

UNIVERSITY OF BIRMINGHAM

PREVENTION, EARLY RECOGNITION AND MANAGEMENT OF MATERNAL INFECTIONS AND SEPSIS

by

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ABSTRACT

Introduction:

Maternal sepsis is the 3rd leading cause of maternal mortality globally. Sepsis is the second most frequent abortion related complication in low- and middle-income countries. Infection after miscarriage is a serious problem and can cause death and disability. This thesis evaluates the effectiveness of routine antibiotic prophylaxis in surgical management of miscarriage (Aim 1) and describes the implementation and evaluation of FAST-M bundle care tools (MEOWS chart, decision tool, and FAST-M treatment bundle) in a low-resource setting within Pakistan (Aim 2). FAST-M, a bundle developed in collaboration with the WHO and validated in Africa, consists of five components: Fluids, Antibiotics, Source identification and control, assessment of the need to Transport or Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate). FAST-M intervention aims to improve the recognition and management of maternal sepsis; it has not yet been validated in Asia.

Methods: Two studies were undertaken as part of this PhD research. (1) A systematic review was conducted to synthesise the effectiveness of routine antibiotic prophylaxis in individuals undergoing uterine evacuation procedures to treat miscarriage (Aim 1). (2) A feasibility study with sequential mixed method intervention design was conducted in women with suspected maternal sepsis admitted at the LUMHS hospital Hyderabad in Pakistan to evaluate the outcomes of FAST-M intervention. Qualitative data was collected in the first phase for the adaptation of FAST-M bundle care tools. This was then followed by the implementation of contextual-based modified tools in the study setting. The implementation outcomes were evaluated using both the

quantitative and qualitative methods to validate the study findings. Quantitative comparisons were drawn before and after the implementation to distinguish study outcomes (Aim 2).

Results: Study 1: Six studies with a total of 4371 participants undergoing uterine evacuation procedures to treat miscarriage were included in our review. A metanalysis restricted to studies with low risk of bias (3 trials with 3737 participants, 85% of total participants;) found a 43% reduction in the risk of developing a uterine infection (pooled RR 0.57, 95% CI 0.37 to 0.86, I^2 = 0%, high certainty evidence). Study 2: Following the FAST-M intervention, significant changes were observed. Improvements were seen in the monitoring of oxygen saturation measurements [25.5% vs 100%; difference: 74%; 95% CI:68.4%-80.5% p<0.01], fetal heart rate assessment [58% vs100%; difference:42.0%; 95% CI: 33.7% to 50.3%; p=<0.01], and measurement of urine output [76.5% vs 100%; difference 23.5%; 95%CI: 17.6% to 29.4%; p<0.01]). An additional improvement in overall patient monitoring was reported by the HCPs in the qualitative study. Women with suspected maternal sepsis received all components of the treatment bundle within one hour of sepsis recognition [0% vs70.5%; difference 70.5%; 95%CI: 60.4% to 80.6%; p<0.01]. The healthcare providers' views were positive about the intervention, its outcomes, and long-term sustainability.

Conclusion:

The systematic review ascertained a significant reduction in the risk of uterine infection rates with antibiotic prophylaxis during surgery to treat miscarriage based on three trials assessed to have low risk of bias included in the meta-analysis. This PhD research also demonstrated that the implementation of the FAST-M intervention was feasible and significantly improved the quality

of maternal sepsis care, including enhanced early identification and management of maternal sepsis.

DEDICATION

This thesis is dedicated to the loving memory of my parents, **Mussaret** and **Naseer** who always believed in my ability to be successful in the academic arena. You both are loved beyond words and missed beyond measure. Mom, I would not have the ambition and strength to achieve this accomplishment and follow my passion without your support and encouragement when I started PhD journey- thank you!

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LIST OF ABBREVIATIONS

AJK- Azad Jammu and Kashmir

AMR- Antimicrobial resistance

AMS- Antimicrobial stewardship

ANC- Antenatal care

BHUs – Basic Health Units

Bpm- beats per minute

BScN- Bachelors of Science in Nursing

CDC- Center for Disease Control and Prevention

CEMACH- Confidential Enquiry into Maternal and Child Health

CFIR- Consolidated Framework for Implementation Research

CGF- Cochrane Gynecology and Fertility

CI- Confidence Interval

CMV- Cytomegalovirus

COVID- Coronavirus Disease

CRF- Case Report Form

E.Coli- Escherichia Coli

EMONC- Emergency Obstetrics and Neonatal Care

EPMM- Ending Preventable Maternal Mortality

ER- Emergency Room

ERC- Ethical Review Committee

FAST-M- Fluids, Antibiotics, Source control, assessment of the need to Transport/Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate)

FGD- Focus Group Discussion

FHR- Fetal Heart Rate

GAS- Group A Streptococcus

GB- Gilgit Baltistan

GBD- Global Burden Disease

GBS- Group B Streptococcus

GLOSS- Global Maternal Sepsis Study

HCPs- Health Care Providers

HDUs- High Dependency Units

HICs- High Income Countries

HIV- Human Immunodeficiency Virus

HODs- Head of Departments

HSV- Herpes Simplex Virus

ICT- Islamabad Capital Territory

ICU- Intensive Care Unit

IMR- Infant Mortality Rate

IPC- Intervention Prevention Control

IRMNCH- National Integrated Reproductive Maternal and Neonate Health Strategy

IV- Intravenous

KIIs- Key Informant Interviews

KPK- Khyber Pakhtunkhwa

LUMHS- Liaquat University of Medical Health Sciences

LMICs- Low- and Middle-Income Countries

MAP- Mean Arterial Pressure

MDG- Millennium Development Goal

MDR- Multidrug resistant

MEWS- Modified Early Warning Signs

MEOWS- Modified Early Obstetrics Warning System

MMR- Maternal Mortality Rate

MNCH- Maternal Neonatal Child Health

MSMI- Maternal Sepsis and Maternal Infections

NAP- National Action Plan

OBGYN- Obstetrics and Gynecology

omqSOFA- obstetric modified quick Sequential Organ Failure Assessment

OR- Operating Room

PDHS- Pakistan Demographic and Health Survey

PG- Postgraduate trainee

PID- Pelvic Inflammatory Disease

PROM- Pre-labor Rupture Of Membrane

qSOFA- quick Sequential Organ Failure Assessment

RCT- Randomised Controlled Trial

RCOG- Royal College of Gynecology

RHCs- Rural Health Centers

RPOCs- Retained products of conception

RR- Relative Risk

RV- Rubella Virus

SAMM- Severe Acute Maternal Morbidity

SARS- severe acute respiratory syndrome

SDGs- Sustainable Development Goals

SIRS- Systematic Inflammatory Response Syndrome

SOFA- Sequential Organ Failure Assessment

SOS- Sepsis in Obstetrics Score

SPSS- Statistical Package for Social Sciences

SSC- Surviving Sepsis Compaign

SSG- Surviving Sepsis Guidelines

SSI- Surgical Site Infection

STIs- Sexually Transmitted Infections

UK- United Kingdom

UNICEF- United Nation's Children's Fund

UTIs- Urinary Tract Infections

WASH- Water Sanitation and Hygiene

WBC- White blood count

WHA- World Health Assembly

WHO- World Health Organisation

Chapter One

INTRODUCTION

1.1. Purpose of this chapter

The introductory chapter describes maternal health in global settings with a particular focus on maternal infections and sepsis. Maternal health in Pakistan will be discussed and risk factors for maternal infection and sepsis in Pakistan and other low-middle-income countries will be explored. Existing approaches to the prevention of maternal infection and sepsis, its recognition, and management in high and low-resource settings will be examined towards the end, highlighting gaps in the evidence base. The chapter will conclude with the aims and objectives of the research and an overview of the proceeding thesis structure.

1.2. Overview of maternal health in the global settings

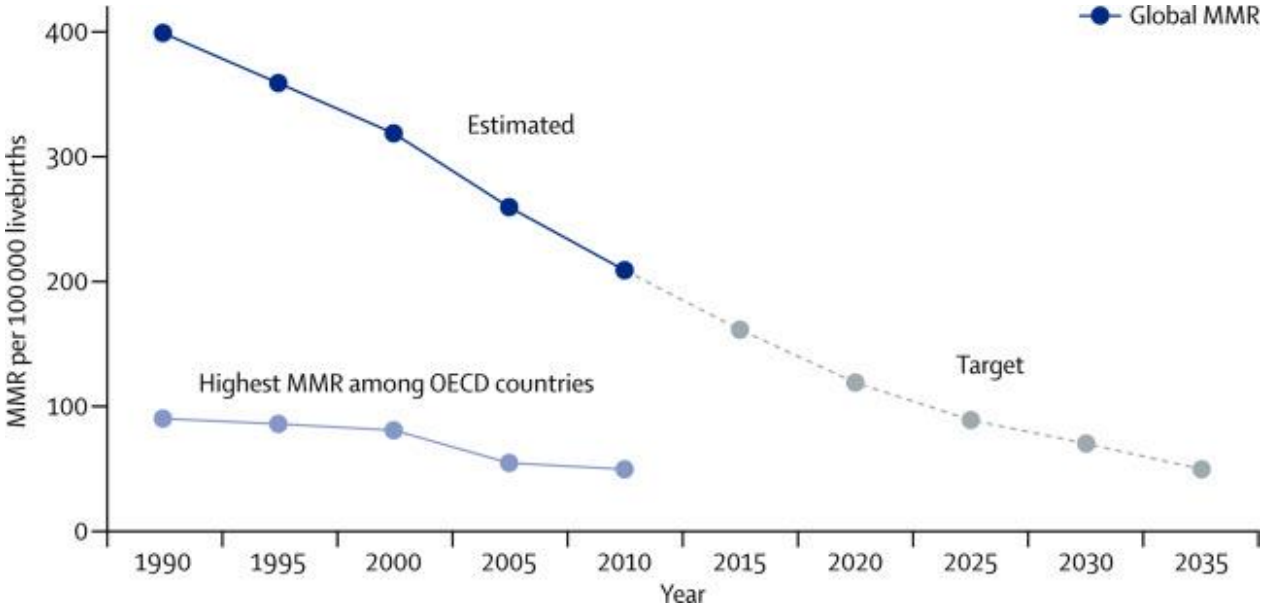
Approximately 210 million women conceive pregnancy every year around the world [1]. It is estimated that 287,000 mothers die during pregnancy and after delivery [2]. Around 95% of all these women die in low middle income countries (LMICs) [2], and most of these maternal deaths occur during birth or within the first 24 hours of delivery [3]. In 2020, the maternal mortality rate (MMR) in LMICs was 430 per 100 000 live births vs 12 per 100 000 live births in high income countries (HICs) [4].

Maternal mortality is described as "Death of women while pregnant or within 42 days of termination of pregnancy irrespective of the duration and the site of pregnancy from any cause related to or aggravated by the pregnancy or its management but not from incidental or any accidental causes" [3]. As per World Health Organisation (WHO), there are direct and indirect causes of maternal mortality. Direct obstetric deaths result from complications developing during pregnancy, childbirth, and abortion (e.g., obstructive labor, excessive bleeding) [4]. The cause of indirect death includes any pre-existing condition (e.g., an existing cardiac or renal disease) that is exacerbated by the physiological effect of pregnancy and results in maternal mortality [2].

Worldwide, around 810 women die daily because of complications that develop during pregnancy and labor [5]. Women from least developed countries have more pregnancies, and they are at greater risk of death due to related complications than women of HICs during their lifetime [4] i.e., 1 in 49 in in LMICs in comparison to 1 in 5300 in HICs [2]. Most of the maternal mortality, 87% (253 000) have been reported from Sub-Saharan Africa and Southern Asia; 70%

(202 000) were reported from Sub-Saharan Africa, while South Asia accounted for 16% (47 000) of maternal deaths in 2020 [2]. These countries lagged in achieving the millennium development goal (MDG) 5 which was aimed to decrease maternal deaths by 3/4th until 2015 (there was only a 45% reduction in maternal mortality ratio) [5] **(Fig 1.1)**.

Figure 1.1. Estimated and target maternal mortality rate (1990-2035)



Source: Bustreo F, Say L, Koblinsky M, Pullum TW, Temmerman M, Pablos-Méndez A. Ending preventable maternal deaths: the time is now. The Lancet Global Health. 2013 Oct 1;1(4): e176-7.

The sustainable development goals (SDGs) were introduced in 2015 by the United Nations in replacement of MDGs [6]. The target of SDG 3 is to "reduce MMR to 70 per 100,000 live births by the end of 2030 **(fig 1.1),** with no country having a maternal mortality rate of more than twice the global average" [7]. The global MMR in 2020 was 223 per 100 000 live births and to achieve

a rate below 70 by the year 2030 requires a decrease of 11.6% annually, a national percentage that has only occasionally been attained so far [2]. Furthermore, WHO also emphasised the implication of its vision targeted toward ending preventable maternal mortality (EPMM) as an important global strategy [7-8].

Worldwide, despite a 34% reduction in maternal mortality, there are few countries whose annual rate of reduction in mortality is less than 5% [2] **[Appendix 1.1].** It is estimated that over 1.6 million lives of mothers are at cost of death by 2030, due to the slow rate of reduction in maternal mortality [9]. Although, the majority of these maternal deaths can be prevented by well-known healthcare solutions to manage complications that lead to maternal mortality [5].

