulfield L, Baqui A. Delivery-related complications and early postpartum morbidity in Dhaka, Bangladesh. International Journal of Gynecology & Obstetrics. 2005; 91(3):271–278.

59. Ghani N, Rukanuddin RJ, Ali TS. Prevalence and factors associated with postpartum vaginal infection in the Khyber agency federally administered tribal areas, Pakistan. Journal of Pakistan Medical Association. 2007; 57(7):363.

60. Gözüm S, Kiliç D. Health problems related to early discharge of Turkish women. Midwifery. 2005; 21(4):371–378. https://doi.org/10.1016/j.midw.2005.02.005 PMID: 16024147

61. Shiraam V, Shah P, Rani M, Palani G, Sathiyasekaran B. Postpartum morbidity and health seeking pattern in a rural community in South India–population based study. Indian Journal of Maternal and Child Health. 2012; 14(3):10.

62. Andersson N, Omer K, Caldwell D, Dambam MM, Malkudi AY, Effiong B, et al. Male responsibility and maternal morbidity: a cross-sectional study in two Nigerian states. BMC Health Services Research. 2011; 11(2):S7.

63. Suthee Panichkul M, Boonprasert K, Komolpis S, Panichkul P. The association between meconium-stained amniotic fluid and chorioamnionitis or endometritis. J Med Assoc Thai. 2007; 90(3):442–447. PMID: 17427518

64. Al-Ostad G, Kezouh A, Spence AR, Abenhaim HA. Incidence and risk factors of sepsis mortality in labor, delivery and after birth: Population-based study in the USA. Journal of Obstetrics and Gynaecology Research. 2015; 41(8):1201–1206. https://doi.org/10.1111/jog.12710 PMID: 25876287

65. Dotters-Katz S, Patel E, Grotegut C, Heine R. Acute infectious morbidity in multiple gestation. Infectious Diseases in Obstetrics and Gynecology. 2015; 2015:173261. https://doi.org/10.1155/2015/173261 PMID: 25684973

66. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal and obstetric complications of pregnancy are associated with increasing gestational age at term. American Journal of Obstetrics and Gynecology. 2007; 196(2):155.e1–6.

67. Braun D, Bromberger P, Ho NJ, Getahun D. Low rate of perinatal sepsis in term infants of mothers with chorioamnionitis. American Journal of Perinatology. 2016; 33(02):143–150.

68. Edwards SE, Grobman WA, Lappen JR, Winter C, Fox R, Lengueirand E, et al. Modified obstetric early warning scoring systems (MOEWS): validating the diagnostic performance for severe sepsis in women with chorioamnionitis. American Journal of Obstetrics and Gynecology. 2015; 212(4):536.e1–8.

69. Cheng YW, Shaffer BL, Bryant AS, Caughey AB. Length of the first stage of labor and associated perinatal outcomes in nulliparous women. Obstetrics & Gynecology. 2010; 116(5):1127–1135.

70. Ayzac L, Caillat-Vallet E, Girard R, Chapuis C, Depaix F, Dumas A-M, et al. Decreased rates of nosocomial endometritis and urinary tract infection after vaginal delivery in a French surveillance network, 1997–2003. Infection Control & Hospital Epidemiology. 2008; 29(6):487–495.

71. King JR, Korst LM, Miller DA, Ouzounian JG. Increased composite maternal and neonatal morbidity associated with ultrasonographically suspected fetal macrosomia. The Journal of Maternal-Fetal & Neonatal Medicine. 2012; 25(10):1953–1959.

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

73. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLoS ONE. 2013; 8(7):e67175. https://doi.org/10.1371/journal.pone.0067175 PMID: 23843991

74. Tippawan Liabsuetrakul M, Suchonwanich Y. Birth rates and pregnancy complications in adolescent pregnant women giving birth in the hospitals of Thailand. J Med Assoc Thai. 2014; 97(8):785–790. PMID: 25345252

75. Callaghan WM, MacKay AP, Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991–2003. American Journal of Obstetrics and Gynecology. 2008; 199 (2):133.e1–8.

76. Leth RA, Møller JK, Thomsen RW, Uldbjerg N, Nørgaard M. 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. 2009; 88(9):976–983. https://doi.org/10.1080/00016340903147405 PMID: 19642043

77. Knowles S, O'sullivan N, Meenan A, Hanniffy R, Robson M. Maternal sepsis incidence, aetiology and outcome for mother and fetus: a prospective study. BJOG: An International Journal of Obstetrics & Gynaecology. 2015; 122(5):663–671.

78. Liu S, Liston RM, Joseph K, Heaman M, Sauve R, Kramer MS. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. CMAJ. 2007; 176(4):455–460. https://doi.org/10.1503/cmaj.060870 PMID: 17296957

79. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Maternal and Child Health Journal. 2008; 12(4):469–477. https://doi.org/10.1007/s10995-007-0256-6 PMID: 17690963

80. Palmer WL, Bottle A, Aylin P. Association between day of delivery and obstetric outcomes: observational study. BMJ. 2015; 351:h5774. https://doi.org/10.1136/bmj.h5774 PMID: 26602245

81. Guendelman S, Thornton D, Gould J, Hosang N. Obstetric complications during labor and delivery: assessing ethnic differences in California. Women's Health Issues. 2006; 16(4):189–197. https://doi.org/10.1016/j.whi.2005.12.004 PMID: 16820523

82. Goff SL, Pekow PS, Avrunin J, Lagu T, Markenson G, Lindenauer PK. Patterns of obstetric infection rates in a large sample of US hospitals. American Journal of Obstetrics and Gynecology. 2013; 208 (6):456.e1–13.

83. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016; 388(10053):1545.

84. United Nations DESA/Population Division. World Population Prospects 2017 [Internet]. 2017 [cited 2019 May 9]. Available from: https://population.un.org/wpp/Download/Standard/Fertility/.

85. Sway A, Nthumba P, Solomkin J, Tarchini G, Gibbs R, Ren Y, et al. Burden of surgical site infection following cesarean section in sub-Saharan Africa: a narrative review. International Journal of Women's Health. 2019; 11:309. https://doi.org/10.2147/IJWH.S182362 PMID: 31191039

86. Sobhy S, Arroyo-Manzano D, Murugesu N, Karthikeyan G, Kumar V, Kaur I, et al. Maternal and perinatal mortality and complications associated with caesarean section in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet. 2019; 393(10184):1973–1982.

87. Bianco A, Roccia S, Nobile CG, Pileggi C, Pavia M. Postdischarge surveillance following delivery: the incidence of infections and associated factors. American Journal of Infection Control. 2013; 41(6):549–553. https://doi.org/10.1016/j.ajic.2012.06.011 PMID: 23219668

Appendix B: PRISMA Checklist for manuscript 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title: A systematic review and meta-analysis
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction paragraph 1. "Infection is an important preventable cause of maternal morbidity and mortality… However, the frequency of infection in pregnancy is poorly understood…. Infection remains the one major direct cause of maternal morbidity without a published systematic literature review of incidence"
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction paragraph 3 "This review focusses on recent epidemiological evidence for the incidence of 'maternal peripartum infection', defined by the World Health Organization (WHO) in 2015 to encompass infections of the genital tract and surrounding tissues from onset of labour or rupture

			of membranes until 42 days postpartum”
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods paragraph 1 PROPSERO CRD42017074591
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods/*Exclusion criteria* “All identified studies were systematically assessed, irrespective of language or study design” Exclusions included studies with: “Only a subgroup of women at higher risk of infection than the general population of peripartum women (e.g. only caesarean section deliveries or only women with diabetes) Data collected before 1990. If a study spanned 1990 but disaggregated by year, data from 1990 onwards were used Conference and poster abstracts” Methods/*Outcome definitions* The WHO definition of Maternal Peripartum Infection “We considered this to encompass specific constituent infections, namely chorioamnionitis in labour, puerperal endometritis, and wound infection following caesarean section, perineal tear or episiotomy. We included sepsis occurring within the defined time-period, restricted to sepsis of genital tract or wound origin where possible.”

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods/*Search strategy* "We searched Medline, EMBASE, Global Health, Popline, CINAHL, the Latin American and Caribbean Health Science Information (LILACS), Africa-Wide Information and regional WHO on-line databases using Global Index Medicus from January 2005 to June 2016." Methods/Screening and data extraction
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Appendix Search strategies for all databases included
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods/*Exclusion criteria* Studies were excluded if their titles or abstracts met the listed exclusion criteria "We sought the full-text for all remaining studies, including those where the abstract had insufficient information to make a decision. The same exclusion criteria applied to full texts." Methods/*Screening and data extraction* "SW and AM double-screened 300 (~1%) title and abstracts to ensure consistency; the rest were single-screened. Queries were resolved through discussion. Full-text screening and extraction was conducted by SW, AM and MB, with approximately 8% of articles double-screened and extracted to ensure consistency"
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from	Methods/*Screening and data extraction* As above – 8% of articles were extracted in duplicate.

		investigators.	"Nine authors were contacted to clarify study eligibility."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods/*Screening and data extraction* "Data extracted included language, location and dates of study, study population, study design, sampling, outcome definition, denominator, time-period for observing infection, data source, diagnosis, and incidence of infection" Full details in S2 Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods/*Critical appraisal of studies* "We appraised the quality of each study outcome according to criteria in Table 1, adapted from Joanna Briggs Institute criteria for assessing incidence/prevalence studies" Table 1. – Quality Assessment Criteria Assess for selection bias, attrition bias and measurement bias. Table 2. Standard definitions for infection outcomes Used to assess measurement bias Methods/*Data management and analysis* paragraph 3 Subgroup analysis of studies meeting all quality criteria "to obtain a weighted pooled estimate of incidence of each infection outcome, for 1) all studies, 2) high quality studies"
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods/*Data management and analysis* paragraph 3 "a weighted pooled estimate of incidence of each infection outcome"
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods/*Data management and analysis* paragraph 4 "Infection incidence risk (as a proportion) was transformed using the

			Freeman-Tukey transformation to approximate a normal distribution and stabilise the variance. Because study designs and outcome definitions varied, we used random effects to combine study estimates. The tau^2 measure of between-study heterogeneity was estimated using restricted maximum likelihood. The pooled estimates were back-transformed and results presented as proportions."