Around 15-20 million women suffer globally each year from maternal morbidity [9], World Health Organisation (WHO) defined maternal morbidity as "any health condition attributed to and/or complicating pregnancy and childbirth that has a negative impact on the woman's wellbeing and/or functioning" [10]. Almost 118 women experience life-threatening events of "near miss mortality" or Severe Acute Maternal Morbidity (SAMM) [11].

WHO has defined SAMM as "the condition of a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy" [11]. The major complications that comprise 80% of all maternal death and severe acute maternal morbidity include severe bleeding after delivery, high blood pressure i.e., eclampsia and pre-eclampsia, delivery complications, infections (usually after delivery) and unsafe abortion [11-15].

1.3 Maternal infection

Maternal infection is defined as "any infection that occurs during pregnancy, childbirth, postabortion, or postpartum period" [16]. The physiological changes in pregnant patients make them more susceptible to infection and so maternal infections are commonly observed in them [17-18]. A recent study by WHO showed that 70.4 women per 1000 live births had a maternal infection, and 11 women per 1000 live births had severe maternal outcomes related to infection [16]. LMICs had the highest ratio of infection and related serious maternal outcomes while HICs had the lowest. [16].The latest global burden diseases data (GBD) shows that direct (obstetric) infections are the main cause of maternal deaths, and could also lead to ectopic pregnancy, infertility, chronic pelvic inflammatory disease, and increased likelihood of early neonatal infection [19-20]. Millions of newborn deaths occur yearly because of vertical fetal transmission of infection during pregnancy and childbirth [17,21].

Infections can develop at different sites throughout pregnancy and labor [21-22]. Miscarriages increase the risk of infections in early pregnancy [22]. Pre-labor rupture of membrane (PROM) followed by chorioamnionitis in the 2nd and 3rd trimesters [23]. Endometritis and chorioamnionitis can also develop during labor and delivery after prolonged and induced labor, previous infections of the lower genital tract, ruptured membranes, too frequent vaginal examinations, and invasive procedures (forceps used, invasive electronic fetal monitoring, and urinary bladder catheterisation) [16,17, 22, 23].

According to WHO reports, newborn and maternal deaths occur mainly in the postpartum period**.** [24-25]. Puerperal infection is characterised by "bacterial infection of the genital tract that occurs

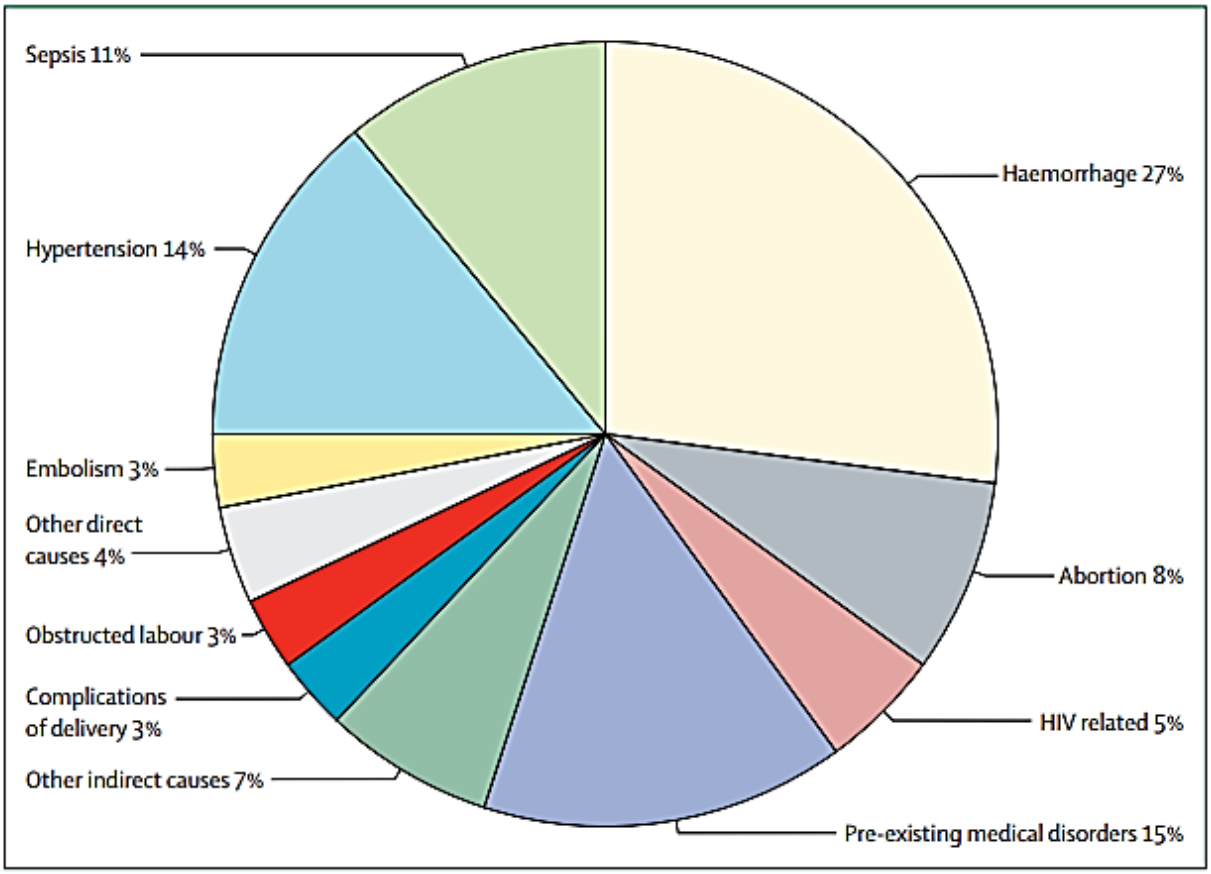
within 28 days after miscarriage, induced abortion, or childbirth" [17]. In the postpartum period, the most common site of infection is uterine endometrium (endometritis) [17-18]. The other types of puerperal infections include operative wound sites, such as a cesarean incision or episiotomy, urinary tract, pyelonephritis, breast (mastitis), and tetanus [25-27]. While other infections such as sexually transmitted infections (STIs), Malaria, human immunodeficiency virus (HIV), and other viral and fungal infections are also responsible for complicating pregnancy, childbirth and puerperium [28].

However, the most frequent and serious types of maternal infections are pyelonephritis, chorioamnionitis, and endometritis [17]. Likewise, Escherichia coli (E coli) is the most common pathogen identified; found in blood samples of almost one-half of the pregnant and postpartum patients [29-31]. E. Coli is also the most prevalent isolate detected in cases of chorioamnionitis and endometritis [32]. Other common organisms include Group B streptococcus (GBS), Staphylococcus aureus (SAS), Listeria monocytogenes, and anaerobic bacteria [33-35]. However, Staphylococcus**,** and group A Streptococcus (GAS) are considered as top risk factors for maternal mortality [36].

There are many viral infections responsible for an increased risk of maternal death. The most common associated pathogens are varicella zoster, influenza, and herpes simplex virus (HSV) [37-39]. The threat to microbial infection in pregnancy also influences different organs of infant. For instance, HSV, rubella virus (RV), Toxoplasma gondii, cytomegalovirus (CMV), and other viruses may result in stillbirth, premature birth, and even neurological defects after childbirth. [40].

Maternal infection can lead to sepsis, death, or disability to the mother, and other unfavorable outcomes [17-18]. Women in health facilities suffer from high rates of maternal infections and despite it being the 3rd most common direct cause of maternal death **(Fig 1.2)** has been given less attention than other leading causes of maternal mortality like obstetrical hemorrhage and hypertensive disorders [5, 41]. The voids in the knowledge of this issue are the number of women affected, sources of infection, causative organisms, and risk factors for sepsis and their unfortunate poor outcomes/results such as septic shock.

Fig 1.2. Common causes of maternal mortality



Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. The Lancet global health. 2014 Jun 1;2(6): e323-33.

1.4.Maternal Sepsis:

According to WHO in 2017, maternal sepsis is defined as "a life-threatening organ dysfunction caused by a dysregulated host response to infections during pregnancy, childbirth, post-abortion, or the postpartum period" [42]. Sepsis can involve any system in the body and is associated with irreversible multiorgan failure, and eventually death in severe forms [17]. Data indicates that globally 25-40% of maternal mortality occurs due to sepsis during the peripartum period [43].

Among women who dies of sepsis, approximately 50 women experience sepsis related morbidity [19]. As per estimate 5.7 million cases of preexisting maternal disorders were complicated with sepsis in 2017 [43].

Whereas the actual frequency and complications of maternal sepsis are not widely known. Due to a lack of evidence, clear, and implacable definitions of maternal infection, an adequate assessment related to it is found challenging. A broad criteria and definitions being utilised to define maternal sepsis [42]. Consequently, the new definition evolved, which reflected the thinking embedded in the 2016 Third International Consensus Definition for Sepsis and Septic Shock (SEPSIS-3) for the general population [44].

The available data from HICs reported an incidence of 9 to 49 per 100,000 deliveries/year, based on the population and definition used [45]. In contrast to the fact, the paucity of data from LMICs makes it difficult to decide the incidence of maternal sepsis in those countries [46]. Its case mortality is exceptionally high as compared to other pregnancy complications [29,34]. It is estimated that the case fatality rates vary from 4 to 50% in Asia and Africa [47], with the highest rate reported in Central and South Asia [16].

Maternal infection easily advances to sepsis if not treated timely and properly [17-18, 45]. In pregnancy and the postpartum period, maternal immunological and physiological transformation, and fetal development, may weaken the physical capacity of mother to respond to infection leading to increased risk of sepsis [18,21]. The absence of a clear definition of maternal sepsis not only makes it challenging to assess its burden across different settings but might also affects the clinical

care and might lead to misdiagnosis, delayed or improper treatment due to similarities in physiologic changes occurring in pregnancy and sign and symptoms of sepsis [37,42].

Normal physiological changes during pregnancy in the cardiovascular, respiratory, and immune systems are responsible for a possible rapid decompensation at the onset of sepsis [18, 42, 48, 49]. An increase of approximately 30%-50% in intravascular volume during pregnancy, and the subsequent increase of 10 to 20 beats per minute (bpm) in heart rate along with vasodilation resulting in the decline of blood pressure masks signs of sepsis [48]. Respiratory changes in pregnancy lead to a decrease in oxygen reserve, subsequently decreasing the capacity of mother to compensate for severe infection possibly leading to metabolic acidosis [49]. Immunological changes include a decline in cell-mediated immunity and inflammatory responses as one of the predisposing factors to infection [50].

The increased vulnerability to infection and penetration of microorganisms in the genitourinary tract leads to ascending infections such as chorioamnionitis and pyelonephritis [27,34, 50] which sometimes can prompt septic shock [51]. In case of viral infections, patients usually present with pneumonia but may also present with acute respiratory distress syndrome, or septic shock, coagulopathy, hepatitis and encephalitis [52-53]. The mortality rate of 1.3% in pregnancy was assessed due to coronavirus disease in 2019 (COVID-19) [54]. However, the COVID-19 pandemic is ongoing and accessible data is scarce to date and does not support pregnancy as being a major factor in the severity of the disease.

Parasitic infections such as malaria, helminth and amoeba infections can be devastating to both mother and fetus, leading to severe sepsis and mortality to the mother and miscarriage, stillbirth, preterm birth, and fetal growth restriction to the fetus [55-56]. The mortality rate associated with fungal sepsis is observed very high but its prevalence in pregnancy and postpartum is rare [57].

Current data on the global burden of diseases showed that 17,000 deaths have been caused by maternal sepsis and other maternal infections (MSMI) [58]. The maternal deaths caused by MSMI in Central Sub-Saharan Africa was 71.54 out of 100,000 live births while Eastern Sub-Saharan Africa reported around 31.04% of MSMI [58]. Whereas South Asia experienced the most incident cases (6,219,971 in 1990 and 5,495,269 in 2017) and the reported deaths due to MSMI were 8.37 per 100,000 live births in 2019 [12,16, 59].