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods/*Data management and analysis* paragraph 3 Subgroup analysis of studies meeting all quality criteria – at low-risk of bias "to obtain a weighted pooled estimate of incidence of each infection outcome, for 1) all studies, 2) high quality studies"
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods/*Data management and analysis* paragraph 3 Pre-specified subgroups – high quality and world regions "weighted pooled estimate of incidence of each infection outcome, for 1) all studies, 2) high quality studies, and 3) stratified by world region" Methods/*Data management and analysis* paragraph 4 Sensitivity analysis "As sensitivity analyses we calculated standardised residuals and removed outliers with p>0.05 (based on the t distribution). We

			compared heterogeneity and precision intervals before and after the removal of outliers." Methods/*Data management and analysis* paragraph 5 Pre-specified meta-regression of world region and study characteristics "We used meta-regression and reported odds ratios (OR) to explore whether world region or study characteristics influenced infection incidence. Infection risk was log-transformed and univariate random effects models used to explore associations between each variable and odds of infection."
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results/Paragraph 1 "Figure 1 shows the 31,528 potentially relevant articles identified, of which 1543 were eligible for full-text review after title and abstract screening. We could not find two full-texts. Of the remaining 1541 full-texts screened, 111 were included" Reasons for exclusion indicated in the Flow Diagram, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	S3 Tables 1-5 include extracted study characteristics
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S4 Table 6 indicates quality score (risk of bias) at study level for each study. S3 tables 1-5 indicates the score at outcome level
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Summary data S3 Tables 1-5. Forest plots for each outcome Fig. 2-6.

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3 Subgroup meta-analysis of high-quality studies only,
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Sensitivity 16(234). Subgroup analysis by world region for each outcome: forest plots Fig. 2-6. Meta-regression Tables 4-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion paragraph 1 – Main findings. "Pooled infection incidence in high-quality studies was 3.9% for chorioamnionitis, 1.6% for endometritis, 1.2% for wound infection and 1.1% for maternal peripartum infection. Pooled incidence of sepsis was 0.05%." Relevance
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion paragraph 3 – risk of bias at study and outcome level "The quality of many studies was poor, with potential for bias. Measurement bias was possible in 63% of studies, primarily because the infection was not defined or the definition used was too broad and risked over-estimating incidence." Discussion paragraph 5 – limitations from 'study extent' "For all outcomes apart from sepsis, there was evidence that study extent was associated with infection. Pooled incidence was up to five times higher in single-facility studies compared to estimates using nationally-representative databases"

			Discussion paragraph 6 – limitations from study follow-up period "Longer follow-up (risk) period was unsurprisingly associated with higher sepsis incidence, and a similar trend was observed with the other outcomes but lacked statistical evidence." Discussion/Strengths and weaknesses, paragraph 2 – limitations at review level. For example: "We did not limit our review to population-level studies potentially over-estimating infection incidence as discussed above. In addition, we did include groups of low-risk women and so our pooled estimates may be an underestimate. Due to marked between-study heterogeneity studies are given almost equal weight regardless of their size with potential for bias from small study effects."
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion/Conclusion "infection remains an important complication of childbirth. Incidence risk appears lower than modelled global estimates, although the difference in definition limits comparability. The review highlights the paucity of data from LMICs and the marked heterogeneity in study designs and infection definitions. Better quality research, using standard definitions and follow-up after hospital discharge, is required to improve comparability between different study settings and to demonstrate the influence of risk factors and protective interventions."
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Uploaded separately

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix C: Search Strategy for manuscript 1

Medline/EMBASE/Global Health

1. Maternal text adj5 sepsis text
2. Maternal infection (text OR Mesh)
3. ((Maternal text adj2 complication text) OR maternal complications Mesh) AND infection
4. 1 or 2 or 3
5. Prevalence text
6. Prevalence Mesh
7. 5 or 6
8. 4 and 7
9. Restricted to Human/2005 Current

Maternal/pregnancy terms

Texts	
matern* OR pregnan* OR childbirth OR intrapartum OR intra-partum OR postpartum OR post-partum OR postnatal OR puerperal OR puerperium OR parturition OR obstetric OR labo*r OR partum OR deliver* OR perineal OR perineum OR caesarean	

Sepsis

Texts	
sepsis OR septic OR septic?em* OR endometritis OR metritis OR endomyometritis OR endoparametritis OR amnionitis OR placentitis OR membranitis OR infect* OR cervicitis OR vaginitis OR organ failure	

Maternal Infection

Texts	[MeSH]
Chorioamnionitis OR ((puerperal or childbed or postpartum or post-partum) adj (fever or pyrexia)) OR puerperal peritonitis	Chorioamnionitis/ OR pregnancy complications, infectious/ OR puerperal infection/

Maternal Complications with infection

Texts	[MeSH]
(Pregnan* or obstetric or postpartum or post-partum or maternal) adj2	Pregnancy complications/ OR obstetric labor complications/ or puerperal disorders/

(complication* or morbidit* or outcomes or near-miss)	
AND	
(sepsis or septic or fever or infection* or pyrexi*)	

Prevalence/incidence/study

Texts	[MeSH]
prevalence OR proportion OR percent* OR frequency OR incidence OR rate* OR cohort OR longitudinal study OR follow-up study OR prospective study OR retrospective study OR cross-sectional OR intervention study OR trial OR community-based study OR population-based study OR observational study OR evaluat* OR audit OR epidemiology	prevalence/ OR incidence/ OR epidemiology/ OR epidemiologic methods/ OR clinical studies as topic/ OR epidemiologic studies/
NOT	
case report* or comment or practice guideline* or editorial or consensus development conference or guideline* or legal case* or legislation or newspaper article or patient education handout or retracted publication	

Results

- Medline 10,934
- EMBASE 17732
- Global Health 6196

CINAHL plus - Results 4790

Using the terms above:

1. Maternal text N5 sepsis text
2. Maternal infection (text OR Mesh)
3. ((Maternal text N2 complication text) OR maternal complications Mesh) AND infection
4. 1 or 2 or 3
5. Prevalence text
6. Prevalence Mesh
7. 5 or 6
8. 4 and 7
9. Restricted to 2005-Current & Excluded MEDLINE records

Global Index Medicus – Results 1539.

Restricted to Western Pacific (WPRIM), Eastern Mediterranean (IMEMR), South-East Asian (IMSEAR) and Africa (AIM) Regions and the WHO library (WHOLIS) and 2005-2016.

Search in title, abstract, subject

1. Maternal text
2. Sepsis text
3. Prevalence text
4. 1 and 2 and 3

Maternal Text

matern* OR pregnan* OR childbirth OR intrapartum OR intra-partum OR postpartum OR post-partum OR postnatal OR puerperal OR puerperium OR parturition OR obstetric OR labo*r OR partum OR deliver* OR perineal OR perineum OR caesarean

Sepsis Text

sepsis OR septic OR septicem* OR septicaem* OR endometritis OR metritis OR endomyometritis OR endoparametritis OR amnionitis OR placentitis OR membranitis OR infect* OR cervicitis OR vaginitis OR "organ failure"

Prevalence Text

prevalence OR proportion OR percent* OR frequency OR incidence OR rate* OR cohort OR "longitudinal study" OR "follow-up study" OR "prospective study" OR "retrospective study" OR cross-sectional OR "intervention study" OR trial OR "community-based study" OR "population-based study" OR "observational study" OR evaluat* OR audit OR epidemiology

POPLINE – Results 539

Restricted to 2005-2016

"matern* sepsis" ~5 OR "pregnancy sepsis" ~5 OR "childbirth sepsis" ~5 OR "intrapartum sepsis" ~5 OR "intra-partum sepsis" ~5 OR "puerperal sepsis" ~5 OR "postpartum sepsis" ~5 OR "post-partum sepsis" ~5 OR "postnatal sepsis" ~5 OR "puerperium sepsis" ~5 OR "parturition sepsis" ~5 OR "obstetric sepsis" ~5 OR "labor sepsis" ~5 OR "labour sepsis" ~5 OR "deliver* sepsis" ~5 OR "matern* infection*" ~5 OR "pregnancy infection*" ~5 OR "childbirth infection*" ~5 OR "intrapartum infection*" ~5 OR "intra-partum infection*" ~5 OR "puerperal infection*" ~5 OR "postpartum infection*" ~5 OR "post-partum infection*" ~5 OR "postnatal infection*" ~5 OR "puerperium infection*" ~5 OR "parturition infection*" ~5 OR "obstetric infection*" ~5 OR "labor infection*" ~5 OR "labour infection*" ~5 OR "deliver* infection*" ~5 OR "perineal infection*" ~5 OR "perineum infection*" ~5 OR "caesarean infection*" ~5 OR "puerperal fever" OR "childbed fever" OR "postpartum fever" OR "post-partum fever" OR "puerperal pyrexia" OR "postpartum pyrexia" OR "post-partum pyrexia" OR "puerperal peritonitis" OR chorioamnionitis OR endometritis

Africa Wide Information – Results 3067

Restricted to 2005-Current

(matern* or pregnan* or childbirth or intrapartum or intra-partum or postpartum or post-partum or postnatal or puerperal or puerperium or parturition or obstetric or labo*r or partum or deliver* or perineal or perineum or caesarean) N5 (sepsis or septic or septic?em* or endometritis or metritis or endomyometritis or endoparametritis or amnionitis or placentitis or membranitis or infect* or pyrexi* or cervicitis or vaginitis or organ failure or chorioamnionitis or puerperal fever or childbed or puerperal peritonitis or Chorioamnionitis+ or puerperal infection+)

LILACS – Results 1955

Matern? Or Embaraz? Or parto or alumbramiento or nacimiento or intraparto or postparto or postnatal or puerperal or puerperio or trabajo de parto or perineo or perineum or cesárea AND Sepsis or séptico or septicemia or endometritis or parametritis or amnionitis or infección or fiebre or cervicitis or vaginitis or falla sistémica or corioanmionitis or fiebre puerperal

Appendix D: Data Extraction form for manuscript 1

#	Question	Response codes
1	Language of paper	(1) English (2) French (3) German (4) Spanish (5) Portuguese (6) Chinese (7) Russian (8) Other Specify_____
	STUDY POPULATION	
2	Study Period	Month/Year Month/Year |____|___| |____|___| to |____|___| |____|___|
3	Countries included	
4	Number of study sites included (within and across countries)	
5	Which category(ies) best describes the study population at the study sites?	(1) Rural (2) Urban (3) Periurban/slum (4) Population not well described
6	Where were women recruited from?	(1) Community (2) Health centre (3) Hospital (4) Other Specify_____
7	When were women recruited?	(1) During pregnancy (2) After PROM (3) During delivery (4) Postpartum
8	If recruited at ANC, what percentage of women attend ANC in the study population?	
9	If recruited at delivery, what percentage of women attend for facility delivery in the study population?	
10	Place of delivery (select all that apply)	(1) Home (2) BEmONC centre (3) CEmONC centre (Caesarean section provided) (3) Unknown

		(4) Other Specify_____
11	Was a particular subgroup of women studied	(1) None (2) Caesarean section (3) Diabetes (4) Obesity (5) Pre-term PROM (6) PROM at term (7) Preterm labour/delivery (8) Induction of labour (9) HIV (10)Other Specify_____ (11)Other Specify_____
12	Was the whole study sample comprised of women from this subgroup?	(1) Yes (2) No (3) N/A
13	What proportion of the total population of pregnant women are in this subgroup?	
14	Any other remarks on Study Population	
	STUDY DESIGN AND SAMPLING	
15	Study design	(1) Cross-sectional (2) Cohort/Longitudinal (3) Controlled Trial (4) Incidence/Prevalence Survey (5) Unknown/unclear (6) Other Specify_____
16	Sampling	(1) Random sample Specify the method of randomization _____ (2) Non-random sample Specify the method of sampling _____ (3) Total population (i.e. census or all admissions) (4) Unknown/unclear (5) Other

		Specify_____
17	Exclusion Criteria	
18	Of those sampled, how many women refused to take part or did not respond?	
19	Were refusers different to those taking part in the study?	(1) Yes (2) No (3) Unknown
20	Total number enrolled in the study	
22	Number of the study subjects lost to follow-up (or those not included in the final analysis for cross-sectional designs and RCTs)	
23	Are the characteristics of the study subjects who refused or were lost to follow-up different from the rest of the population?	(1) YES (2) NO (3) NK
24	Any other remarks on Design and Sampling	
	STUDY OUTCOME	
25	What is the definition of sepsis/infection used in this study?	
26	What was the denominator	(1) Pregnancies (2) Women delivered (3) Live births (4) Live and still births (combined) (5) Unknown/unclear (6) Other Specify_____
27	When did follow-up for infection start?	(1) Antepartum (2) Rupture of membranes (3) Onset of labour (4) Postpartum (specify day)_____ (5) Unknown/unclear
28	When did follow-up end?	(1) Antepartum (2) Intrapartum (3) Postpartum (specify day)_____

		(4) Unknown/unclear
29	Is infection the primary outcome of the study?	(1) YES (2) NO (3) NK
30	Were other outcomes studied?	(1) YES (2) NO (3) NK
31	Was Maternal infection the exposure in the study?	(1) YES (2) NO
32	If yes, what was the outcome?	
33	What data source was used to establish the outcome of infection for the study?	(1) Medical Record (2) Special Survey/Interview (3) Clinical data collected for the study (4) Unknown/unclear (5) Other Specify_____
34	Where was the woman assessed to establish the outcome of infection?	(1) Home (2) Health centre (3) Hospital (4) Unknown/unclear (5) Other Specify_____
35	Who diagnosed/identified the infection?	(1) Doctor/clinician (2) Nurse/midwife (3) Other trained health provider (4) Lay/community worker (5) Unknown/unclear (5) Other Specify_____
36	Was active surveillance used to identify women with infection postpartum	(1) YES (2) NO
37	If **yes,** describe the method used	
38	Any other remarks on study outcome	
39	Any other comments	

MATERNAL Infection			
Incidence			
(i)	(ii)	(iii)	(iv)
Outcome studied	No of cases (numerator)	Total deliveries/live births (denominator)	Proportion of women with infection

Appendix E: Published version of manuscript 3

PLOS ONE

RESEARCH ARTICLE

Postnatal infection surveillance by telephone in Dar es Salaam, Tanzania: An observational cohort study

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Data Availability Statement: According to Tanzanian ethics guidelines as reflected in the project data management plan and data transfer

Abstract

Introduction

Maternal and newborn infections are important causes of mortality but morbidity data from low- and middle-income countries is limited. We used telephone surveillance to estimate infection incidence and risk factors in women and newborns following hospital childbirth in Dar es Salaam.

Methods

We recruited postnatal women from two tertiary hospitals and conducted telephone interviews 7 and 28 days after delivery. Maternal infection (endometritis, caesarean or perineal wound, or urinary tract infection) and newborn infection (umbilical cord or possible severe bacterial infection) were identified using hospital case-notes at the time of birth and self-reported symptoms. Adjusted Cox regression models were used to assess the association between potential risk-factors and infection.

Results

We recruited 879 women and interviewed 791 (90%). From day 0–7, 6.7% (49/791) women and 6.2% (51/762) newborns developed infection. Using full follow-up data, the infection rate was higher in women with caesarean childbirth versus women with a vaginal delivery (aHR 1.93, 95%CI 1.11–3.36). Only 24% of women received pre-operative antibiotic prophylaxis before caesarean section. Infection was higher in newborns resuscitated at birth versus newborns who were not resuscitated (aHR 4.45, 95%CI 2.10–9.44). At interview, 66% (37/56) of women and 88% (72/82) of newborns with possible infection had sought health-facility care.

Conclusions

Telephone surveillance identified a substantial risk of postnatal infection, including cases likely to have been missed by hospital-based data-collection alone. Risk of maternal

agreement, it is not recommended to share potentially sensitive individual-level data, even after attempting to de-identify it. Therefore, anyone wishing to access this data will need to request written consent from Ifakara Health Institute who own the data. The data can be accessed from the IHI repository https://data.ihi.or.tz/index.php/catalog/edit/1. Anyone requesting the data will be required to submit a brief abstract narrating the reasons for requesting access to the data. The system will send an email to the data team and the local PI.

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: SLW, AMK, AK, WM and WJG received personal salary funded by The Soapbox Collaborative for their work on the study. SLW received a Research Degree Travel Grant from LSHTM. AMR received salary from the UK Medical Research Council and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. Other authors declare no competing interests. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

endometritis and newborn possible severe bacterial infection were consistent with other studies. Caesarean section was the most important risk-factor for maternal infection. Improved implementation of pre-operative antibiotic prophylaxis is urgently required to mitigate this risk.

Introduction

Preventing maternal and newborn infections is a high priority in the World Health Organization's (WHO) vision of good quality care for pregnant women and newborns [1]. Pregnancy-related sepsis is estimated to cause 11% of maternal mortality [2] and infection is responsible for 23% of newborn deaths [3] with the vast majority in low- and middle-income countries (LMICs). Increasing health-facility births in LMICs [4] presents an opportunity to reduce disease incidence through strengthened infection prevention initiatives.

Despite the importance of maternal and newborn infection, we have limited knowledge of the frequency in high-burden countries. A systematic review of maternal peripartum infection included only seven sub-Saharan Africa (SSA) studies (one from Tanzania [5]) and none were considered high quality [6]. From meta-analysis, the regional estimate for endometritis was 1.7% and for wound infection was 3.4%. A systematic review of possible severe bacterial infection (pSBI) using the Young Infant Clinical Signs Study (YICSS) criteria [7] estimated 6.2% of newborns in SSA were affected (six studies, none from Tanzania). The case-fatality risk was 14.1% [8].

The majority of severe maternal infections occur postpartum, arising from the genito-urinary tract or wounds [9, 10], and presenting after the woman has been discharged home following childbirth [11]. The majority of newborn deaths from infection occur after the first week of life [3]. Community follow-up is therefore necessary to capture all cases of infection. Home visits are resource intensive, consequently many studies only report infection up to the time of hospital discharge following facility childbirth. Mobile telephone surveillance is a possible alternative, with emerging evidence of feasibility and validity to monitor surgical site infection (SSI) in SSA [12, 13], and postnatal outcomes in India [14].

Responding to the limited data on maternal newborn infection incidence in SSA our observational cohort study aimed to estimate the incidence and risk factors for infection in women and newborns in the four weeks following hospital childbirth in urban Tanzania, using hospital case-notes from the time of birth and telephone surveillance. We also assessed the feasibility of mobile telephone assessment for infection, described care-seeking behaviour following infection and explored possible consequences of infection; hospital readmission, depression and reduced maternal function.

Methods

This study was a collaboration between London School of Hygiene and Tropical Medicine (LSHTM) and Ifakara Health Institute (IHI) and based at two of the three public Regional Referral Hospitals in Dar es Salaam; Amana (Ilala district) and Temeke (Temeke district). Each hospital conducts approximately 1,000 births per month. It was a sub-study of a pilot evaluation of training in environmental cleaning [15].

Two research nurses per hospital recruited eligible women from postnatal wards every Monday to Thursday. They sampled from all women who gave birth in the previous 24 hours using a random number application [16] with probability proportional to delivery mode (caesarean or vaginal). Eligible women were aged 18 years or older with access to at least one

mobile telephone and providing signed or witnessed thumbprint consent. Women admitted to the intensive care unit were ineligible. Women provided up to three mobile telephone numbers; one or two of their own and one for a relative or neighbour. Replacements were sampled in the same way when potential participants were unavailable or ineligible.

Two research nurses at IHI offices in Dar es Salaam interviewed each woman twice by telephone in Kiswahili, starting seven and 28 days after recruitment. Nurses made four telephone call attempts, over seven days, to reach each woman.

Outcomes and exposures

The primary outcomes were 1) possible maternal postnatal infection (one or more of caesarean surgical site infection, urinary tract infection, perineal wound infection or endometritis) and 2) possible newborn infection (either of pSBI or umbilical cord infection). Each outcome was measured as a rate, and as the day 7 (early infection) and day 8–28 cumulative risk. Infections were identified from women's hospital case-notes around the time of childbirth or from self-reported symptoms during telephone interview using standard definitions [7, 17, 18]. These definitions were adapted by the first author to include only symptoms and signs easily reported by the women (Table 1). Secondary outcomes were each individual infection listed above, plus mastitis.

Potential risk factors were extracted from hospital case-notes; maternal age, gestational age, parity, HIV, diabetes, hypertensive disorder, haemorrhage, prelabour rupture of membranes (PROM), induction of labour, delivery mode, postpartum haemorrhage (PPH) and infection during labour. Possible consequences of infection collected during telephone interview were self-reported readmission, depression assessed using a validated 5-question modified Edinburgh Postnatal Depression Scale (EPDS) and functionality according to five common postpartum activities (S1 Appendix).

Data collection

Data was entered on tablets with Open Data Kit (ODK), using unique identification (ID) numbers to maintain confidentiality. Data was extracted from maternal paper case-notes after hospital discharge, including demographics, pregnancy and childbirth history, infection diagnosed during admission and antibiotics prescribed (S2 Appendix). Telephone interviews with women consisted of pre-coded closed questions on the history of specific symptoms of infection, day of symptom onset, care-seeking behaviour, and readmission to hospital. At day-28, women were also asked questions on depression and function (S1 Appendix). Women with infection symptoms were advised to attend a health-facility if they hadn't already. In cases of maternal depression or neonatal death, women were offered referral to social welfare liaison for counselling and support.

Research nurses received six days training in recruitment and data collection, including two days at the hospitals when they piloted the tools on 24 women. Telephone interview nurses additionally conducted pilot interviews with the same 24 women over two days.

Study size

With 900 women and an estimated 10% loss to follow-up at day-28, we would have 95% confidence to estimate a maternal infection risk of 3%±1.2% with 80% power. Our daily recruitment target was 12–20 women per hospital.

Data management

Data was cleaned and analysed using STATA 16. Gestational age was grouped as preterm (<37 weeks) or term (37–42 weeks). The depression score was grouped as no depression (0–5)

Table 1. Syndromic infection definitions used.