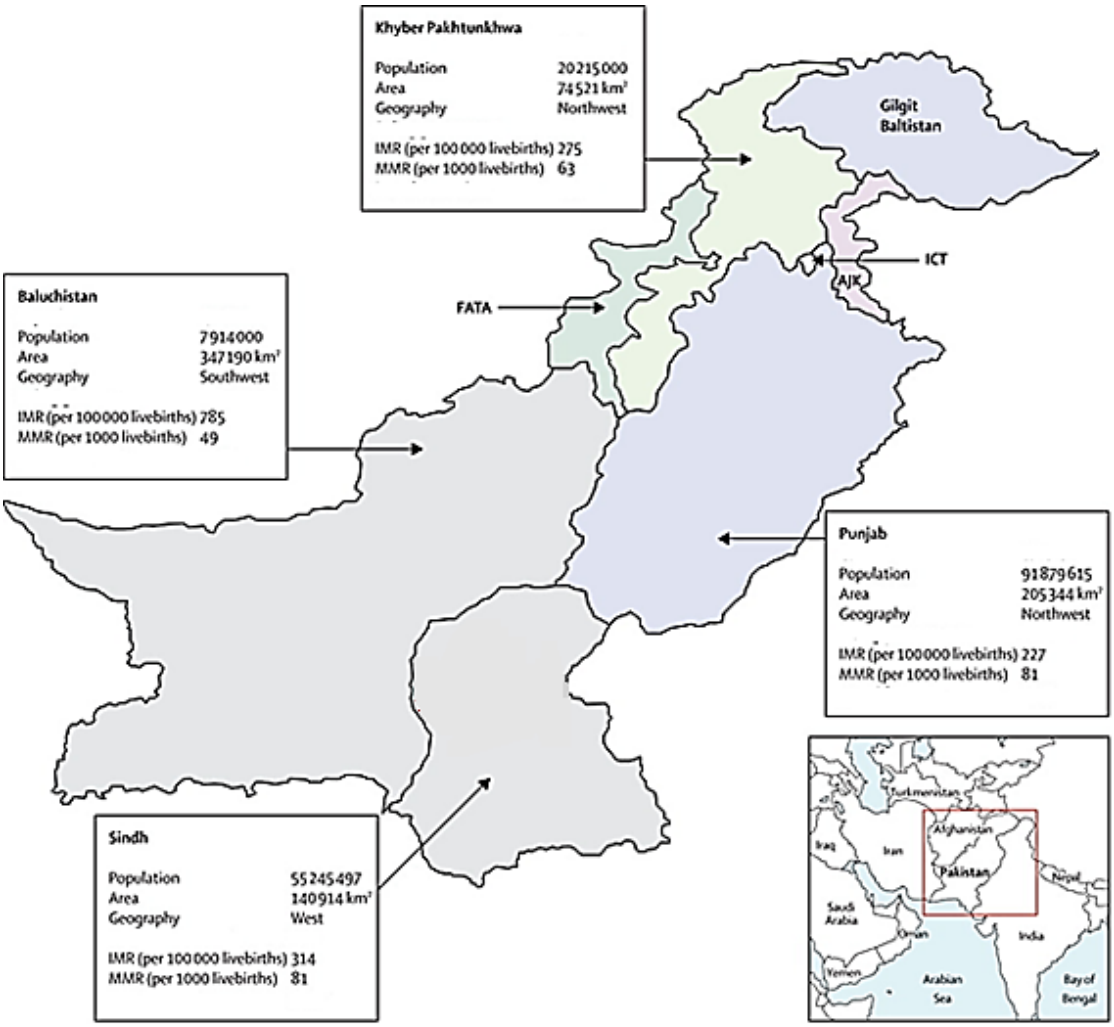
1.5. Situation in Pakistan

Pakistan with a population of over 225 million [60] ranked sixth, among the most populated countries, and 64% of population of the country resides in rural areas [61]. Currently, Pakistan is undergoing rapid increase in its population, and keeping the current rate it may be the fifth most-populated country in the world by 2050 [61]. The country has a life expectancy of 66.5 years in men and 64.5 years in women, and the literacy rate is 49% among the 15–45-year age group (females 43%, males 56%) [61-62]. It is estimated that about 21% of the population in Pakistan is living below the subsistence level, however, these figures have been debated as underestimated [63].

There are two main classes of society in Pakistan i.e., high socioeconomic, and low socioeconomic classes [64]. The high class mainly controls the country's business with power status and public money and this control is constant because of informal regulations and laws protecting them and no rule exists against them to suppress their power [64]. The lower class struggles for their basic rights such as poverty, elevation, justice, and democracy. Although more complex and societal structure exists within the country. The succeeding rulers may have failed the common man and civic society is unstable in Pakistan, democracy is gradually but consistently taking root [65].

The country has wide disparities in terms of mortality and morbidity rates specifically MMR and IMR (Infant Mortality Rate) among all four provinces (Punjab, Sindh, Baluchistan, and Khyber Pakhtunkhwa (KPK), the federal capital-Islamabad Capital Territory (ICT), and two administrative regions (Gilgit- Baltistan (GB) and Azad Jammu and Kashmir (AJK)) (**Fig 1.3)** [62]. The rates are consistently higher in rural areas as compared to urban areas. Moreover, differences between districts and provinces are also observed in rates of wasting and stunting among children and women of reproductive age [63]. This is greatly influenced by socioeconomic traits, including maternal education, household wealth index, and residence.

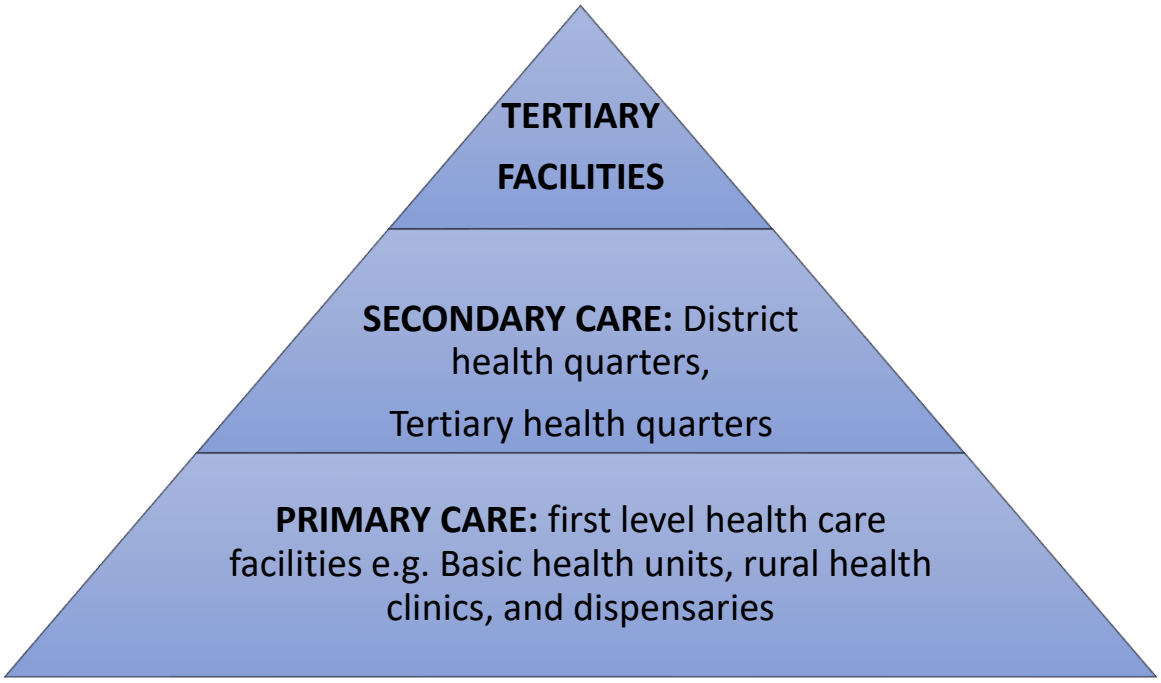
Figure 1.3. Provincial characteristics of Pakistan



All four provinces have defined their standard for service delivery of hospitals, including infrastructure, service packages, human resources, medical supplies, equipments, information systems, etc. [65]. While health has been assigned to the provinces as a prime liability, inflation has disintegrated the progressing resources related to it and provision of primary healthcare programs.

In Pakistan, healthcare is delivered through a three-leveled health system: primary, secondary, and tertiary **(Figure 1.4).** A significant part of expenditures within the health system is restricted to tertiary level of care, there has been a lack of investment in strengthening health services at the district level, especially the Basic Health Units and Rural Health Centres [60,65].

Fig 1.4. Health care system structure in Pakistan



There is a National Integrated reproductive Maternal and Neonate Health Strategy (IRMNCH-2016-20) in Pakistan, focusing on the training of staff, supervision, referral system and quality of care delivered in the general aspect of maternal and newborn services [66]. However, there is an earnest need to resolve social determinants influencing maternal, newborn, and child health

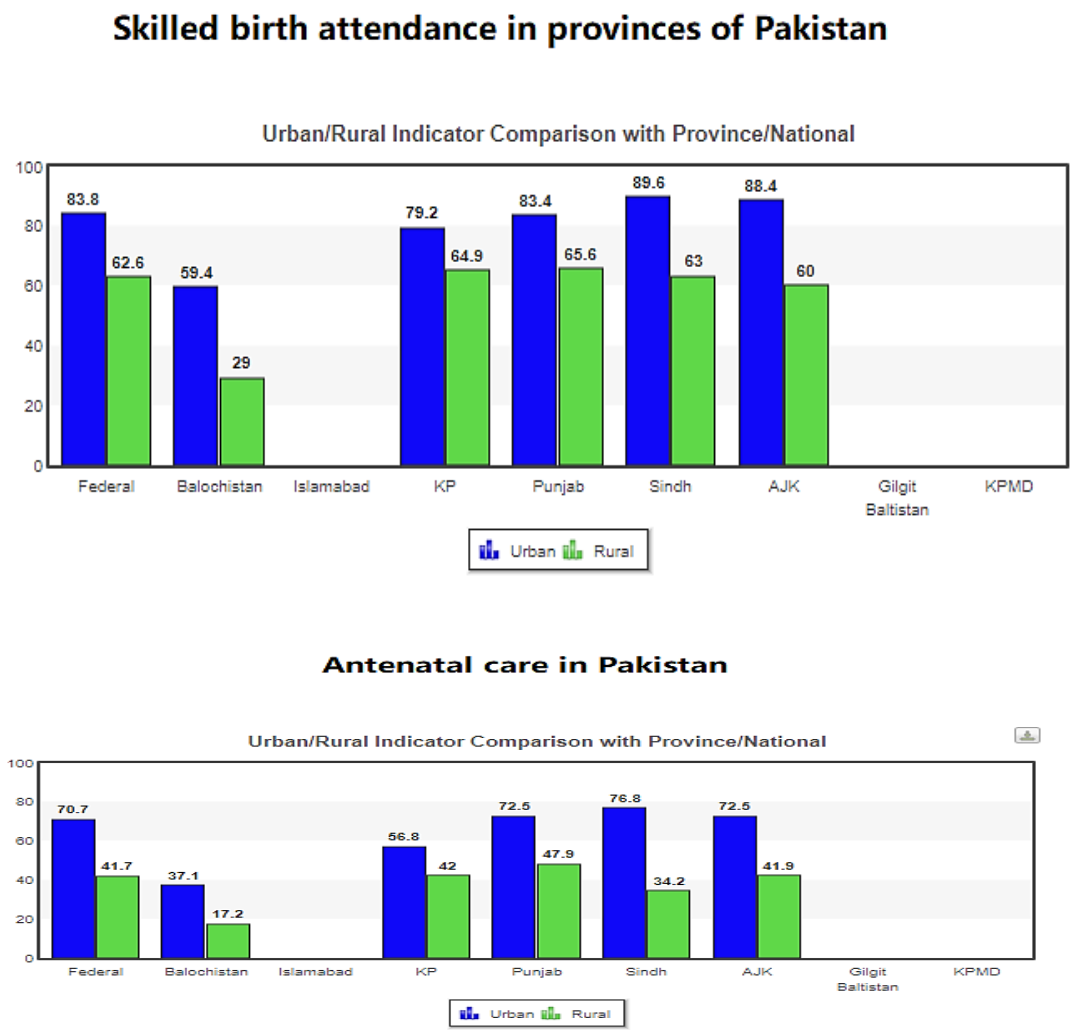
(MNCH), relatable to important issues of women's status, their empowerment and education, environment development, and hygiene, water, and sanitation [67].

1.6. Maternal health in Pakistan

Pakistan is one of the six countries contributing to more than 50% of all maternal deaths worldwide [60] and ranked 53rd among the list of countries with the highest maternal death [60-61]. Pakistan Demographic and Health Survey 2012-13, reveals that the country bears one of the highest burdens of both neonatal mortality (55 per 100- live birth), and maternal mortality (276/ 186 deaths per 100,00 live birth) [68].

The majority of maternal deaths are caused by complex interactions of health, economic, social, and cultural related factors [69]. Early marriages; higher birth rates; common disease burdens e.g., anemia, tuberculosis; low status of women; inequities mostly caused by disparities in socioeconomic status that include wealth, rural-urban region, unequal access to resources, education and household infrastructure are the contributing factors in maternal death and illness in the LMICs [69-70]. Moreover, the wide disparities between urban and rural areas for the utilisation of services such as antenatal care and delivery services by skilled birth attendant is major root cause of the problem of complicated maternal health in developing countries [69]. Likewise, Pakistan demographic health survey (2017-2018) also shows huge disparities between urban and rural utilisation of maternal services [62]. These figures illustrate that majority of women in rural Pakistan do not receive maternal care as compared to their counterparts residing in urban areas. **Figure 1.5.** represents the rural urban discrepancies of different provinces of Pakistan.

Figure 1.5. Urban-rural disparities in maternal health services in Pakistan

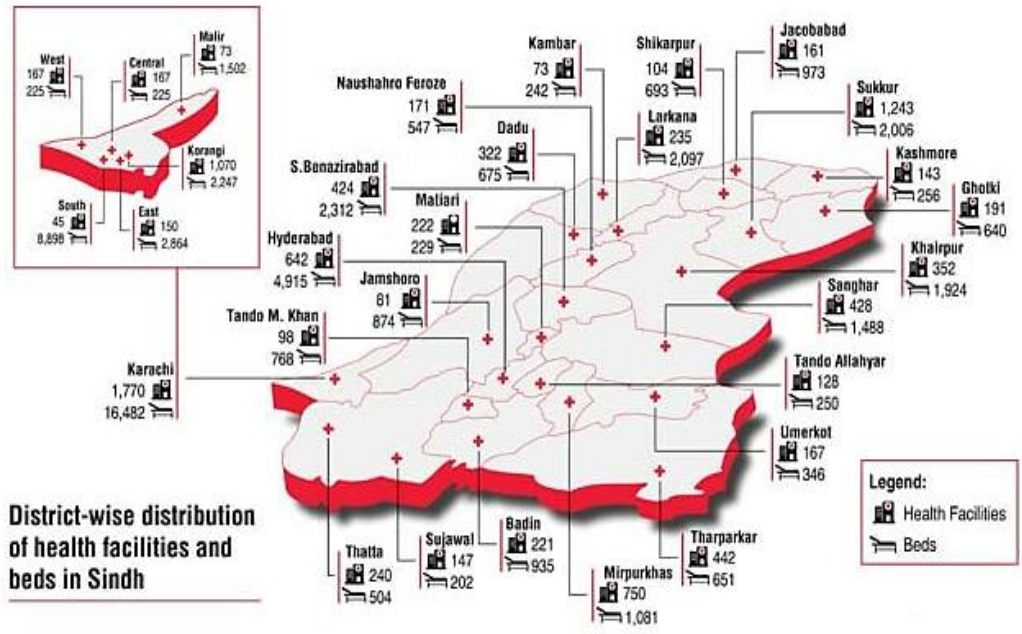


Source: Pakistan Demographics and Health Survey (2017-2018)

In Pakistan, the rural areas of Sindh province have several health facilities **(Fig 1.6)** yet there is still a high rate of maternal mortality in the province **(Fig 1.3).** A local study found that pregnant and postnatal women received 1.9 fewer services in the Sindh region as compared to other regions

in the country [71]. Area of residence was related to the number of maternal health services availed, reflecting discrepancies in the availability of facility resources at the regional level. Data shows that in urban areas 81% of women delivered in hospitals, whereas only 50% of deliveries took place in facilities in rural areas [72]. Women who delivered at home were found two times more likely to develop complications during pregnancy, childbirth, or in the postpartum period [73]. The complications included obstructed labor, antepartum/postpartum bleeding, pre-eclampsia, eclampsia, and suspected respiratory tract infections [73].

Figure 1.6: Number of health facilities in the province of Sindh, Pakistan



***Source: Report compiled by the Sindh Healthcare Commission, available with* The Express Tribune (July, 2019)**

The complications of pregnancy and childbirth lead to one death every 40 minutes and disability for childbearing women [12]. About 34.5% of deaths of these women are due to infectious diseases [58-59]. It is reported in Pakistan Demographic Health Survey (PDHS 2006), that sepsis is a third leading cause and accounts for 14% of maternal deaths [74]. A maternal mortality rate of 21.68% was reported by a local study due to puerperal sepsis [71], nearly identical to earlier studies from the same institution [75-76], and comparable to studies from other major cities of Pakistan [77-78]. However, these figures are likely to be underestimated due to variations in existing criteria and definitions being utilised to define maternal sepsis and related epidemiological implications**.**

Some definitions only included genital tract infections (endometritis, chorioamnionitis), while others included incidental infections (Malaria), or infections from other organ systems, such as Pneumonia [42]. These variations may have implicated on accurate assessment of burden related to maternal sepsis across different settings in the country. In addition, one of the major obstacles to implication is the absence of proper and timely data. Pakistan has solely depended on time taking and expensive cross-sectional surveys to gain up-to-date information and progress of assessment on critical issues such as direct etiology/causes of morbidity and mortality, which are not obtainable at the provincial level [60].

Worldwide, postpartum hemorrhage and eclampsia are responsible for most cases of severe maternal morbidity (SAMM) followed by sepsis [15,37]. Concomitantly, the events leading to SAMM or ‘near miss’ in Pakistan follow the same order, with postpartum hemorrhage, eclampsia, and sepsis accounting for 51%, 8.5%, and 4.2% cases, individually [79]. Mode of delivery, lacerations, hemorrhage and multiple vaginal examinations are major contributors to

sepsis that may develop within a few hours of delivery [71,79]. In addition, there are multifactorial reasons for persistently high maternal mortality due to sepsis in the country such as low socioeconomic conditions, unskilled home deliveries in unhygienic conditions, prolonged labor, induced miscarriage, anemia, and late referrals to hospital [60].

The proportion of maternal morbidity and mortality is still not reduced in Pakistan despite increase in institutional deliveries [80-81]. The ineffectiveness of the health care system secondary to the lack of emergency obstetric and neonatal care (EMONC) services and the absence of fully trained staff at the primary and secondary care level was found to be the primary reasons [81]. Moreover, the absence of a multidisciplinary team approach and an integrated referral system in rural areas worsened the situation [81]. Many women do not arrive at emergency hospital facilities for treatment even on developing obstetric complications [82].

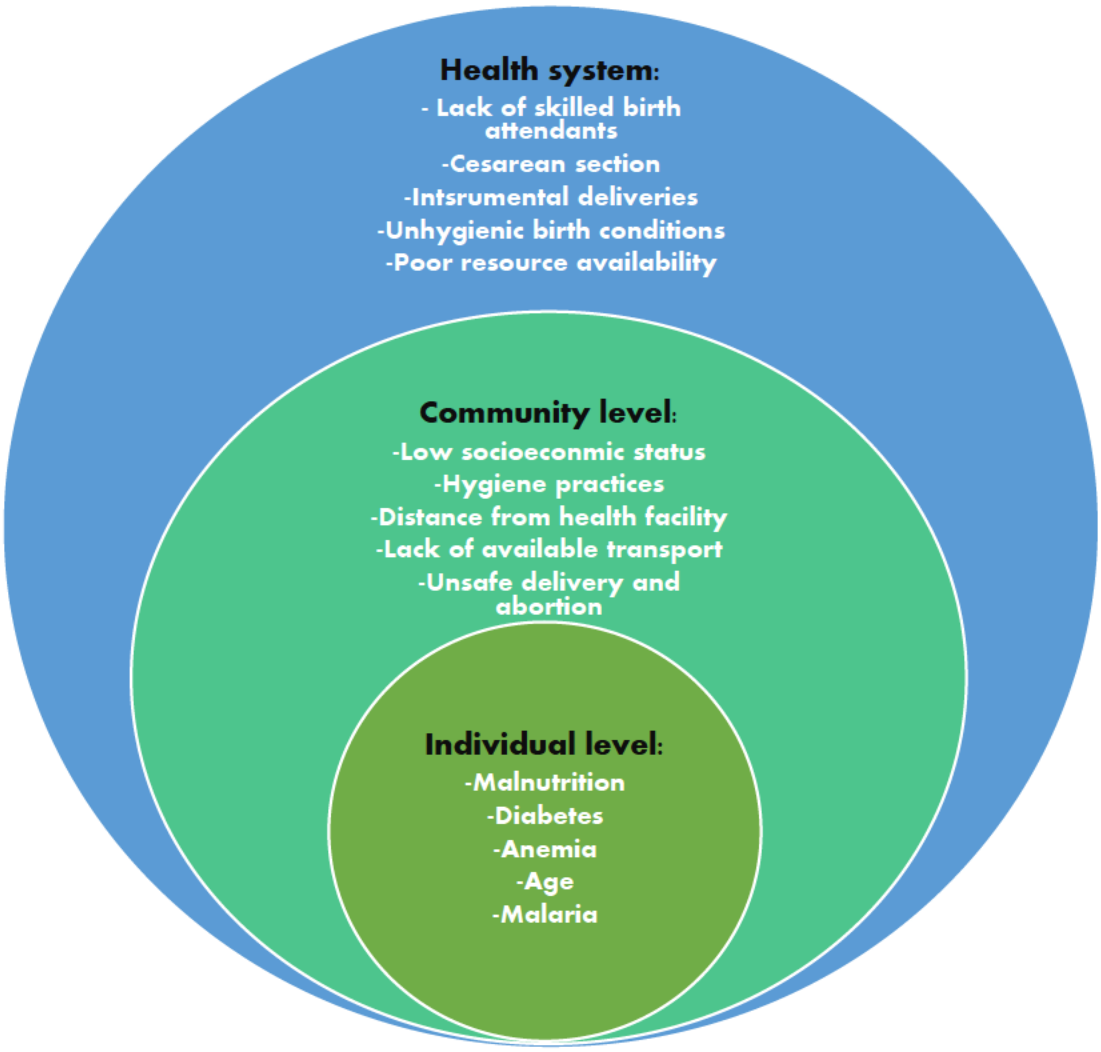
The approaches endorsed for safe labor include skilled birth attendants and timely referral to a well-operating and equipped healthcare system are reflected in Pakistan's official maternal health policy [66,82]. The quality of care is even more unfortunate in referral hospitals than in primary-level hospitals [72,83]. Only a few numbers of studies have inspected the quality-of-care issues in Pakistan, mainly focusing only on the organisational part of care including trained personnel, medicines and supplies, and caregivers' knowledge and standard of care rather than exploring the performance of care providers in hospital [68, 71-72]. The virtual absence of proper and regular monitoring during labor and birth, for example, not taking the vital signs of newborns and women is a matter of concern [84]. A tremendous opportunity for appropriate provision of care is often

missed by the policymakers, care providers, and researchers by not recognising the significant factors that increase the risk of maternal and newborn morbidity in the country.

1.7. Risk factors for Maternal Infection and Sepsis in Pakistan and other LMICs:

The risk of infection increases during pregnancy, labor, and childbirth and can extend to sepsis leading to septic shock causing a high expenditure on health care and patients, prolonged stay at the hospital, and high maternal death [50]. Along with other contributing factors in maternal death and illness in the LMICs, various healthcare practices that include self-medication, no antenatal visits to women, and vaginal examination could escalate the risk of infection in pregnant women [50, 59, 85]. Several other risk factors have been identified among pregnant women and postpartum period that are associated with maternal infection and sepsis and broadly categorised at an individual, community and health system level using the ecological model of health **(Fig 1.7).** The social ecological model focuses on multiple factors that might affect health and conceptualises health broadly [86].

Fig 1.7. Multilevel factors contributing to maternal infections



A study conducted in Pakistan observed 230 (6.28%) patients presented with puerperal sepsis out of 3658 admissions. All patients were anemic, 209 (90.86%) patients were unbooked, 126 (54.78%) patients had home delivery, 129 (56.08%) patients had a frequent vaginal examination,

in 228 (99%) patients no aseptic measures were taken, 111 (48.26%) patients had prolonged rupture of membrane, 30 (9.13%) patients had an unsafe miscarriage and 107 (46.52) patients had prolonged labor [85]. Several other common risk factors for maternal infections and sepsis in LMICs are described in subsequent sections.

1.7.1. Cesarean section

The association of puerperal sepsis with the birth attendant and institutional delivery care is well recorded [87]. It is often caused by invasive procedures such as cesarean or instrumental delivery and vaginal examinations when infective organisms causing puerperal sepsis are introduced by birth attendants. The cesarean section is one of the most frequent obstetrics surgical procedures [87]. The odds of bacterial infections are significantly correlated with the cesarean section compared to the spontaneous vaginal delivery; the reported rate of bacterial infections is 1% to 25% which is 5 to 20 times higher when compared to normal delivery in developing countries [88]. Peripartum infections which include urinary tract infections, endometritis, and wound infections are all related to the deliveries conducted through cesarean section [87-88]. Additionally, the cesarean section birth increases the risk of postpartum endometritis by 27% and tends to be 20 times more likely to be caused than in normal deliveries [89].

Numerous studies have found a direct relation between cesarean section delivery and a high risk of sepsis among women [87-89]. The maternal sepsis risk is three times more in women with wound infection or surgical site infection and is more likely to develop after the cesarean section delivery [90]. The surgical site infection (SSI) rate following cesarean section is higher in LMICs

i.e., 3-24% than HICs i.e., 3-11% [91]. A study from Uganda reported that the cesarean section accounted for 46.2% of the SSI rate among women admitted to the obstetrics and gynae wards [92]. Another study showed that 10.3% of women were diagnosed with SSI following lower segment cesarean section [93].

According to the PDHS survey of 2017-2018, the rate of cesarean sections is 22% and post-cesarean complications are high in Pakistan [62]. A study found a high rate of post-cesarean infection among women, particularly in emergency cesarean sections due to prolonged rupture of membrane and multiple intrapartum vaginal examinations [87,88]. The post-cesarean complications included endometritis, fever, and wound infection [88]. Furthermore, post-cesarean infection complications include urinary tract infections, re-operation, wound dehiscence, and disseminated intravascular coagulation [87-89-].

1.7.2. Unsafe abortion

Unsafe abortion significantly contributes to maternal morbidity and mortality [94]. Globally, it is projected that around 25 million unsafe abortions occur yearly [95]. Unsafe abortion caused 47,000 deaths globally every year between 1990-2008, with infection being the major cause of death [94-95]. It is estimated that seven million women undergo abortion-related treatment, and five million women suffer disability because of its complications [94].

Evidence suggests that developing countries account for 97% of all unsafe abortions [96]. The rate of unsafe abortion was high in LMICs i.e., 49.5% vs low in HICs 12.5% [96]. Hence, often caused by poverty, social inequality, the denial of women's human rights, and restricted abortion

law in LMICs [94-96]. Studies from developing countries of Latin America and Africa show that women with lower education, ethnic minorities, and lower income are more likely to have unsafe abortions due to their ignorance of the accessibility methods of safe abortion care [97]. Women in these countries usually end up with unsafe abortion procedures for unplanned pregnancies, and most of these abortions are conducted in privacy with unhygienic practices [97]. Around 20-50% of women experience adverse outcomes due to unsafe abortion practices and require admission to the hospital [95,97].

The adverse health outcomes of unsafe abortion include hemorrhage, peritonitis, injury to the vagina, cervix, abdominal organs, and uterus, bowel necrosis, infection, and sepsis [98]. The infectious complications following abortion are significant pregnancy outcomes, especially in developing countries as social determinants of health reduce access to quality obstetrical care in these countries [98].