Infection	Questions to women	Definition	Standard definition adapted
Caesarean Section Surgical Site Infection (SSI)	At the site of your caesarean section (cut/operation on your abdomen) have you experienced:	Either I. OR, (V. AND one or more of II-IV.), OR two or more of VI-VIII	CDC[a]
	I. Pus discharge		
	II. Pain		
	III. Swelling		
	IV. Redness		
	V. Wound breakdown (wound edges separated)		
	Have you experienced:		
	VI. Fever		
	VII. Abdominal pain		
	VIII. Foul-smelling or pus vaginal discharge		
Urinary Tract Infection (UTI)	Have you experienced:	Either (I. and II.) OR, three or more of I-V.	SIGN[b]
	I. Pain passing urine		
	II. Urinary frequency–passing urine more often		
	III. Urinary urgency–need to pass urine quickly/ difficulty in holding urine		
	IV. Fever		
	V. Abdominal pain		
Perineal wound infection	At the site of a perineal wound (cut or tear in the vagina) have you experienced:	Either, I. OR, (IV AND one or both of II and III.)	CDC[a]
	I. Pus discharge		
	II. Pain		
	III. Swelling		
	IV. Wound breakdown (wound edges separated)		
Endometritis	Have you experienced:	Two or more of I-III where II is not explained by UTI and III is not explained by perineal wound infection.	CDC[a]
	I. Fever		
	II. Abdominal pain		
	III. Foul-smelling or pus vaginal discharge	In women with caesarean section this was counted as an organ space SSI	
Mastitis	Have you experienced:	Either, I. OR, both II. and III.	CDC[a]
	I. Swollen, hard area of the breast		
	II. Painful, red breast		
	III. Fever		
pSBI	Has your baby experienced:	One or more of I-VII.	YICSS[c]
	I. Fever		
	II. Very cold (low temperature)		
	III. Very fast breathing		
	IV. Chest indrawing (sucking in the ribs when breathing)		
	V. Convulsions/fits		
	VI. Poor feeding/not feeding		
	VII. Only moving when stimulated		
Umbilical cord infection	Has your baby experienced:	One or both of I. and II.	CDC[a]
	I. Redness around the umbilical cord stump		
	II. Pus discharge from umbilical cord stump		

a)Centres for Disease Control [18]

b) Scottish Intercollegiate Guidelines Network [17]

c)Young Infants Clinical Signs Study [7].

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or possible depression (6–30). Maternal function questions were analysed individually as "any" or "no difficulty" in performing the function.

Duplicate ID numbers and data entry errors were corrected where possible using hospital case-notes or comparing with other study data. Any remaining discordant data was dropped. There was inconsistency in the occurrence of stillbirths between data sources, therefore stillbirths were not analysed. Data on twin and triplet newborns was also inconsistent and in addition an error in ODK programming meant only data from the first baby was useable.

Statistical analysis

Women's demographic and pregnancy data was described by delivery mode. Rates of infection were calculated from delivery until the day-28 telephone call using reported days from delivery to start of symptoms. Symptoms reported at both day-7 and day-28 were counted as distinct infection events if they started over 14 days apart, or if they met criteria for different infection types and started over seven days apart, or if initial symptoms had resolved by the day-7 interview. Date of death and infection data were not collected from babies who died before the day-7 interview, therefore these babies were excluded from infection outcome analyses. Babies who died after the day-7 interview contributed to infection analyses up to day 7. Using Cox regression with robust standard errors to account for clustering by person, we explored associations between potential risk factors and the rate of maternal postnatal infection or possible newborn infection. Proportional hazards assumptions were checked using tests based on Schoenfeld Residuals. Factors showing evidence of association in the crude analysis ($p<0.1$) were explored further in multivariable models. Maternal age and delivery hospital were considered *a priori* confounders for risk of maternal postnatal infection. We restricted the parameters in the final models to 10% of the number of outcomes. For missing risk-factor data, we carried out multiple imputation using chained equations (MICE) because most variables were categorical, creating 10 imputed datasets. Delivery mode and hospital were included as auxiliary variables. Women whose case-notes were missing were excluded from risk-factor analysis.

We report the highest level of care sought by women and newborns with possible infection and the percentage readmission to hospital for those with and without infection. We describe maternal depression and function at day-28 and explore associations with early postnatal infection using chi-squared tests and logistic regression.

Ethics

The study was approved by the Tanzanian National Institute for Medical Research, IHI Institutional Research Board and LSHTM Research Ethics Committee. Written informed consent was obtained from women on the postnatal wards. Willingness to continue in the study was confirmed at the start of each telephone interview. There was no public or patient involvement in the study design or interpretation of results. The Soapbox Collaborative supported the study following external peer review of the study proposal.

Results

Between 15th March and 9th May 2018, research nurses recruited 879 women into the study, sampling from a total of 2,110 deliveries (18% caesarean section) (Fig 1). We interviewed 791 (90%) women at least once, providing data until day 7, and 753 (86%) completed the day-28 interview. Final interview occurred between 7 and 43 (median 29) days after delivery. Most women whose only interview was at day-28, reported that their telephone battery was not charged at day-7.

Case-notes were not located for 39 women. In the remaining 840, missing data was minimal except gestational age (39%). Mean age was 25 (range 18–45) years. Fewer than 3% of women

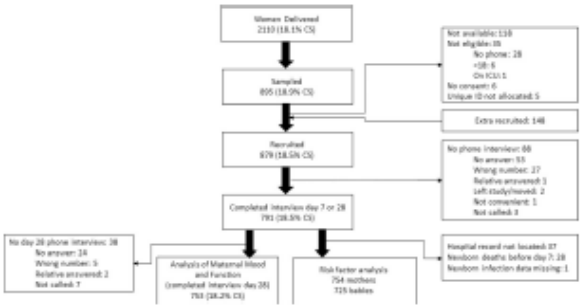

Fig 1. Flow diagram.

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were referred-in. Induction and augmentation of labour, including artificial rupture of membranes, were uncommon (each <3%) but occurred more frequently at Amana Hospital than Temeke Hospital (S2 Table). Among vaginal births (n = 692), seven were breech and three were by vacuum extraction. Vaginal tears were experienced after 36% of vaginal deliveries and episiotomy was rare (Table 2). Among 829 liveborn babies, bag-and-mask resuscitation and admission were more common both following caesarean section and at Amana Hospital (Table 2, S1 Table). Average length of stay after delivery was 0.8 days following vaginal delivery (range 0–8) and 2.4 days post-caesarean section (range 0–7).

Antenatally, 7.4% of women received antibiotics, primarily for prophylaxis before caesarean section or following PROM. Postnatally, 62% of all women were prescribed antibiotics: 94% of women undergoing caesarean section and 98% of all women giving birth at Amana hospital were prescribed antibiotics (Table 3).

Infection risk and rate

No postnatal maternal infections were documented in hospital case-notes at the time of birth and there were no maternal deaths. Among all 791 women with at least one telephone interview, 47 (5.9%) reported possible postnatal infection starting day 0–7. Symptoms of UTI affected 22 (2.8%) women and symptoms of endometritis affected 12 (1.5%). Among 146 women with caesarean section, 15 (10.3%) reported possible postnatal infection of whom 12 (8.2%) had symptoms of SSI (Table 4). From day 8–28, 9/753 (1.2%) developed possible postnatal infection. The rate of possible infection was 79.4 (95% Confidence Interval (CI) 61.1–103.2) per 1000 women per month.

Before the first interview, 28 (3.5%) babies were stillborn or died and one was missing infection data. Of the remaining 762 babies, 51 (6.7%) developed possible newborn infection from day 0–7, almost entirely attributable to pSBI (47, 6.2%) (Table 4). From day 8–28, another six babies died and 30/719 (4.3%) babies developed possible infection, one of whom had two episodes of infection. The rate of possible infection was 121.1 (95% CI 97.5–150.3) per 1000 babies per month. Three of these babies were diagnosed with sepsis in the maternal case-notes. For two of these three cases, no infection symptoms were reported by the mother at telephone interview.

Women sought care in a health facility following 37/56 (66%) episodes of possible postnatal infection: 24 (43%) at their delivery hospital, 8 (14%) at another hospital, and 5 (9%) at a lower level health facility. Babies were taken to a health facility following 72/82 (88%) episodes of

Table 2. Demographic, pregnancy and newborn factors by mode of delivery for 840 women and 829 liveborn babies with maternal hospital case-notes.

	Vaginal Delivery n(%) (N = 692)	Caesarean Section n(%) (N = 148)	Total n(%) (N = 840)
Maternal age in years			
18–24	288 (41.6)	50 (33.8)	338 (40.2)
25–29	193 (27.9)	42 (28.4)	235 (28.0)
30+	197 (28.5)	52 (36.1)	249 (29.6)
Missing	14 (2.0)	4 (2.7)	18 (2.1)
Parity			
Nulliparous	234 (33.8)	52 (35.1)	286 (34.1)
1	205 (29.6)	50 (33.8)	255 (30.4)
2	125 (18.1)	23 (15.5)	148 (17.6)
3+	106 (15.3)	19 (12.8)	125 (14.9)
Missing	22 (3.2)	4 (2.7)	26 (3.1)
Preterm birth (<37 weeks gestation)	59 (8.5)	22 (14.9)	81 (9.6)
Missing	287 (41.5)	42 (28.4)	329 (39.2)
Hypertensive disorders[a]	18 (2.6)	16 (10.8)	34 (4.1)
Missing	4 (0.6)	2 (1.4)	6 (0.7)
HIV	29 (4.2)	8 (5.4)	37 (4.4)
Missing/not available	14 (2.0)	1 (0.7)	15 (1.8)
PROM	25 (3.6)	4 (2.7)	29 (3.5)
Missing	2 (0.3)	1 (0.7)	3 (0.4)
Episiotomy	10 (1.5)	NA	10 (1.2)
Missing	14 (2.0)	NA	14 (1.7)
Perineal tear	250 (36.1)	NA	250 (29.8)
Missing	3 (0.4)	NA	3 (0.4)
PPH	7 (1.0)	2 (1.4)	9 (1.1)
Missing	2 (0.3)	0	2 (0.2)
Antibiotics in labour	26 (3.8)	36 (24.3)	62 (7.4)
Missing	5 (0.7)	1 (0.7)	6 (0.7)
Antibiotics postpartum	382 (55.2)	139 (93.9)	521 (62.0)
Missing	5 (0.7)	3 (2.0)	8 (1.0)
Newborn Factors	**Vaginal (N = 681)**	**CS (N = 148)**	**Total (N = 829)**
Apgar Score at 5 minutes <7	5 (0.7)	5 (3.4)	10 (1.2)
Missing	2 (0.3)	1. (0.7)	3 (0.4)
Bag and mask resuscitation	9 (1.3)	8 (5.4)	17 (2.1)
Missing	2 (0.3)	2 (1.4)	4 (0.5)
Admission	10 (1.5)	12 (8.1)	22 (2.7)
Missing	0	2 (1.4)	2 (0.2)

[a]Hypertensive disorders: 2 eclampsia, 19 pre-eclampsia, 17 pregnancy-induced hypertension.