Infection after an incomplete or complete abortion (induced or spontaneous) is often caused by infection of residual products of conception within the uterine cavity [99]. As per an estimate, around 10-20% of pregnancies end in spontaneous abortion or miscarriage [100]. Surgery is performed among women who are in situations where immediate intervention is required that include hemodynamic instability, hemorrhage, or any signs of infection [101]. Surgery is necessary in these cases to eliminate the residual products of conception, and the most common surgical procedure performed worldwide is uterine evacuation to treat miscarriage [101].

The rate of infection in women of LMICs following miscarriage surgery was found to be higher i.e., 30% when compared to HICs (6%) [102]. The uterine infection is a significant complication of the procedure and can lead to severe illness and death [103]. The long-term outcome of the infection can result in infertility, pelvic pain and increased risk of ectopic pregnancy [102-103].

1.7.3. Poor access to care and quality of care

It is anticipated that the rate of infection can widely be reduced by healthcare facilities and providers through the provision of adequate delivery of care [80, 82]. Poor access to maternal and perinatal health care significantly increases women's risk of adverse outcomes during pregnancy and labor. In LMICs, maternal deaths are largely caused by poor access to healthcare services, which is evidenced by a relatively low rate of trained birth attendants and institutional deliveries [104].

During childbirth, skilled birth attendants play an important role in preventing maternal deaths [105]., Unintended home deliveries conducted by unskilled professionals lead to an increased rate of maternal and newborn morbidity and mortality [106-108]. Various studies from Ghana showed that the majority of women who delivered at their houses were assisted by untrained professionals during labor [109-111]. The major complications of home delivery are retained placenta, postpartum hemorrhage and maternal or neonatal infection [105-106, 108]. The report of the State of World Children (2009) recognises the key features of developing sepsis in the regions with a high rate of maternal deaths, account for 60% of deliveries conducted at home by unskilled birth attendants with a lack of aseptic measures, hand, and perinatal hygiene [112].

Numerous studies conducted in Pakistan found home delivery an important contributor to maternal sepsis and reported that the odds of infection were 2.7 (95% CI; 1.1–6.2) times among women who delivered by untrained health professionals at homes in unhygienic conditions as compared to deliveries conducted at health facility [72, 83, 87]. However, trained health professionals' deliveries reduce the risk of direct complications such as hemorrhage and sepsis [106]. Factors like good access, adequate quality of care, and safety are basic to all health systems when considering contamination of infection resulting from childbirth.

The majority of patients in developing countries prefer to go to private hospitals as compared to public hospitals [80,82,84]. One of the local studies stated that an increased dependence of women in private hospitals over public ones, due to the common perception of a better level of care at a private hospital [72]. Though the quality of care is compromised in both public and private healthcare facilities.

Moreover, women who attended at least one Antenatal Care (ANC) visit are more likely to give birth with a skilled birth attendant [105]. ANC assists women to encourage health-seeking behaviors, and healthy home practices and recognises complications correlated to pregnancy [105]. As per the demographic health survey of Nigeria, less than 33% of women were delivered by skilled health professionals and 65% of women who were pregnant availed the antenatal care [113]. The lack of utilisation of antenatal care is observed as dreadful among pregnant women [114]. A local study shows that women who didn't seek antenatal care were at a greater risk to develop sepsis [68]. The results of this study are comparable to those stated by an earlier study,

which recognised that the odds of maternal deaths were 3.6 (95% CI, 1.8–7.0) times greater among those who had no ANC visit [82].

1.7.4 Facility structural and physical resource factors

There are several structural and environmental factors that enhance the maternal infection and sepsis risk in the health care facility. Inadequate medical supply chains (lack of antibiotics availability) and limited access to referral centers or intensive care units are part of the health system infrastructure that raises the risk of infection and related complications [69]. In addition, the shortage of basic environmental needs in the health care sector for instance compromised health infrastructure (e.g., lack of water supply, cleanliness in the facility), lack of hygiene items (e.g., gloves, cleaning agent, detergent) and poor hygiene practices increase 34 times risk of maternal deaths among women with sepsis [115].

1.7.5. Human and behavioural factors

Data suggests that inadequate hygiene practices at the time of labor, introduce the infection to the genital tract either via poor hand hygiene or contaminated surfaces that can cause infections leading to sepsis [115]. In addition, a shortage of staff at the health care facility could lead to an increased risk of infection as the patient's quality of care could be compromised [80-81]. The quality of care at public hospitals in LMIC's is compromised due to a shortage of staff and an excessive burden of patients [84].

1.7.6. Health systems/political factors

The significance of a strong health system is considered an essential pathway to decreasing maternal mortality and achieving improvements in maternal health [116]. There are a number of barriers that prevail in LMIC in lowering the sepsis burden, especially in low-resource settings. The factors which contribute to this in these countries are health inequity, poverty, low resilience, political corruption, and under-resourced acute healthcare delivery and public health systems [47,116]. Moreover, malnutrition, limited vaccine coverage, poor preventive health care, substandard living conditions such as inadequate sanitation and ventilation, bed sharing, indoor air pollution, and exposure to animal and environmental vectors upsurge the infection risk [117]. All mentioned factors could contribute to excessive bleeding, labor complications, infections, and sepsis among pregnant women during delivery and childbirth [106, 116-117].

1.8. Infection control practices:

Weak infection prevention and control practices are common causes of high infection rates and the subsequent increased maternal mortality [69]. The risk of developing a secondary healthcare-associated infection may be up to 20 times higher in LMICs than in HICs [70]. Research suggests that in developing countries the infection prevention control practices are not adequately practiced [69-70]. Measures and resources to prevent sepsis, such as the use of sanitisers and handwashing are important and need to be clear and in place for the patients who are at risk of developing an infection [115].

In LMICs, inadequately resourced health facilities in rural areas play a significant role in the development of maternal sepsis in women as it restricts their approach to use of obstetric care

[58,69]. Poor WASH conditions dissuade women to seek care, hence compromising patient dignity and eroding human rights as acknowledged in United Nations General Assembly to have access to safe drinking water, hygienic purposes, and sanitation facilities [118-119]. According to an estimate, one in five healthcare sectors in low-income countries lack proper sanitation, and 55% of healthcare sectors have a shortage of basic water facilities [115]. As per the literature, poor sanitation facilities along with a shortage of water supply led to maternal deaths caused by sepsis and hemorrhage [115-119].

Incorporating WASH services in health facilities is vital for universal quality of health coverage, infection prevention control (IPC), patients' safety, maternal and child health particularly for childbirth practices [118]. WASH in a healthcare facility is also part of the Sustainable Development Goal (SDG) 2030 [120]. The target of SDGs 6.1 and 6.2 refers to access to drinking water, sanitation, and hygiene universally and equitably for all [120]. Further, WASH in a healthcare facility is associated directly with a lot of health goals, like reducing maternal mortality (SDG target 3.1) [120-121].

In the context of Pakistan, very scant data is available on WASH services at health care facilities and information on the assessment of infection control practices such as hand washing, waste separation, disinfection, and disposal practices on a national level [120]. According to data by UNICEF [115], only 16% had basic sanitation facilities while data for basic water services in healthcare facilities is insufficient. Whereas basic hygiene facilities estimated coverage by 2021 is 55% in Pakistan [120]. Improvements and maintenance in infection control measures are required as a part of the delivery of care for the health system to work efficiently.

According to WHO, timely detection and treatment of maternal infection and sepsis along with proper infection control practices in the facilities can prevent women from developing complications associated with pregnancy and childbirth [16]. A resolution was passed in the World Health Assembly on 'Improving the Prevention, Diagnosis, and Management of Sepsis' in May 2017 [122]. Some interventions, including patient-care bundles, antibiotic usage, and trigger tools can improve monitoring and management and decrease the deaths and morbidity related to infections in the general and obstetric population [16, 122]. Yet, data is inadequate as to how maternal infections are identified and treated by healthcare providers and how well these interventions are followed, especially in low-resource settings. This evidence is required to improve the quality of care to reduce preventable infection-related severe maternal morbidities and deaths. These interventions are described in the next sections and deliberated in subsequent chapters of this thesis.

1.9 Prevention of Maternal sepsis

In the early 20th century, a rise in maternal mortality occurred, even whilst facility-based delivery in hospitals was becoming more common in Western countries [123]. The worsening of outcomes was due to the spread of infection among women in labor due to the use of invasive obstetric procedures and by inadvertent transmission from the attending health professional [123]. The significance of antiseptic techniques subsequently became extensively known and by middle of the century with the introduction of new antibiotics, sepsis related death rate in developed world was markedly reduced [124].

Hand hygiene plays a pivotal role in the prevention of infection. WHO guidelines have focused on the prevention of transmission of infection through good hand hygiene practices [124]. As per WHO recommendations, “healthcare workers should practice hand hygiene throughout ‘five moments’: before touching a patient; before an aseptic/clean procedure; after exposing to bodily fluids; after touching a patient; and after touching a patient's surroundings” [124]. It’s recommended to clean hands after toileting with water and soap, or an antiseptic agent can be used to clean the hands [124]. WHO has also given evidence-based guidance on the measures that must be taken during pregnancy and childbirth to decrease the risk of infections among patients, including prophylactic antibiotics administration and treatment guidelines for infections [125].

1.9.1. Antibiotics Prophylaxis

The most well-known and effective way globally to treat and intervene in maternal infection is the use of prophylactic antibiotics [126]. The use of intrapartum antibiotics prophylaxis at the time of labor and delivery subsides the risk of preterm pregnancy, neonatal infections, and chorioamnionitis [127]. Numerous studies have emphasised the advantages of antibiotic prophylaxis during pregnancy and childbirth [128-130]. According to WHO guidelines, prophylactic antibiotics are recommended in the first, and second trimesters and in preterm premature rupture of membrane (PPROM), while it’s not recommended in second or third trimester in preterm labor with intact amniotic membranes, and in PROM at or near term [131]. However, for cesarean section, antibiotics are recommended before skin incision [131-132].

The proper use of topical antiseptic agent, operational techniques, prophylactic antibiotics administration can reduce the post-operative risk of infection [133]. A multicentre randomised trial involving pregnant women in labor who were planning a vaginal delivery, antibiotic prophylaxis led to a considerably decrease rate of maternal sepsis and related death [134]. It has been shown that women who undergo a cesarean section have a 52- times greater chance of infection if prophylactic antibiotics are not administered than those who have a vaginal delivery [135]. A Cochrane review found that antibiotic prophylaxis was helpful among women with cesarean delivery and was able to reduce the complications that include fever, endometritis, wound infection, and other serious maternal infections [136].

A randomised trial conducted on women undergoing unscheduled and non-elective cesarean delivery showed that when prophylactic azithromycin was added to standard pre-incision compared to placebo, a 50% reduction was found in surgical site infections [134]. A systematic review also provided convincing evidence that women who receive prophylactic antibiotic undergoing cesarean section procedure have reduced risk of endometritis, and wound infection, and 60-70% of the reduction was seen in serious maternal infection [137]. Although, these findings have not yet changed the guidelines and there are still debates on the use of prophylaxis antibiotics to reduce infections with the growing risk of antimicrobial resistance (AMR) for mother and neonate.

The extensive use of antibiotics in women during labor and childbirth may lead to AMR in pathogens responsible for the development of maternal sepsis [138]. However, an emerging trend

has been observed in the use of prophylaxis antibiotics in maternity setups globally [136]. According to an analysis by WHO, more than 50% of all medicines, including antibiotics, are unnecessarily used, and prescribed [139-140]. The condition where antibiotics are misused in pregnancy includes prophylaxis in the operational delivery and caesarean section, prevention of preterm birth, prevention of neonatal streptococcal sepsis, prevention of preterm birth, urinary tract, and genital infections, and chorioamnionitis [138].

There is a continuous increase in antimicrobial resistance (AMR) globally due to the rapidly increasing emergence of resistant bacteria [138]. The recent WHO surveillance data from 22-high and low-income countries reported that AMR is observed high in frequent bacterial infections while E. coli and Klebsiella pneumonia (K. pneumoniae) are found as the most common resistant pathogens [141]. This increasing trend of antibiotic use is expected to be high in LMICs because of development projects and the betterment of public access to health services [142].

A study conducted in 15 maternity units in India and Bangladesh reveals that 87% of the antibiotics were administered to all peripartum women [142]. It is believed that antibiotics are being sold without any medical prescription in LMICs, so the actual quantity of antibiotics sold is underestimated which on other hand gives rise/ contributes to antibiotic-resistant bacteria multidrug-resistant (MDR) such as Staphylococcus aureus (S. aureus), E. coli, and K. Pneumoniae [142]. The resistance to amoxicillin, third-generation cephalosporin, and other uropathogenic antibiotics in the pregnant population especially in the region of Africa, creates a challenging situation to manage Urinary tract infections (UTIs) during pregnancy [143-145].

Pakistan is positioned third for antimicrobial consumption among LMICs [146], with an increased consumption of 67% between 2000 to 2015, increasing AMR rates [147]. Mortality is found to be high among patients with infections related to the multi-drug-resistant organism (MDR) including typhoid, tuberculosis, and malaria [142]. The country faces many challenges to the execution of the National Action Plan (NAP) for antimicrobial resistance (AMR); these include a lack of diagnostic and financial resources along with excessive use of antimicrobials in hospitalised patients as prophylaxis, and sale of antimicrobials without prescription at the community level [147].

The most significant step in managing a systematic inflammatory response is declaring the cause and the reason for initiating proper treatment; along with defining infective etiology to prescribe the appropriate antibiotic [148]. While the improvement of laboratory resources and structured surveillance technique for developing an antibiogram is widely needed in LMICs and hence will improve antimicrobial prescribing [149]. Limited availability and high cost were found to be the main drivers of inconsistency between actual and desired antimicrobial treatment in LMICs. Medical professionals may not prescribe the desired treatment to which the organism appeared susceptible due to lack of access to antimicrobials [149].

The cost of AMR to national economies and their health system has a huge influence on the patient's productivity or their caretakers due to the duration of stay in hospital, and the need for intensive and critical care [139,150]. The execution of an antimicrobial stewardship (AMS) program in all health facilities, rational use of antibiotic in medical undergraduate training and

other objective strategies of the National Action Plan on AMR can possibly enhance the optimised use of antibiotics in pregnancy [150].

1.9.1.1. Antibiotics Prophylaxis for the surgical management of miscarriage

Around 208 million adolescents and women become pregnant each year worldwide [1], but 10 to 20% of pregnancies end in spontaneous abortion [151-152]. The worldwide abortion rate was estimated at 35 per 1,000 females from 2010–2014 [153], rates approximate 27 per 1,000 in HICs and 37 per 1,000 in LMICs [154]. Around 84 million (40%) of pregnancies in LMICs end in either induced abortion or miscarriage [153]. It is estimated that 30 women die for every 100 000 unsafe abortions in developed regions [95]. The number rises to 220 deaths per 100 000 unsafe abortions in developing regions [94-95].

The abortion related complications lead to around 5 million admissions in LMICs with sepsis supposedly causing 10% of maternal deaths being the second most frequent complication [155-159]. Although it is difficult to ascertain the rates of infection related to abortion in LMICs but given that almost all unsafe abortions occur in these countries [159], the rates are expected to be higher than in HICs [159]. In Pakistan most of the 2.2 million induced abortions occurring each year are unsafe, resulting in an estimated 700,000 life-threatening complications including sepsis [160-161].

Around 10 to 100 deaths per 100,000 abortions in countries like Pakistan are caused by septic abortion [162]. Septic abortion is a possible complication of both medical and surgical abortions

and can occur due to procedure itself (e.g., nonsterile technique, trauma) or retained products of conception (RPOCs) [163]. It occurs in less than 0.4% of patients undergoing safe abortion and first trimester uterine aspiration, but the frequency is much higher in those undergoing unsafe abortions [164]. The estimated rate of infection after surgical abortion is 0.1–4.7% worldwide [165].

In low-income settings, surgical intervention after abortion is normally a result of incomplete abortion [165-166], and 70% of all gynaecological admissions are represented by this procedure [167]. Infection occurs in up to 30% of women and is a serious complication of miscarriage surgery in LMICs [155], with potentially substantial mortality and morbidity implications [168-170]. However, almost every morbidity and death related to abortion could be prevented [171].

The use of antibiotic prophylaxis after the surgical management of induced abortion to reduce the risk of infection endorsed by international and national guidelines [172-173]. These guidelines are supported by robust evidence on the clinical effectiveness of prophylactic antibiotics given before surgical abortion [174-175]. Whereas there is very limited evidence to support the routine use of antibiotic prophylaxis in the surgical management of miscarriage [176], and unless there is a sign or symptom of infection**.** Present guidelines do not indorse the use of antibiotics before miscarriage surgery [155].

In the United Kingdom (UK) it is increasingly common for antibiotic prophylaxis to be used at the time of medical or surgical abortion. Either a routine prophylaxis or screen-and-treat protocol should be in place [177]. A single dose of Doxycycline is widely used as supported by evidence

for 24 hours of coverage, while some clinicians prefer to administer a single 1 g dose of azithromycin [177-178]. Metronidazole is given in addition to azithromycin or doxycycline at the time of either surgical or medical abortion but sufficient evidence to support the routine use is scarce [166, 177-178].

Antibiotic prophylaxis at the time of abortion significantly reduces the likelihood of infection after procedure [174]. A randomised controlled trial (RCT) showed that prophylaxis was less expensive and more effective than a screen and-treat approach for bacterial vaginosis, gonorrhoea, and Chlamydia [179]. A systematic review reported post-abortion infection occurred in <0.4% of cases [156] who received universal prophylaxis for Chlamydia infection [156].

In LMICs, the question of whether to use prophylactic antibiotics in routine for surgical management of miscarriage is particularly important. Rates of miscarriage surgery are high in these countries due to low acceptance of non-surgical management approaches [180]. Considering the lack of clinical evidence, some of the guidelines do not recommend antibiotics [181], while other guidelines recognise the lack of evidence, yet they promote the use of prophylactic antibiotics based on general findings from other indications [182]. Therefore, a systematic review was conducted as part of this PhD study to evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage and will be presented in a subsequent chapter.

1.10 Management of maternal infection and sepsis

Following widespread efforts to emphasise and support facility-based deliveries, the majority of women are now delivering in hospitals [81]. However, due to the increased number of women in the facility, the quality of care has been compromised which has a direct impact on the mother and infants' health [16, 84]. Almost 8% to 12% of obstetric patients are admitted to higher level of care units because of sepsis and as compared with other complications in pregnancy, there is a very high case fatality rate of maternal sepsis [29,34].

The diagnosis of sepsis can be challenging during pregnancy and puerperium. As progression of sepsis can lead to death, early detection may help prevent further complications and is essential for timely treatment and enhanced maternal outcomes [37,49,55]. Late recognition of sepsis is a significant cause of avoidable maternal deaths and morbidity, resulting in delayed escalated care and treatment, which are critical to saving lives [45-46,49]. One key challenge is to create and validate tools to support the reliable and correct assessment of patients with suspected sepsis and encourage a timely response in this medical emergency.

There are only some pregnancy specific and evidence-based guidelines for healthcare professionals concerning how to best treat, recognise and prevent the early warning signs of maternal sepsis [48-49]. Approaches like adding early warning systems, and standardised and clear diagnostic criteria, alongside management protocol implementation into clinical practice during the first hour of treatment of maternal sepsis and septic shock, can be effective in improving timely, high-quality care and it is hoped this may help in reducing associated maternal mortality globally [183].

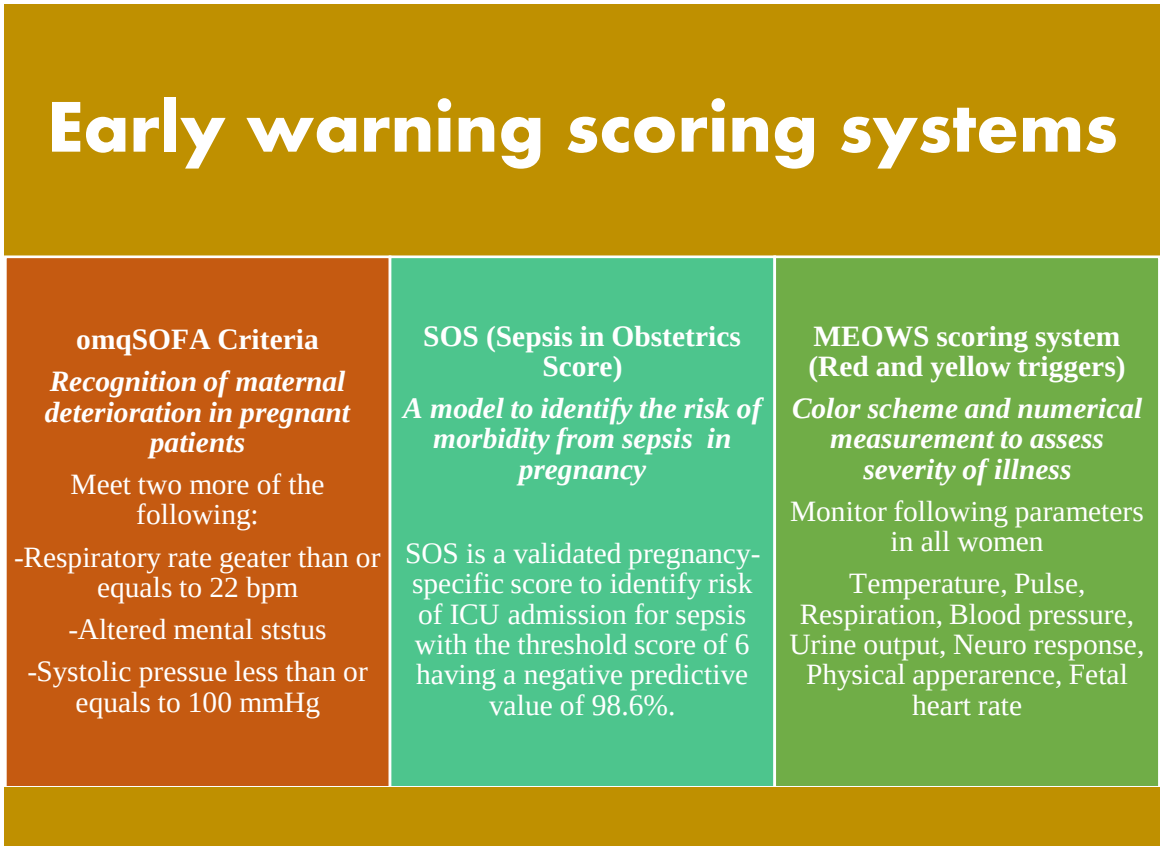
The updated publication of the Surviving Sepsis Guidelines has increased the attention towards identification of critically ill patients in critical care literature [184-185]. The utility of an early warning system during the first 24 hours of hospital admission to identify the severity of illness has been recognised in the general population. It enables early interventions and favors timely admission of a patient to the ICU and referral to specific services as required by the patient's condition [186]. The early diagnosis and initiation of guided treatment of critically ill patients by the emergency department have resulted in better outcomes in terms of mortality [48-49,186]. The Surviving Sepsis Campaign (SSC) criteria can be applied for the identification of critical sepsis cases in the general population, but they were not established for maternal patients [184]. Despite no standardised criteria to vital signs, changes are considered in maternal patients for early signs of infection and to diagnose sepsis [187-188].

Modified Early Warning Score (MEWS) is one of the scoring systems developed for use in the general medical and surgical populations [188-189], and Standard Adult Modified SIRS screening criteria have been proposed to represent normal changes of pregnancy to recognise triggers for sepsis evaluation [190-192]. However, SIRS and ME.WS criteria do not accurately identify patients at risk, for transfer to higher level of care, sepsis, or death with intrauterine infection, and no recommendation is given to its use in an obstetric setting [193].

Many early warning scores have been developed to identify sepsis in pregnancy [186]. The scoring systems that are pregnancy-specific and allow early recognition of maternal deterioration in pregnant populations include omqSOFA (obstetric modified quick SOFA), SOS (Sepsis Obstetrics Score) and MOEWS (Modified Obstetric Early Warning System) (**Fig 1.8**) [186,189].

However, no appropriate validation has been done for omqSOFA, qSOFA, and SOFA scores in pregnant and postpartum populations. Also, qSOFA scores were found weak both in the aspect of sensitivity and specificity in recent publications [185]. This presumably makes it unsuitable to establish its use in obstetric clinical practice.

Fig. 1.8. The pregnancy-specific scoring systems for early recognition of maternal deterioration



SOS score was also used to identify the risk in sepsis patients who required critical care unit admission [194]. However, this scoring system has limitations in its implication in low resource settings as it requires laboratory tests such as WBC count and Lactic acid level. Whereas

MEOWS showed much higher sensitivity in obstetric admissions to intensive care units in the United Kingdom as compared to non-obstetric early warning systems that are used currently in the general adult population [195].

While, at present, there are no ideal tools for screening sepsis in the maternal population [185]. Consequently, the diagnosis of sepsis is yet difficult because of physiological changes in pregnancy and its specific management based and developed on those for the general population [18,27]. Thus, valid criteria are required to recognise possible cases of severe maternal infection (suspected maternal sepsis) to improve perinatal outcomes and timely management of such cases.

According to the report of the 2003-2005 triennial Confidential Enquiry into Maternal and Child Health (CEMACH), the routine use of MEOWS is applicable in obstetric population (**Fig. 1.8)** [196]. This scoring tool is based on physiological parameters such as respiratory, heart rate, systolic blood pressure, and temperature and can be utilised as a bedside tool for routine observation and is also helpful in recognising deteriorated patients and identifying patients who may become critically ill and improves outcomes by timely intervention. Significantly, no laboratory testing is required, and it contains color scheme and numerical measurement to assess severity of illness [197-198].

Literature on the ability of early warning scores is found to be divided regarding its effect on mortality outcomes, even though reducing the number of intensive care admission is considered a significant outcome in low-resource settings [198]. The sensitive and robust early warning score is needed in low-resource settings due to scarce resources, specialised tests, and laboratory

services. Moreover, the outcomes of the implementation of early warning scores on maternal mortality need further investigation in these settings in combination with training protocols, availability of medical advice and appropriate hospital outreach teams. A diagnostic score should be validated in large obstetric populations across different settings, which can overcome agreement among clinicians on vital signs and laboratory findings; added to provide better care to both mothers and infants.

Seacrist et al reviewed cases of death from maternal sepsis and identified several key deficiencies in the care of these women [199]. Failure to diagnose sepsis; failure to initiate a suitable investigation; late management and treatment; delayed involvement of clinicians; failure to isolate the source of infection; failure to consider urgent delivery; delayed involvement of a multidisciplinary team, delay in identifying treatment failure and initiating alternative or additional antibiotic; and failure to transfer to a high level of care are the reason for litigation in maternal deaths from sepsis [37].