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possible infection: 38 (46%) to the delivery hospital, 25 (30%) to another hospital, and 9 (11%) to a lower level health facility.

Associations with infection

There was evidence that caesarean delivery doubled the rate of possible maternal postnatal infection compared to women who had a vaginal delivery, and this association remained after adjusting for maternal age and hospital (adjusted Hazard Ratio (aHR) 1.93, 95% CI 1.11–3.36,

Table 3. Reason for antibiotics prescribed to women in hospital during labour and postpartum by delivery mode.

	Vaginal Delivery n (%)	Caesarean Section n (%)	Total
Antibiotics in labour	**N = 26**	**N = 36**	**N = 62**
Caesarean section prophylaxis	0	34 (94.4)	34 (54.8)
PROM	14 (53.9)	2 (5.6)	16 (25.8)
UTI	1 (3.9)	0	1 (1.6)
Other	8 (30.8)	0	8 (12.9)
None	3 (11.5)	0	3 (4.8)
Antibiotics postpartum	**N = 382**	**N = 139**	**N = 521**
Caesarean section prophylaxis	0	131 (94.2)	131 (25.1)
PROM	2 (0.5)	0	2 (0.4)
Perineal suture	172 (45.0)	0	172 (33.1)
UTI	1 (0.3)	0	1 (0.2)
Routine	190 (49.7)	0	190 (36.5)
IUD	4 (1.1)	0	4 (0.8)
Unknown/not recorded	13 (3.4)	8 (5.8)	21 (4.0)

https://doi.org/10.1371/journal.pone.0254131.t003

p = 0.02). There was also weak evidence of an association between women's age-group and infection (p = 0.06) with the highest infection rates occurring in women aged 25–29 (Table 5).

Bag-and-mask resuscitation at birth was strongly associated with possible newborn infection compared to babies who were not resuscitated (aHR 4.45, 95% CI 2.10–9.44, p<0.001), however this was a rare exposure (n = 11 babies). There was weak evidence for increased possible newborn infection if the mother received antibiotics in labour compared to mothers who did not (Table 6).

In the first seven days postnatal 7/762 mother-baby pairs both experienced possible infection. Mother's with postnatal infection in the first 7 days had an increased risk of their baby suffering possible newborn infection during this time period, compared to mother's without infection (crude Odds Ratio 2.74, 95%CI 1.16–6.48, p = 0.02).

Consequences of infection

At the day-7 interview, 5/43 (12%) women with possible postnatal infection reported they had been readmitted to hospital as compared with only 5/696 (0.7%) women without infection. All women readmitted with infection had given birth by caesarean section. Among 713 babies

Table 4. Maternal and newborn infections occurring up to 7 days after delivery.

Maternal infection	Vaginal delivery n(%) N = 645	Caesarean section n(%) N = 146	Total n(%) N = 791
Postnatal infection	32 (5.0)	15 (10.3)	47 (5.9)
Endometritis	12 (1.9)	NA	12 (1.5)
SSI	NA	12 (8.2)	12 (1.5)
Perineal wound infection	7 (1.1)	0	7 (0.9)
UTI	15 (2.3)	7 (4.8)	22 (2.8)
Mastitis	13 (2.0)	3 (2.1)	16 (2.0)
Newborn infection	**N = 621**	**N = 141**	**N = 762**
Possible newborn infection	40 (6.4)	11 (7.8)	51 (6.7)
pSBI	36 (5.8)	11 (7.8)	47 (6.2)
Umbilical cord infection	5 (0.8)	0	5 (0.7)

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Table 5. Association between potential risk-factors and rate of possible maternal postnatal infection.

Factor	Total women	Episodes of postnatal infection	Person-time (months)	Rate of infection per 1000 person months	Crude HR (95% CI) N = 754[a]	Wald p-value	Adjusted HR (95% CI) N = 754[a]	Wald p-value
All women	791	56	705.3	79.4 (61.1–103.2)				
Delivery mode								
Vaginal	645	39	578.1	67.5	1	0.02	1	0.02
Caesarean section	146	17	127.3	133.6	1.95 (1.12–3.37)		1.93 (1.11–3.36)	
Maternal age (years)								
18–24	303	15	167.9	56.0	1	0.05	1	0.06
25–29	212	23	186.0	123.6	2.20 (1.15–4.28)		2.14 (1.12–4.09)	
30+	223	16	204.3	78.3	1.43 (0.72–2.84)		1.37 (0.69–2.70)	
Hospital								
Amana	403	28	362.0	77.4	1	0.87	1	0.98
Temeke	388	28	343.4	81.5	1.04 (0.62–1.75)		1.01 (0.60–1.70)	
Parity								
0	252	15	224.8	66.7	1	0.81		
1	233	19	206.9	91.8	1.33 (0.69–2.56)			
2	131	11	115.0	95.7	1.37 (0.65–2.89)			
3+	113	8	103.6	77.2	1.16 (0.48–2.81)			
Preterm birth (<37 weeks)								
No	392	30	346.5	86.6	1	0.89		
Yes	69	5	62.5	80.1	0.94 (0.37–2.35)			
Antibiotics in labour								
No	697	48	622.6	77.1	1	0.17		
Yes	51	6	43.7	137.3	1.75 (0.78–3.91)			
Postpartum antibiotics								
No	277	18	246.4	73.0	1	0.49		
Yes	469	37	417.9	88.5	1.22 (0.69–2.16)			

[a]Values imputed for variables with missing data, except for Preterm birth where the amount of missing data was considered too large to impute.

Results shown if >2 infections in a single category. Full results in S2 Table.

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alive at the day-7 interview, 44% with possible infection had been readmitted to hospital compared with 1.8% of those without.

Depression scores ranged from 0–10/30 among 753 women at day-28 interview and 31 (4%) had possible depression (score > = 6). Among 43 women with early postnatal infection (day 0–7), 4 (9.3%) developed possible depression versus 27 (3.8%) of those without infection (OR 2.1, 95% CI 0.64–6.89, p = 0.22, adjusting for death of the baby).

Table 6. Association between potential risk factors and rate of possible newborn infection.

Factor	Total newborns	Episodes of possible infection	Person-time (months)	Rate of infection per 1000 person months	Crude HR (95% CI) N = 725[a]	Wald p-value	Adjusted HR (95% CI) N = 725[a]	Wald p-value
All babies	762	82	677.4	121.1 (97.5–150.3)				
Resuscitation (bag and mask)								
No	709	75	629.9	119.1	1	<0.001	1	<0.001
Yes	11	5	8.7	574.3	4.61 (2.35–9.04)		4.45 (2.10–9.44)	
Antibiotics in labour								
No	674	69	598.5	115.3	1	0.01	1	0.08
Yes	47	10	39.9	250.9	2.15 (1.18–3.91)		2.00 (0.93–4.30)	
Delivery mode								
Vaginal	621	64	552.2	115.9	1	0.35	1	0.95
Caesarean section	141	18	125.1	143.8	1.24 (0.74–2.09)		1.02 (0.55–1.91)	
PROM								
No	698	75	617.7	121.4	1	0.37	1	0.76
Yes	24	4	22.1	180.6	1.53 (0.61–3.84)		1.16 (0.45–2.99)	
Maternal age (years)								
18–24	291	29	256.9	112.9	1	0.51		
25–29	203	27	280.4	149.6	1.34 (0.79–2.28)			
30+	216	22	193.0	114.0	1.05 (0.60–1.84)			
Hospital								
Amana	388	41	347.1	118.1	1	0.94		
Temeke	374	41	330.3	124.1	1.04 (0.67–1.61)			
Preterm (<37 weeks gestation)								
No	376	38	330.6	114.9	1	0.65		
Yes	67	8	59.5	134.5	1.18 (0.57–2.44)			
Postpartum antibiotics								
No	266	21	236.8	88.7	1	0.07		
Yes	452	58	399.5	145.2	1.59 (0.96–2.62)			

[a]Values imputed for variables with missing data, except for Preterm birth where the amount of missing data was considered too large to impute.

Results not shown if <3 infections in a single category. Full results in S1 Table.

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At day-28 interview, 103/752 (13.7%) women reported difficulty with housework and 8/751 (1.1%) reported difficulty washing themselves. Among women with a living baby, 43/718 (6.0%) reported difficulty carrying or caring for their baby and 99.7% were exclusively breast-feeding. Difficulty with each activity was reported more frequently among women with possible early postnatal infection compared to those without infection, but statistical evidence was inconsistent (Table 7).

Table 7. Associations between early maternal postnatal infection (day 0–7) and maternal function at day 28.

	Difficulty washing	Difficulty with housework	Difficulty carrying baby	Difficulty caring for baby
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Postnatal infection				
No	6/709 (0.9)	94/709 (13.3)	39/679 (5.7)	38/679 (5.6)
Yes	2/42 (4.8)	9/43 (20.9)	4/39 (10.3)	5/39 (12.8)
Chi^2 p-value	0.02	0.16	0.25	0.06

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Discussion

We conducted telephone interviews with 791 women at seven and/or 28 days after hospital childbirth in Dar es Salaam, Tanzania. We estimated a rate of 79.4 possible maternal and 121.1 possible newborn infections per 1000 person-months. Women with caesarean birth had twice the rate of infection. Newborns resuscitated at birth had over four times the rate of infection. Women and newborns with possible infection had substantially higher readmission rates compared with those without infection, and there was a trend towards increased depression risk following early infection. Telephone surveillance proved feasible: 97% of the initial sample had access to a mobile telephone and 90% of all recruited women were interviewed at least once.

Global incidence of pregnancy-related infection estimated by the Global Burden of Disease study 2017 equates to 8.2% of livebirths [19], and the recent Global Maternal Sepsis Study (GLOSS) reports prevalence of infection in hospitalised pregnant and postpartum women of 70.4 per 1000 livebirths [10]; however, their broader case definitions prevent direct comparison with our study. Our incidence of endometritis at day-7 (1.5%) is consistent with the 1.7% (95% CI 1.4–2.1%) estimate for SSA from a recent meta-analysis [6]. However, we observed a caesarean surgical site infection risk of 8.2%, which is lower than the 15.6% estimate from a systematic review for SSA [20]. Our incidence of pSBI (6.2%) was the same as the estimate for SSA from a meta-analysis of studies in which health or community workers applied YICSS criteria [21].

Caesarean section is an established risk factor for maternal infection and sepsis [9, 10, 22] and in our study carried a higher risk of both SSI and UTI than vaginal birth. Increasing rates of caesarean childbirth and evidence of antimicrobial resistance (AMR) in subsequent infections [23] demand enhanced infection prevention measures. Pre-operative prophylactic antibiotics are effective [24] and recommended in Tanzania [25], but were documented before only 24% of caesarean sections. Newborn infection could result from pathogens introduced during resuscitation, explaining the strong association seen. Additionally, sick newborns requiring ventilation are at increased risk of infection, supporting calls to improve both intrapartum care and postnatal infection prevention [26].