Global Maternal Sepsis Study (GLOSS) was undertaken to assess the frequency of recommended essential practices for the prevention, early detection, and treatment of maternal sepsis [200]. The study found that around one-third of included women with confirmed or suspected infection did not receive antimicrobials nor did they have a complete set of vital signs recorded upon confirmation or suspicion of infection. The absence of a complete set of vital signs recording was observed in all the facilities included in the study [200].

Whereas a main factor in the survival of maternal sepsis cases is a rapid response from the health system through early identification and management of the infection and its complications; essential to that is the availability of required services in the healthcare facility along with specific resources to assess and treat these cases [201-202]. Numerous health facilities lack the necessary resources, such as intravenous (IV) fluids, basic monitoring equipment for instance pulse oximeters, and simple positive pressure airway systems, to implement current sepsis management guidelines [203].

The aim of maternal sepsis management is to try to stop the progression from sepsis to septic shock [49,122]. The treatment comprises early hemodynamic and respiratory stabilisation, the initiation of empiric broad-spectrum antimicrobial treatment therapy with an agent in the first hour of diagnosis, if possible, control source of infection within the first 12 hours, and the prevention of sequelae and complications [122].

The WHO recommended the use of SCC criteria adjusted for the obstetric population in the absence of specific evidence-based guidelines for this group of the population [126]. These recommended guidelines comprise certain evidence-based interventions, focused on improving the diagnosis and treatment of sepsis [204]. The collections of evidence-based interventions include 3-hour and 6-hour "bundles" which represent certain elements of care, usually three to five items, for a defined care setting and patient population, that when performed consistently and collectively, improve patient outcomes **(table 1.1.)** [205-206].

Table 1.1. Surviving sepsis guidelines

Surviving sepsis campaign bundles (3h and 6h)	
To be completed within 3 hours	***To be completed within 6 hours***
1) Measure lactate levels	Apply vasopressors (for hypotension that doesn't responds to initial fluid resuscitation) to maintain a MAP of greater than or equals to 65 mmHg.
2) Obtain blood cultures prior to antibiotic administration	In the event of persistent hypotension after initial fluid administration (MAP <65mmHg or initial lactate was equals to greater tha 4 mmol/L, reassess volume status and tissue perfusion and document findings
3) Administer broad spectrum antibiotics	Reassess lactate levels if initial elevated
4) Administer 30 ml/kg crystalloid for hypotension or lacatate > 4 mmol/L	

The "hour-1" bundle has been proposed in the update of 2021 SSC guidelines **(table 1.2)** [207], for replacement of the 3-h and 6-h bundles. The 1-hour bundle intends to bring attention that attention to the idea that sepsis is an emerging ailment and enables clinicians to rapidly respond (even though all required interventions may not essentially be undertaken in the first hour) [126]. The principle of the golden hour of sepsis was validated in earlier studies excluding pregnant patients; however, increased risk of maternal death and poor outcomes have been observed with delays in identification of sepsis, escalation of care and timely administration of antibiotics in maternal patients as well [208-209]. Hence, based on the best evidence the golden hour principle is applicable to maternal patients, and maternal sepsis is categorised as an obstetric emergency.

Table 1.2. Surviving sepsis guidelines (1h bundle)

HOUR 1 BUNDLE: INITIAL RESUSCITATION FOR SEPSIS AND SEPTIC SHOCK	
1)	Measure lactate level
2)	Obtain cultures before administering antibiotics
3)	Administer broad spectrum antibiotics
4)	Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate equals to or greater than 4 mmol/L
5)	Apply vasopressors if hypotension during or after fluid resuscitation to maintain a MAP greater than or equals to 64 mmHg
Remeasure lactate if initial lactate elevated (>2mmol/L)	

The bundle-based strategies have been a foundation in improving sepsis management initiatives and proven effective in high-income settings [210]. It has been evident that compliance with the bundle care approach resulted in decreased mortality among sepsis patients in developed countries and enhanced their outcomes [211-212]. In particular, the implementation of the surviving sepsis campaign's bundle has reduced mortality among sepsis patients [212]. However, despite its efficiency, unreliability still prevails for its applicability in low-resource settings [213]. Suggested interventions for sepsis management in high resource settings may not ideally be practical in low-resource settings. This is due to several different characteristic features of sepsis, such as differences in the pathogens, differences in the population at risk, and the available healthcare treatment options in low-resource settings. [16, 126].

The significant factor behind the success of bundle-based approach is that all components should be accessible and applicable to the eligible patient [210, 213]. Also, an important feature of care bundle implementation is its measurement of compliance. At least 95% of fidelity is recommended [214], however, variability is reported in the fidelity of implementation of care bundles in the literature only 53 of the 99 papers reported compliance of the complete bundle [215]. In high-resource settings, studies have struggled to get high levels of bundle compliance, typically ranging between 10 and 43% with total bundle compliance [216-218].

In low-resource settings, no current sepsis bundles can constantly be implemented due to lack of key resources, including laboratory facilities and blood culture sets which limit its compliance [204, 219-221]. It is often hard to recognise which component of bundled treatment to approach first and can be best in aspects of cost, and efficiency, in reducing sepsis mortality and morbidity [222]. The currently available SCC bundles are undoubtedly not attainable in low-income and lower-middle-income settings [204].

Earlier studies suggested that sepsis bundles need to be adjusted for use in a low-resource setting [213-215]. Previous attempts have been taken to develop sepsis care bundles for low-resource settings, however, they are not broadly utilised or adjusted for the pregnant population **(table 1.3.)** [222]. Yet, there are no globally recognised sepsis care bundles in low-resource settings that are particular to the maternal population. Hence, the development of the maternal sepsis care bundle in low resource settings became a global priority [222].

Table 1.3. Comparison of various components of sepsis care bundles

	Surviving sepsis campaign's resuscitation bundle	UK sepsis trust's sepsis six bundle	Dunser el al. Acute care bundle	FAST-M maternal sepsis bundle
Lactate	✗	✗		
Blood culture	✗	✗		
Antibiotics	✗	✗	✗	✗
Fluids	✗	✗	✗	✗
Oxygen		✗	✗	
Urine output*		✗		✗
Monitoring of mother				✗
Monitoring of neonate				✗
Source identification and control			✗	✗
Transfer to higher level care				✗
***Urine output monitoring is a requirement of the monitoring component of the FAST-M maternal sepsis care bundle**				

World Health Organisation and international stakeholders developed "FAST-M" maternal sepsis management bundle for resource-limited settings through international consensus and a synthesis of evidence. The bundle consists of five components: Fluids, Antibiotics, Source identification and control, assessment of the need to Transport or Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate) [222]. A feasibility study was thus conducted as part of this PhD work to evaluate the effectiveness of "FAST-M" and its utilisation in a low resource health care setting located in Sindh province of Pakistan and will be presented in subsequent chapters.

Aim and Objectives of the PhD:

Overall Aim

This PhD research seeks to work towards improving the prevention and management of maternal infections and sepsis.

I will seek to develop a better understanding of how to prevent maternal infection, with this aspect focused on women undergoing miscarriage surgery in global healthcare settings. I will then explore the development and implementation of a complex intervention (including a bundled approach) to improve the early recognition and management of maternal sepsis in a low-resource setting within Pakistan and understand the feasibility of this approach.

Objectives

1. To synthesise the evidence on routine antibiotic prophylaxis in women undergoing uterine evacuation procedures to treat miscarriage.
2. To develop, implement and evaluate the FAST-M maternal sepsis intervention for early recognition, and management of maternal sepsis in a low resource health care setting in Pakistan.

Sub Objectives

1. To adapt FAST-M bundle care tools (MEOWS chart, decision tool, and treatment bundle) to the context of Pakistan.

2. To assess whether the use of the FAST-M intervention is feasible in the local healthcare system and improves sepsis care.
3. To understand the barriers and facilitators to the implementation of this intervention.
4. To evaluate improvement in clinical processes and outcomes after the implementation of FAST-M intervention.
5. To suggest subsequent modifications required to the intervention prior to its further assessment for clinical effectiveness.

Reflections on the PhD journey

This section is a reflection on my background and my journey through the research as a doctoral student. My ambition has always been to help improve the maternal health in Pakistan in whatever capacity I can. After graduating from medical school, I practiced clinical medicine and worked in some private and government hospitals in the metropolitan city (Karachi). As I started working within the health system, I became familiar with the most pressing issues including lack of awareness, access, fragmented and fractured health system in the country that led to my ultimate motivation to pursue a career in research. I obtained post graduate degrees from Australia in public health and health promotion to implement the acquired skills to my future research work and expect to play a part in improving maternal health in my country and revamping our health care systems.

After post-graduation on returning to Pakistan, I joined Aga Khan University Hospital (AKUH)- a research-led organisation as a faculty member on research track in the department of Obstetrics and Gynaecology. My eight years of progressive experience at the institution, has given me the opportunity to broaden my research skills, to be involved in various national and international research projects, publish and present on several platforms and share research finding with policymakers in the country. I intended to take my career as a researcher to the next level by accomplishing a PhD, which builds upon my clinical and research experience to reach my potential to the fullest and achieve greater goals in maternal health research. .

Although my four-year PhD path had been difficult, it had been a unique and a well-rounded experience in its substance. The numerous experiences and challenges I undertook have allowed

me to envisage PhD a bit differently from how I did when I commenced this journey. Considering the nature of my study, it was imperative to utilise both objective and subjective evidence to plan, execute and evaluate the novel intervention in the local context. One of the reasons why low middle-income countries lag in improving the health of people is unrealistic goals and objectives based off global evidence are set for them. This invoked me to hear the voices of health care providers and other key stakeholders working at a low resource health care setting to reflect on their needs for care of maternal patients.

Having graduated in clinical sciences and worked in the medical environments, where I often dealt with numerical values instead of contextual-narrative statements and was enticed into handling clinical data, it was difficult to deliberate on the qualitative paradigm. Further readings of relevant journals and textbooks, undertaking mixed methods courses, and discussions with my supervisors and experts in qualitative research helped me a lot in the whole process. I finally decided to employ qualitative research methods (interviews and focus group discussions) to better understand the perspectives and perceptions of participants.

Nevertheless, by the time I finalised my study protocol and received ethical approvals and was about to begin fieldwork, the COVID pandemic hit the world and halted workplaces, suddenly creating access issues. It was extremely challenging to commence and conduct field research in Pakistan due to COVID upsurge and related lockdowns. This critically affected my timelines, which were delayed by approximately 6-8 months, but I still made progress by writing and publishing the study protocols, including the one for the systematic review which is within the scope of my PhD objectives.

When I could start the field work, I caught-up significantly on lost time. I adhered to my methodology and made continued progress, taking into careful consideration the safety needs of my research team and the participants. While I tentatively identified study participants and the areas of discussion I wanted to explore, it rarely worked out as planned. At the start that made me a bit frustrated as planned meetings didn't happen, especially with government officials, medical consultants, and nurses due to their COVID related busy and unpredictable schedules. Consequently, I had to adjust my plan according to the participants' time, interest and needs.

Another issue I encountered during the initial phase of the study, which was mainly qualitative and was conducted during the peak of the COVID-19 outbreak, was the influence COVID had on the findings. The participants emphasised including a few additional components in the bundle intervention to be tested, which were beneficial in the treatment of COVID. This issue was discussed with my supervisors and a range of local and international health care experts, after which it was decided that these components would be most appropriate for specialist doctors, normally in an ICU environment, hence it would not be suitable in a first response bundle. However, considering the importance of COVID situation and the availability of pulse oximeters at the study site, the recommendation to include oxygen saturation in screening tools to determine the patient’s clinical condition was taken up.

Likewise, focus group discussions were also dominated by talks of COVID due to the upsurge of cases around that time. To combat that, I had to prevent conversations from straying too far from research objectives and recenter the discussion whenever necessary so that relevant findings could be extracted. During the implementation phase, I found that most of the maternal patients enrolled in the study had respiratory tract infection (RTI) and were suspected of COVID-19

infection. However, due to lack of resources and testing kits in the facility, I could not approximate the actual number of COVID cases in my quantitative findings. The qualitative evaluation helped in providing answers to my quantitative assumptions.

In trying to assess and make sense of what made my PhD a successful and positive experience for me, despite the challenges I faced, I believe a few good things came out of this journey. It has made me more confident and persistent. I recognised that, in practice, the complete research process is a robust learning experience. The mixed methods approach I used helped me gain a more complete picture than standalone quantitative research would have. In the end, this led me to achieve something completely new in the context of local setting, focusing on the feasibility of an intervention for early recognition and management of maternal sepsis in a low resource setting; something which apparently had never before been done in Asia.

I am very proud of what I have accomplished and glad to have embarked on this PhD journey. I am privileged to have very supportive supervisors who directed me through several restraints and a dedicated research team who stood by me during the pandemic time. With their support and my self-determination, I was able to produce this thesis in the best possible time and published four papers from my PhD work so far and two papers are about to be published. The fact that I was able to complete this work hopefully means it will have an impact on maternal health globally.

Thesis Structure

This PhD research sought to improve the prevention, recognition and management of maternal sepsis in a low-resource setting. The background to this has been summarised in this chapter. **Table 1.4.** summarises the work to be presented in this thesis and how each objective will be addressed in the subsequent chapters.