Expected associations between prematurity, PROM, PPH, HIV, and either maternal or newborn infection were not evident, but these factors were reported less frequently than expected. Induction and augmentation of labour were similarly infrequent. This could reflect poor documentation at the hospitals or difficulties in extraction. Postpartum antibiotics were not associated with reduced infection incidence, providing no justification for universal prescribing observed at one study hospital. This practice is not recommended nationally or internationally [27], could be a driver of AMR and needs to be challenged. There was some evidence of a crude association between maternal and newborn infection, also found in a systematic review of maternal infection in labour [28], suggesting a shared aetiology for some infections and highlighting the importance of caring for the woman and newborn synergistically.

Depression prevalence (4.1%) was lower than other LMIC studies that also used EPDS at 4–8 weeks postnatal. However, these studies showed considerable heterogeneity

(range 4.9–50.8%) [29]. Telephone follow-up could provide a valuable tool to screen for postnatal depression and warrants further validation. We did not power our study to assess associations between maternal infection and depression or functioning, but our results suggest a trend in that direction, compatible with previous studies of maternal morbidity [29–32].

In our study, 66% of women and 88% of newborns with possible infection had sought health-facility care when interviewed, revealing the important proportion of cases that would be missed by a purely hospital based study. Telephone diagnosis of caesarean site infection achieved high specificity in Kenya and Tanzania [12, 13]. Telephone surveillance detected more cases of SSI than using patient case-notes or written surveys in high-income settings [33, 34]. Mobile telephone access was high in our study sample (97%), and we reached a high proportion of recruited women (90%), supporting the feasibility of telephone surveillance in comparable LMIC settings.

Strengths and limitations

Our study benefited from collecting data on specific components of standard infection definitions during the interview that were used in diagnosis algorithms, rather than relying on women's or data collectors' judgement. We collected data with a short recall period, reducing potential bias, and used symptom start dates to show infection distribution over time and estimate incidence rate. Although we recruited from two tertiary hospitals, we expect the population to be broadly representative of Dar es Salaam region where 94% of women are estimated to give birth in a facility and 17% by caesarean, similar to our study population.

The main limitation of this study is the unknown validity of the questionnaire to identify true cases of infection. We believe that the substantially increased rates of hospital readmission amongst women and newborns with telephone-based diagnosis of infections provide strong post-hoc support for the validity of our approach. Incidence of endometritis and pSBI and the association with caesarean childbirth are all closely consistent with other studies, lending further support to the results. However, we identified fewer cases of SSI than other studies, and we had two cases of neonatal sepsis extracted from hospital case-notes that were not subsequently reported at maternal interview. In addition, newborn deaths from infection were not captured, therefore true infection incidence may be higher than estimated. Furthermore, hospital case-notes were not located for 39 women, in some cases following admission of the baby, potentially reducing estimated infection incidence. It is possible that women who were unwell, or caring for a sick baby, were less likely to answer their telephones, also leading to an underestimate of infection incidence. However, the use of a second telephone number belonging to a friend/relative, the repeated call attempts over seven days and the second interview at day-28 reduce this risk.

Conclusion

Our telephone surveillance study found a substantial and plausible rate of possible infection among mothers and newborns in urban Tanzania in the first month postnatal. Telephone interviews were feasible and identified cases that could be missed by hospital data collection alone. Results were consistent with previous studies, although further validation studies are needed. Therefore, this method of data collection shows promise for further use, both as a research tool and for routine medical practice. This could be of particular benefit during the current COVID pandemic, with concerns about reduced hospital attendance and the encouragement to work remotely. WHO does not recommend the use of routine postpartum antibiotics. Their use in this context showed no benefit and should be challenged. However, better implementation of pre-operative antibiotic prophylaxis for caesarean section is urgently required to mitigate the infection risk in mothers.

Supporting information

S1 Appendix. Telephone questionnaire–Day 28.
(DOCX)

S2 Appendix. Hospital case-note extraction form.
(DOCX)

S1 Table. Demographic, pregnancy and newborn factors by mode of delivery for 840 women and 829 liveborn babies with hospital record data by study hospital.
(DOCX)

S2 Table. Associations between potential risk factors and possible maternal postnatal infection.
(DOCX)

S3 Table. Associations between potential risk factors and possible newborn infection.
(DOCX)

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References

1. Tunçalp Ö, Were W, MacLennan C, Oladapo O, Gülmezoglu A, Bahl R, et al. Quality of care for pregnant women and newborns—the WHO vision. Bjog. 2015; 122(8):1045. https://doi.org/10.1111/1471-0528.13451 PMID: 25929823
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014; 2(6):e323–e33. https://doi.org/10.1016/S2214-109X(14)70227-X PMID: 25103301

3. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bulletin of the World Health Organization. 2015; 93(1):19–28. https://doi.org/10.2471/BLT.14.139790 PMID: 25558104

4. Campbell OM, Calvert C, Testa A, Strehlow M, Benova L, Keyes E, et al. The scale, scope, coverage, and capability of childbirth care. The Lancet. 2016; 388(10056):2193–208.

5. Winani S, Wood S, Coffey P, Chirwa T, Mosha F, Changalucha J. Use of a clean delivery kit and factors associated with cord infection and puerperal sepsis in Mwanza, Tanzania. Journal of Midwifery & Women's Health. 2007; 52(1):37–43. https://doi.org/10.1016/j.jmwh.2006.09.004 PMID: 17207749

6. Woodd SL, Montoya A, Barreix M, Pi L, Calvert C, Rehman AM, et al. Incidence of maternal peripartum infection: A systematic review and meta-analysis. PLoS Medicine. 2019; 16(12). https://doi.org/10.1371/journal.pmed.1002984 PMID: 31821329

7. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. The Lancet. 2008; 371(9607):135–42. https://doi.org/10.1016/S0140-6736(08)60106-3 PMID: 18191685

8. Seale AC, Blencowe H, Manu AA, Nair H, Bahl R, Qazi SA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. The Lancet infectious diseases. 2014; 14(8):731–41. https://doi.org/10.1016/S1473-3099(14)70804-7 PMID: 24974250

9. Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M. Severe maternal sepsis in the UK, 2011–2012: a national case-control study. PLoS medicine. 2014; 11(7):e1001672. https://doi.org/10.1371/journal.pmed.1001672 PMID: 25003759

10. Bonet M, Brizuela V, Abalos E, Cuesta C, Baguiya A, Chamillard M, et al. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. The Lancet Global Health. 2020; 8(5):e661–e71. https://doi.org/10.1016/S2214-109X(20)30109-1 PMID: 32353314

11. Bianco A, Roccia S, Nobile CG, Pileggi C, Pavia M. Postdischarge surveillance following delivery: the incidence of infections and associated factors. American Journal of Infection Control. 2013; 41(6):549–53. https://doi.org/10.1016/j.ajic.2012.06.011 PMID: 23219668

12. Aiken A, Wanyoro A, Mwangi J, Mulingwa P, Wanjohi J, Njoroge J, et al. Evaluation of surveillance for surgical site infections in Thika Hospital, Kenya. Journal of hospital infection. 2013; 83(2):140–5. https://doi.org/10.1016/j.jhin.2012.11.003 PMID: 23332563

13. Nguhuni B, De Nardo P, Gentilotti E, Chaula Z, Damian C, Mencarini P, et al. Reliability and validity of using telephone calls for post-discharge surveillance of surgical site infection following caesarean section at a tertiary hospital in Tanzania. Antimicrobial Resistance & Infection Control. 2017; 6(1):43.

14. Gass JD Jr, Semrau K, Sana F, Mankar A, Singh VP, Fisher-Bowman J, et al. Evaluation of a call center to assess post-discharge maternal and early neonatal outcomes of facility-based childbirth in Uttar Pradesh, India. PloS one. 2018; 13(11):e0207987. https://doi.org/10.1371/journal.pone.0207987 PMID: 30481209

15. Gon G, Kabanywanyi AM, Blinkhoff P, Cousens S, Dancer SJ, Graham WJ, et al. The Clean pilot study: evaluation of an environmental hygiene intervention bundle in three Tanzanian hospitals. Antimicrobial Resistance & Infection Control. 2021; 10(1):1–14. https://doi.org/10.1186/s13756-020-00866-8 PMID: 33413647

16. RandomAppsInc. Random Number Generator Plus. In: Chiou A, editor.: https://github.com/Gear61/Random-Number-Generator; 2015. p. Android 4.0.

17. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. In: Health Improvement Scotland, editor. Edinburgh: SIGN88; 2012.

18. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control. 2008; 36(5):309–32. https://doi.org/10.1016/j.ajic.2008.03.002 PMID: 18538699

19. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018; 392(10159):1789–858.

20. Sway A, Nthumba P, Solomkin J, Tarchini G, Gibbs R, Ren Y, et al. Burden of surgical site infection following cesarean section in sub-Saharan Africa: a narrative review. International Journal of Women's Health. 2019; 11:309. https://doi.org/10.2147/IJWH.S182362 PMID: 31191039

21. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. The Lancet infectious diseases. 2009; 9(7):428–38. https://doi.org/10.1016/S1473-3099(09)70172-0 PMID: 19555902

22. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLOS One. 2013; 8(7):e67175. https://doi.org/10.1371/journal.pone.0067175 PMID: 23843991

23. Bebell LM, Ngonzi J, Bazira J, Fajardo Y, Boatin AA, Siedner MJ, et al. Antimicrobial-resistant infections among postpartum women at a Ugandan referral hospital. PloS one. 2017; 12(4):e0175456. https://doi.org/10.1371/journal.pone.0175456 PMID: 28406949

24. Bollig C, Nothacker M, Lehane C, Motschall E, Lang B, Meerpohl JJ, et al. Prophylactic antibiotics before cord clamping in cesarean delivery: a systematic review. Acta Obstetricia et Gynecologica Scandinavica. 2018; 97(5):521–35. https://doi.org/10.1111/aogs.13276 PMID: 29215155

25. Ministry of Health and Social Welfare—The United Republic of Tanzania. Standard Treatment Guidelines and Essential Medicines List. Fourth ed2013.

26. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? The Lancet. 2014; 384 (9940):347–70.

27. World Health Organization. WHO recommendations for prevention and treatment of maternal peripartum infections. Geneva: 2015.

28. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS medicine. 2013; 10(8): e1001502. https://doi.org/10.1371/journal.pmed.1001502 PMID: 23976885

29. Norhayati M, Hazlina NN, Asrenee A, Emilin WW. Magnitude and risk factors for postpartum symptoms: a literature review. Journal of affective Disorders. 2015; 175:34–52. https://doi.org/10.1016/j.jad.2014.12.041 PMID: 25580764

30. Filippi V, Ganaba R, Baggaley RF, Marshall T, Sloreng KT, Sombié I, et al. Health of women after severe obstetric complications in Burkina Faso: a longitudinal study. The Lancet. 2007; 370 (9595):1329–37. https://doi.org/10.1016/S0140-6736(07)61574-8 PMID: 17933647

31. Guida JP, Costa ML, Parpinelli MA, Pacagnella RC, Ferreira EC, Mayrink J, et al. The impact of hypertension, hemorrhage, and other maternal morbidities on functioning in the postpartum period as assessed by the WHODAS 2.0 36-item tool. International Journal of Gynecology & Obstetrics. 2018; 141:55–60.

32. Machiyama K, Hirose A, Cresswell JA, Barreix M, Chou D, Kostanjsek N, et al. Consequences of maternal morbidity on health-related functioning: a systematic scoping review. BMJ open. 2017; 7(6): e013903. https://doi.org/10.1136/bmjopen-2016-013903 PMID: 28667198

33. Halwani MA, Turnbull AE, Harris M, Witter F, Perl TM. Postdischarge surveillance for infection following cesarean section: a prospective cohort study comparing methodologies. American journal of infection control. 2016; 44(4):455–7. https://doi.org/10.1016/j.ajic.2015.10.023 PMID: 26706153

34. Petrosillo N, Drapeau CM, Nicastri E, Martini L, Ippolito G, Moro ML. Surgical site infections in Italian hospitals: a prospective multicenter study. BMC Infectious Diseases. 2008; 8(1):34. https://doi.org/10.1186/1471-2334-8-34 PMID: 18328101

Appendix F: Questionnaire for manuscript 3

Patient ID Number:_____

Information collected previously from hospital records and last interview:

Delivery mode:

a. Vaginal delivery
b. Caesarean section

Baby alive at last phone survey? Y/N

Number of babies:_____

Introduction

I am _____ from Ifakara Health Institute, phoning to ask questions as part of the CLEAN study.

I would like to ask you about your health since we last spoke 3 weeks ago.

Is this a convenient time to speak? (If No, arrange another time to call back)

Are you happy to continue with the survey? Y/N If Yes, continue with maternal questions

If No, are you happy for the answers from 3 weeks ago and the information from your medical records to still be used in the research? Y/N

Thank her for her time and end.

Maternal questions

Firstly, I will ask some questions about your health:

1. Have you been unwell or suffered any problems/complications since we phoned you 3 weeks ago? Y/N If No -> Qu.3
2. If Yes, Can you describe the problem and any diagnosis given (free-text).

_____

3. For each of the following symptoms, can you tell me if you have experienced it in the last 3 weeks (since we phoned) and if you are still experiencing it today?

	Symptom	Last 3 weeks Y/N	Today Y/N
a.	Fever		
b.	Abdominal pain		
c.	Foul-smelling or pus vaginal discharge		
d.	Vaginal bleeding (heavier than spotting)		
e.	Pain passing urine		

r.	Urinary frequency – passing urine more often		
g.	Urinary urgency – need to pass urine quickly/difficulty in holding urine		
h.	At the site of your caesarean section (cut/operation on your abdomen)		
	I. Pus discharge		
	II. Pain		
	III. Swelling		
	IV. Redness		
	V. Wound breakdown (wound edges separated)		
i.	At the site of a perineal wound (cut or tear in the vagina)	Option of 'no perineal wound'	
	I. Pus discharge		
	II. Pain		
	III. Swelling		
	IV. Wound breakdown (wound edges separated)		
j.	Painful, red breast		
k.	Swollen, hard area of the breast		
l.	Productive cough (coughing up sputum)		
m.	Difficulty breathing		

If No to Qu.1 and all of Qu.3 -> Qu. 7

4. How many days after giving birth did these symptoms start?
5. Where did you seek help for these problems? Tell me each place or person.
    a. Hospital where delivered
    b. A different hospital
    c. A lower level healthcare facility
    d. A private clinic
    e. A pharmacist/drug store
    f. A local shop (not a drug store)
    g. A traditional healer/doctor
    h. A family member
    i. A friend/neighbour
    j. Other – describe _____
    k. Did not seek help - If current symptoms, advise to seek medical help
6. What diagnosis were you given? (Write 'unknown' if the woman does not know/remember. Write 'no diagnosis' if a diagnosis was not made e.g. if she only spoke to a friend or shop owner)

7. Have you taken any medicine in the last 3 weeks? (Mark any that apply and give name of drugs if known)
    a. Amoxil/amoxicillin
    b. Metronidazole
    c. Ampiclox
    d. Erythromycin
    e. Ciprofloxacin
    f. Alu/duocotexin/Mceto (oral antimalarial)
    g. Iv/im Artesunate/Artemether (antimalarial)
    h. Paracetamol
    i. Other
    j. Unknown treatment
    k. No treatment

8. Have you been readmitted to hospital in the last 3 weeks? Y/N If No, -> Qu.10
9. Was it the same hospital where you gave birth? Y/N
10. When were you readmitted (How many days after giving birth?)____

11. Are you currently breastfeeding your baby? Yes, exclusive/ Yes, mixed, /No

For the next questions, I would like you to say how difficult you find the following activities – not difficult, a little difficult or very difficult

12. Washing your whole body? Not at all/little/very
13. Taking care of your household responsibilities e.g. cleaning/cooking? No responsibilities/Not difficult/little/very
14. Picking up and carrying your baby? Not at all/little/very
15. Taking care of your baby e.g. washing them? Not at all/little/very

The next few questions ask about how you have been feeling in the last 7 days. These statements are about how you have felt in the past week (7 days), not just how you feel today. I will read the statements and give you a choice of responses.

In the last 7 days:

16. Have you looked forward to things with enjoyment?
    a. As much as I ever did (0)
    b. Rather less than I used to (1)
    c. Definitely less than I used to (2)
    d. Hardly at all (3)
17. Have you been so unhappy that you have had difficulty sleeping?
    a. Yes, most of the time (3)
    b. Yes, sometimes (2)
    c. Not very often (1)
    d. No, not at all (0)

18. Have you felt sad or miserable?
    a. Yes, most of the time (3)
    b. Yes, sometimes (2)
    c. Not very often (1)
    d. No, not at all (0)
19. Have you been so unhappy that you have been crying?
    a. Yes, most of the time (3)
    b. Yes, sometimes (2)
    c. Not very often (1)
    d. No, not at all (0)
20. Have thoughts of harming yourself occurred to you?
    a. Yes, most of the time (3)
    b. Yes, sometimes (2)
    c. Not very often (1)
    d. No, not at all (0)

Add up all the points for Qu. 13-17. Maximum score is 15.

If a woman scores 6 or more or has thoughts of harming herself, say to her, "there seem to be many things that are making you sad. This can be common for women who just gave birth. Would you like me to speak to your relative? Or would you like to speak to a social welfare officer?

Newborn Questions (if baby was alive at the last phone survey). Otherwise go to Qu.10

Now I will ask some questions about your baby:

1. Has your baby been unwell or suffered any problems/complications since we phoned you 3 weeks ago? Y/N – If No -> Qu.3
2. If Yes, Can you describe the problem and any diagnosis given.

NB If the baby has died, give condolences, then ask sensitively if the mother knows what her baby died from and if the baby died at home or in hospital. Free-text any information she provides. Offer your condolences again and ask her if she would like to speak to someone from the social welfare team. If so, offer to pass on her contact details to them. Go to Qu.10. Do not proceed with further questions about the baby. Text the contact details for the social welfare team to her after the interview

3. For each of the following symptoms, has your baby experienced it in the last 3 weeks, and are they experiencing it today?

	Symptom	Last 3 weeks Y/N	Today Y/N
a.	Fever		
b.	Very cold (low temperature)		
c.	Very fast breathing		

d.	Chest indrawing (sucking in the ribs when breathing)		
e.	Convulsions/fits		
f.	Poor feeding/not feeding		
g.	Only moving when stimulated		
h.	Redness around the umbilical cord stump		
i.	Pus discharge from the umbilical cord stump		

If No, to Qu.1 and Qu.3 -> Qu.6

4. How many days after birth did these symptoms start?
5. Where did you seek help for your baby? Tell me each place or person.
    a. Hospital where delivered
    b. A different hospital
    c. A lower level healthcare facility
    d. A private clinic
    e. A pharmacist/drug store
    f. A local shop (not a drug store)
    g. A traditional healer/doctor
    h. A family member
    i. A friend/neighbour
    j. Other – describe _____
    k. Did not seek help - If current symptoms, advise to seek medical help
6. What diagnosis was your baby given? Write 'unknown' if the woman does not know/remember. Write 'no diagnosis' if a diagnosis was not made e.g. if she only spoke to a friend or shop owner

_____

7. Has your baby had any medicine in the last 3 weeks? (Mark any that apply and give name of drugs if known)
    a. Amoxil/amoxicillin
    b. Metronidazole
    c. Ampiclox
    d. Erythromycin
    e. Ciprofloxacin
    f. Alu/duocotexin/Mceto (oral antimalarial)
    g. Iv/im Artesunate/Artemether (antimalarial)
    h. Paracetamol
    i. Other
    j. Unknown treatment
    k. No treatment
8. Was your baby admitted to hospital in the last 3 weeks? Y/N If No, -> Qu.10

9. Was it the same hospital where your baby was born? Y/N
10. When were they admitted? (How many days since birth?)_____

If there is more than one baby (twins/triplets) then repeat all newborn questions

11. Thank you for your time.

This is the last time we will phone you as part of this study. Thank you very much for helping us. It is important that you attend your local health facility in 2 weeks' time for your baby to receive their first immunisations.

Appendix G: Hospital record extraction form for manuscript 3

Patient ID Number:_____

Date of extraction:_____

Date of admission:_____

Demographics

Age of woman:

Referred from another health facility Y/N

Address:

Pregnancy history

Gravidity (number of pregnancies):

Parity (number of births at admission):

Gestational age at birth in weeks:

Number of babies in this pregnancy:

Comorbidities

Diabetes Yes/No/Unknown

Gestational Diabetes Yes/No/Unknown

Pre-eclampsia Yes/No/Unknown

Eclampsia Yes/No/Unknown

Pregnancy-induced hypertension Yes/No/Unknown

Antenatal haemorrhage Yes/No/Unknown

HIV positive Yes/No/Unknown

Labour

Premature rupture of membranes Y/N

Induction of labour Y/N

Artificial rupture of membranes Y/N

Augmentation of labour Y/N

IV line Y/N (look at observation chart)

Delivery

Date of delivery/birth:

Mode of delivery:

a. Spontaneous vertex delivery
b. Breach delivery
c. Vacuum extraction
d. Caesarean section

Episiotomy Y/N

Perineal tear Y/N

Perineal sutures Y/N

Newborn outcomes

Stillbirth Y/N If yes, skip to Infection questions

Apgar score at 5 minutes

Baby required suction Y/N

Baby required bag and mask Y/N

Baby admitted to neonatal ward Y/N

Baby with suspected sepsis

Baby received antibiotics Y/N

Baby alive at discharge Y/N

Postpartum

Postpartum haemorrhage Y/N

Mother's temperature postpartum:

Mother alive at discharge Y/N

Date of discharge:_____

Infection/Antibiotic use in mother

Antibiotics received in labour Y/N.

If Yes, antibiotics given

a. Ampicillin
b. Ampiclox
c. Metronidazole
d. Ceftriaxone
e. Amoxicillin
f. Gentamicin

g. Erythromycin
h. Benzylpenicillin
i. Other_____

Reason for antibiotics

a. Surgical prophylaxis – caesarean section
b. PROM
c. Manual removal of placenta
d. Perineal suture
e. Haemorrhage (APH/PPH)
f. Infection
g. Other:_____
h. Unknown

Infection diagnosed:

a. Chorioamnionitis
b. Urinary tract infection
c. Respiratory tract infection
d. Sepsis
e. Other_____
f. Unknown

Antibiotics received after delivery Y/N
If Yes, antibiotics given

a. Ampicillin
b. Ampiclox
c. Metronidazole
d. Ceftriaxone
e. Amoxicillin
f. Gentamicin
g. Erythromycin
h. Benzylpenicillin
i. Other_____

Reason for antibiotics

a. Surgical prophylaxis – caesarean section
b. PROM
c. Manual removal of placenta
d. Perineal suture
e. Haemorrhage (APH/PPH)
f. Infection
g. Other:_____
h. Unknown

Infection diagnosed:

a. Chorioamnionitis
b. Urinary tract infection
c. Respiratory tract infection
d. Sepsis
e. Endometritis
f. Wound infection/SSI
g. Other_____
h. Unknown

Appendix H: Ethics approvals for manuscript 2 and 3

THE UNITED REPUBLIC OF TANZANIA

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NIMR/HQ/R.8c/Vol. I/654

27th February 2019

Dr. Abdunoor Mulokozi Kabanywanyi
Ifakara Health Institute
P.O. Box 78373
Dar es Salaam

RE: ETHICAL APPROVAL FOR PROTOCOL AMENDMENT

This letter is to confirm that your application for amendment of a protocol on the study entitled: The clean study: a before-&-after study to assess the effectiveness of a training to improve environmental hygiene in healthcare facilities (Kabanywanyi A. M. et al) Ref. NIMR/HQ/R.8a/Vol. IX/2842, dated 07th August 2018, has been granted ethical clearance to be conducted in Tanzania.

The approval is for the following amendment:

1. Conducting a telephone surveillance of postpartum infections – a cohort of 900 women delivering in two of the study hospitals (Temeke and Amana) in March to April 2019 will be recruited (30 women per day for 6 weeks). This data represents additional layer of individual-level information on women after discharge from hospital which will indicate the proportion of possible HAIs occurring after discharge as well as an indication on where these women seek care for themselves and their new-borns.

Approval is valid until 06th August 2019.

Name: Prof. Yunus Daud Mgaya

[redacted]

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

[redacted]

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN

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3rd December, 2018

National Institute for Medical Research
P O Box 9653
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Email; headquarters@nimr.or.tz

Dr. Abdunoor M Kabanywanyi,
Ifakara Health Institute,
P O Box 78373,
Dar es Salaam.

Ref: IHI/IRB/AMM/ No: 13-2018

AMENDMENT APPROVAL

On 30th November 2018, the Ifakara Health Institute Review Board (IHI-IRB) reviewed and approved protocol amendment for the study titled ***"The Clean study: The Clean study: a before-&-after study to assess the effectiveness of a training to improve environmental hygiene in healthcare facilities"*** submitted by P.I. Dr. Abdunoor M Kabanywanyi. The protocol for this study was previous approved with number IHI/IRB/No: 006 – 2018.

Key amendments include:

1. Telephone surveillance of postpartum infections – intention to conduct a telephone surveillance of postpartum infections – A cohort of 900 women delivering in two of the study hospitals (Temeke and Amana) in March to April 2019 will be recruited (30 women per day for 6 weeks).
2. Assessment of water purity that is being used for cleanliness in the three hospitals.
3. Addition of three new investigators and changed the status of on one investigator.
4. Additional funds to cater for the planned activities as reflected in the budget of £10,000.00/-.

The following documents were reviewed and approved by the Ifakara Health Institute Review Board:

1. Study Protocol version #04 of 21st November 2018
2. Informed consent Forms English and Kiswahili
3. Data Collection Forms English and Kiswahili
4. Budget
5. Investigators' CVs

The IRB reserves the right to undertake field inspections to check on the protocol compliance

[redacted]

IRB Secretary
Dr. Mwifadhi Mrisho

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United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Susannah Woodd
LSHTM

5 February 2019

Dear Susannah,

Study Title: I STEP (Infection Surveillance by Telephone Early Postpartum)

LSHTM Ethics Ref: 16204

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Alex Aiken CV	14/09/2017	1
Investigator CV	Wendy Graham CV	14/09/2017	1
Protocol / Proposal	Protocol_ Clean Study_Resubmission_v5_29052018	29/05/2018	5
Local Approval	Approval IHI IRB	06/06/2018	1
Local Approval	LSHTM Letter of approval	11/07/2018	1
Local Approval	CLEAN study NIMR_IRB certificate	17/08/2018	1
Investigator CV	CV18_short_WooddS	19/11/2018	1
Protocol / Proposal	Appendix XIII_Extraction form	19/11/2018	1
Information Sheet	Appendix XIV_Consent form mothers	23/11/2018	1
Information Sheet	Appendix XIV- Ridhaa ya mama	23/11/2018	1
Protocol / Proposal	Appendix XIIa_English Questionnaire_day7	23/11/2018	1
Protocol / Proposal	Appendix XIIb_English Questionnaire_day30	23/11/2018	1
Protocol / Proposal	I-STEP study proposal	27/11/2018	2
Investigator CV	Temp CV Oona Campbell	27/11/2018	1
Local Approval	approval_amend	10/01/2019	1
Protocol / Proposal	Appendix XIIb_Infection Surveillance Telephone Questionnaire_day30_v2	17/01/2019	2
Protocol / Proposal	I-STEP study proposal_v3	22/01/2019	3
Covering Letter	Response to ethics committee	22/01/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

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http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix I: Reflexivity Statement

I have prepared a reflexivity statement using some questions suggested by BMJ Global Health to reflect on my role as PhD student based in a northern institution who conducted part of my PhD work in Tanzania.

Overall, my PhD addresses the prominent global maternal health issue of infection and sepsis. The systematic review of infection came from discussions at the WHO maternity morbidity working group, which included regional representation, and the design was influenced by the working group's pre-existing template for maternal morbidity reviews. In applying this template to the specific question of infection, I sought advice from other researchers and a librarian at LSHTM with expertise in conducting reviews. I also collaborated closely with a Colombian obstetrician and researcher to decide on inclusion criteria and infection definitions.

The results were shared with all co-authors, and within a team at WHO, providing the opportunity to comment and contribute to the interpretation. Co-authors of the published systematic review included all researchers who assisted with screening and data extraction. The second author on the systematic review was the Columbian obstetrician who contributed substantially to the design, data collection and interpretation. Another co-author was from China – she located and screened the Chinese articles, and extracted data from the six articles that were included.

The primary data collection component of my PhD was part of a larger CLEAN study in Tanzania. Prior to starting the PhD I was involved in clinical work and research in parts of Africa (including Tanzania) and Asia. Some of this work related to infection prevention in maternity units and demonstrated some gaps in infection prevention practices and the concerns from healthcare workers about women's risk of infection. During visits to our study hospitals in Dar es Salaam as part of developing the larger CLEAN study, we learnt about ongoing government initiatives to improve quality of care with a large focus on infection prevention. I also met with health officials who were considering establishing surveillance of surgical site infection, and were keen to explore effective methods. However, alongside this local and global interest in the subject, I am also aware that I was part of a team specifically funded to conduct research into maternal infection and infection prevention. I therefore did not consider research into other maternal health issues, or work with local researchers and

policy makers to assess where they placed infection in relation to other maternal health priorities.

I discussed the idea for the infection surveillance study with the local PI (from the Ifakara Health Institute) for the CLEAN study, consulted him about the details and adapted the design following his advice. However, I developed the main study design by myself, with input from colleagues at LSHTM. During the course of the study, I learnt that the local PI would have preferred more time and resources for training and supervising the data collectors, which would have been likely to have improved the quality of the data collection, but would have been difficult to achieve within our budget. We also received feedback from the hospital leadership that they had also wished for more involvement in the design, and would have preferred their own staff to collect the data, although this was not supported by our local PI. On reflection, it would have been beneficial to spend more time in consultation with the research institute, the study hospitals and the regional health office before designing the study. This may have strengthened the methods, improved the accuracy of data collection, encouraged interest in the results and enabled them to be more directly applicable to future surveillance or research carried out locally.

Local researchers received a direct grant from the Soapbox Collaborative to carry out the research, and were able to recruit, train and supervise the data collectors, and to collaborate on data cleaning and writing of publications. The grant was small and only lasted for the period of data collection and a few weeks afterwards, so it did not fully cover the time needed for analysis, interpretation and writing. The larger CLEAN grant supported the local PI for a longer period.

The raw data was entered onto ODK and downloaded in London. Results and analysis of all CLEAN study data were shared and discussed with partners at an interpretation workshop, and results tables were circulated to all authors of papers. Excel files of the cleaned data are stored with the National Institute of Medical Research Tanzania and can be accessed with the permission of the local PI (in line with local regulations).

The research nurses were trained in data collection methods; recruitment and consent of participants, use of ODK to enter data, extraction of hospital records and telephone interview skills. There was not scope within the PhD to develop analytical skills of partners beyond myself. Co-authors of the published results of the study included the two nurses conducting telephone interviews, who also contributed to the interpretation of the results. The other

nurses who recruited participants and extracted hospital record data are acknowledged. The local PI is included as second author. The plan for the unpublished paper is to have four authors from Tanzania, with the local PI as the senior author.

My PhD has not contributed to improvements in local infrastructure. However, the larger CLEAN study aimed to improve knowledge and skills of hospital staff in the practice of environmental hygiene through a training programme. Cleaning supplies were also provided.

A dissemination workshop was held for the CLEAN study, during which my PhD study results were shared with local stakeholders including representatives from the study hospitals, regional health offices and Ministry of Health. Results were also shared with all the data collectors and their views and interpretation were sought. The two papers on infection surveillance were circulated for comments. Specific hospital-level results were discussed with hospital staff during private discussions after the main workshop. One of the study collaborators and co-author of the unpublished paper is from Ministry of Health and in a position to apply any relevant results.

Unfortunately, one of the hospitals did not send any senior staff to the dissemination meeting. Ideally there would have been an opportunity to meet with the leadership teams and discuss the results in more detail. In addition, it might have been valuable to have a number of individual conversations with key stakeholders for example to discuss how the results of the surveillance study could feed into. On reflection, devoting more time to this exercise would be a valuable way to ensure the results could be taken up.