Table 1.4. Summary of work to be presented in this thesis

Chapter	Population	Study design	Outcome/s
Chapter 1: Introduction	N/A	Narrative literature review	N/A
Prevention of maternal infections			
Chapter 2: Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage	Women undergoing uterine evacuation procedures to treat miscarriage	Systematic review	**Primary outcomes:** 1.Uterine infection. 2.Adverse effects of treatment **Secondary outcomes:** 1.Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage 2.Pelvic inflammatory disease (PID) 3.Hospitalisation for treatment of infection
Early recognition and management of maternal infections and sepsis			
Chapter 3: Evaluation of the feasibility of the FAST-M intervention in Pakistan: *a study protocol*	1) Key informant interviews and focus group discussions with: HCPs including physicians, nursing staff, healthcare administrators 2) Women who are pregnant or within 6 weeks of miscarriage, pregnancy termination, or delivery	A mixed methods study	1.Optimised FAST-M bundle care tools 2.Information and insights on barriers and facilitators for its local use.
Chapter 4: Adaptation of the FAST-M maternal sepsis intervention for implementation in Pakistan	Key informant interviews and focus group discussions with: HCPs including physicians, nursing staff, healthcare administrators	A qualitative exploratory study	Views and insights on application of FAST-M in the local context
Chapter 5: Early recognition and management of maternal sepsis in Pakistan	Women who are pregnant or within 6 weeks of miscarriage, pregnancy termination, or delivery	A feasibility study with before and after design	1.The proportion of patients admitted with indications of sepsis, who received appropriate monitoring (full set of vital sign measurements on admission

			recorded on MEOWS chart). 2.The proportion of women with suspected maternal sepsis receiving the FAST-M treatment bundle (including each bundle component) within 1 hour of identification of sepsis.
Chapter 6: Evaluation of the FAST-M maternal sepsis bundle care intervention in Pakistan:	Focus group discussions with: HCPs including physicians, nursing staff, healthcare administrators	A qualitative exploratory study	Views and insights on maternal and clinical outcomes for long term sustainability
Chapter 7: Conclusions			

Chapter 2

PROPHYLACTIC ANTIBIOTICS FOR UTERINE EVACUATION PROCEDURES TO TREAT MISCARRIAGE: A SYSTEMATIC REVIEW

This chapter forms part of the section of this thesis addressing the prevention of maternal infections. This chapter comprises a systematic review concerning the use of prophylactic antibiotics to prevent potential infections arising from miscarriage surgery. I will begin by talking about the incidence of miscarriage and infections relating to miscarriage surgery. I will then go on to describe the process by which numerous databases were searched, and ultimately six studies were selected, analysed and their findings discussed.

Content from this chapter has been published

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Contributions of authors

AW, SI, AA, CM, DL conceived the idea, AW, SI, AA, CM, DL designed the review, MM, AW coordinated the overall review, RP (FRG information specialist) designed research strategies, AA, SI, CM, AW screened the studies, SI, AA, CM, JC extracted the data, AW, CM did the statisctical analysis and the interpretation, AW, JC graded the evidence, AW, SI, CM wote the manuscript of the review, AC, AMG, DL, CM, JC provided general guidance on the review, AMG, KB, WM performed the previous work that served the foundation of this review.

Abstract

Background

One in six individuals experience miscarriage in their lifetime. Miscarriage is defined as the unintended loss of pregnancy in the first 24 weeks, although there are global variations with some countries reporting miscarriage up to 28 weeks of pregnancy. Incomplete and missed miscarriage can be managed without treatment (conservatively), or it can be treated with medicines or with surgery. Surgery involves the removal of the pregnancy tissue. Infection is a serious complication of this surgery and can result in serious illness and death. Infection can also have long-term consequences on fertility. Clinical evidence and guidance are clear that antibiotic treatment is needed for individuals experiencing miscarriage with signs and symptoms of infection; however, it is less clear whether prophylactic antibiotics are routinely necessary at the time of surgery (uterine evacuation procedures to treat miscarriage).

Objectives

The objective of this review is to evaluate the effectiveness of routine antibiotic prophylaxis in individuals undergoing uterine evacuation procedures to treat miscarriage.

Search methods

We searched the Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase, Global Health (Ovid), Scopus (conference abstracts only) and grey literature in May 2022; and checked references and contacted study authors and experts in the field to identify additional studies.

Selection criteria

Randomised controlled trials comparing prophylactic antibiotics with placebo or no treatment were included. Trials with a cluster-randomisation design and trials published only in abstract form were also eligible for inclusion. We included all types of miscarriage treated with surgical uterine evacuation. There was no gestational age limit. We excluded individuals with signs and symptoms of infection.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted and checked data for accuracy, and assessed the certainty of evidence using the GRADE approach. Primary inference was based on high quality evidence. We contacted authors of ongoing trials for additional information.

Main results

Six studies with a total of 4371 participants undergoing uterine evacuation procedures to treat miscarriage were included in our review. When all studies were considered, we found that prophylactic antibiotics may have little or no effect on uterine infection after surgical management of miscarriage compared with placebo or no treatment, but this evidence was assessed to be of low certainty (RR 0.78 95% CI 0.47 to 1.28, I^2 = 50%, six studies, n= 4371). Meta- analysis showed that when only studies with low risk of bias were considered, the effect was larger and of high certainty, resulting in a 43% reduction in the risk of developing a uterine infection (RR 0.57 95% CI 0.37 to 0.86, I^2 = 0%, 3 studies, n=3737, 85% of total participants; high certainty). Both the overall estimate and meta-analysis limited to studies with low risk of bias were consistent with a reduction in uterine infection with prophylactic antibiotics. A single study reported on adverse

effects and found that prophylactic antibiotics may slightly increase the risk of vomiting (RR 1.20, 95%CI 0.61 to 2.38, I^2 = n/a, 1 study, n=3404; low certainty of evidence), but may result in little or no difference in the risk of having diarrhoea (RR 0.92, 95% CI 0.51 to 1.65, I^2 = n/a, 1 study, n= 3404); the evidence for both of these findings was of low certainty. A single study reported on allergy and found that prophylactic antibiotics may increase the risk of allergy (RR 3.01, 95%CI 0.12 to 73.76, I^2 = n/a, 1 study, n=3404) and the study reported no cases of anaphylaxis (very low certainty). Meta-analysis of three studies found that prophylactic antibiotics may reduce antibiotic treatment to treat infection, but the evidence was very uncertain (RR 0.94 95% CI 0.54, 1.64, I^2 63%, 3 studies, n= 3574: very low certainty of evidence). Meta-analysis of three studies also found that prophylactic antibiotics probably reduce hospitalisation for treatment of infection; the evidence was of moderate certainty (RR 0.76 95% CI 0.40 to 1.46, I^2 = 0%, 3 studies, n= 3859: moderate certainty of evidence)

Authors' conclusions

When all studies were considered, the evidence suggested that routine antibiotic prophylaxis may reduce uterine infection amo.ng individuals undergoing uterine evacuation procedures to treat miscarriage, but the evidence is of low certainty. A meta-analysis based on three trials assessed to have low risk of bias demonstrated a larger effect size with high certainty, resulting in a 43% reduction in the risk of uterine infection rates with antibiotic prophylaxis. Prophylactic antibiotics probably reduces hospitalisation for treatment of infection based on moderate certainty evidence and may reduce the need for a course of antibiotics to treat infection after uterine evacuation procedures to treat miscarriage, but this evidence was very uncertain. Data were limited and

uncertain with regard to potential adverse effects such as vomiting, diarrhoea, allergy and anaphylaxis.

2.1 Plain language summary

2.2.1. Antibiotics to prevent infection after surgery to treat miscarriage

Miscarriage is common with around 1 in 6 pregnant people having a miscarriage in their lifetime. Miscarriage is the unintended loss of pregnancy before 24 completed weeks, although the definition varies around the world. A miscarriage can be treated in three different ways; expectantly (waiting for the pregnancy tissues to pass), medically (with medicines to help expel the pregnancy tissue), or surgically.

Surgery to treat miscarriage (often known as uterine evacuation) is a common surgical procedure, but it has been shown to increase the risk of individuals developing an infection in the womb when compared to other ways of treating miscarriage (medical or expectant).

Infection after miscarriage is a common problem and has been reported to be as high as 30% in some low-income countries. Infection after miscarriage is a serious problem and can cause death and disability. It can also have long-term consequences on fertility.

Antibiotics are given before or during many surgical procedures to prevent infection (prophylaxis), including surgery to perform an abortion (often known as termination of pregnancy).

There is clear evidence of benefit of giving antibiotics to individuals undergoing surgical abortion, and clear evidence on giving antibiotics to individuals having surgery to manage miscarriage when they have signs or symptoms of an infection. There is, however, no clear evidence on giving antibiotics routinely to patients having surgery to treat miscarriage in the absence of signs of infection.

The aim of our review was to evaluate whether giving antibiotics around the time of miscarriage surgery, to prevent infection, would help lower the risk of infection and whether their routine use was associated with any serious side effects.

We collected and analysed all the relevant studies to answer this question (date of search: 8th May 2022). We identified 6 studies with 4371 individuals who had surgery to treat miscarriage and were either given antibiotics or placebo or no treatment across eight countries.

When considering all of the included studies that assessed routinely giving preventive antibiotics during surgery to treat miscarriage, we found that this may result in little or no difference in the risk of getting a uterine infection. However, when we combined the findings from only the three high quality studies, we found that giving preventive antibiotics reduces the risk of infection in the uterus after surgical treatment for miscarriage. We found that preventive antibiotics may reduce hospitalisation for treatment of infection but could not be certain about the effect of preventive antibiotics on antibiotic treatment of infection. The review results were uncertain about whether routinely giving preventive antibiotics causes side effects or complications such as vomiting, diarrhea, or allergic reactions.

2.2.2. Summary of findings

Table 2.1. Summary of findings for uterine infection and adverse effects

Outcome	Assumed risk (control)	Corresponding risk (intervention)	Risk ratio	Certainty	Risk difference with antibiotics	Certainty of effect
Uterine Infection	42 per 1000	31 per 1000	0.78 (0.47 to 1.28)	⨁⨁◯◯ LOW[a]	11 fewer per 1,000 (22 fewer to 12 more)	Possible no difference
Vomiting	9 per 1000	10 per 1000	1.20 (0.61 to 2.38)	⨁⨁⨁◯ MODERATE[b]	1 more per 1,000 (4 fewer to 12 more)	Probable no difference
Diarrhoea	13 per 1000	12 per 1000	0.92 (0.51 to 1.65)	⨁⨁⨁◯[b] MODERATE	1 fewer per 1,000 (6 fewer to 8 more)	Probable no difference
Allergy	Not estimable	1 per 1000	3.01 (0.12 to 73.76)	⨁⨁◯◯[a] LOW	Not estimable	Possible no difference
Anaphylaxis	Not estimable					

a Evidence downgraded for serious study limitations and imprecision

b Evidence downgraded for imprecision

2.2 Background

2.2.1 Description of the condition

Over 208 million people around the world become pregnant each year [223], but an estimated 10% to 20% of pregnancies end as a miscarriage [224-229]. One in six individuals experience miscarriage in their lifetime [230] Miscarriage is defined as the unintended loss of pregnancy in the first 24 weeks [22], although this is defined differently around the world with some countries reporting miscarriage up to 28 weeks of pregnancy [231]. Miscarriage, induced abortion and ectopic pregnancy collectively were estimated to be responsible for around 193,000 deaths between 2003 and 2009 [5].

The term ‘abortion’ refers to ‘induced abortions’ and ‘miscarriage ‘is preferred to ‘incomplete or missed (spontaneous) abortion’. The language used around miscarriage is important to individuals and their families [231]. The change in terminology has been supported by patient organisations and clinicians for several decades [232-240]. The use of the term miscarriage is also supported by researchers and early pregnancy special interest groups, for consistency [241]. There are a variety of terms used to describe both miscarriage and abortion, but for this review miscarriage will refer to missed or incomplete miscarriage and abortion will refer to induced abortion.

The common clinical signs and symptoms associated with miscarriage can vary with the type of miscarriage that an individual is experiencing and the gestational age or size of the pregnancy [242]. A complete miscarriage is when all the pregnancy tissue is expelled from the uterus. This is associated with heavy vaginal bleeding, severe abdominal pain and the passage of all the pregnancy

tissue. Complete miscarriage does not require any interventions for treatment. Incomplete miscarriage is likely to be associated with vaginal bleeding and abdominal pain, as the pregnancy tissue has been partly expelled from the uterus [243]. Missed miscarriage (sometimes known as delayed or silent) is when a non-viable pregnancy is identified via ultrasonography. All the pregnancy tissue is retained in the uterus, so individuals may have no symptoms or a small amount of vaginal bleeding [243].

Incomplete and missed miscarriage can be treated expectantly, medically or surgically. Expectant management involves waiting for the pregnancy tissue to pass naturally. Medical management involves medications (mifepristone plus misoprostol or misoprostol alone) to make the uterus expel the pregnancy tissue. Surgical management involves the removal of the pregnancy tissue during surgery. A recent Cochrane Review [244], found that medical and surgical methods of uterine evacuation to treat miscarriage were more effective than when compared with expectant management. Expectant management was found to have the lowest chance of successful uterine evacuation and the highest chance of serious complications, including the need for unplanned or emergency surgery. The evidence, however, did suggest that surgical methods of uterine evacuation carried higher risks of pelvic infection when compared to medical methods of uterine evacuation or expectant management.

Uterine evacuation procedures to treat miscarriage are a common reason for hospital admission, with some hospitals in low-income settings reporting up to 70% of gynaecological hospital admissions for miscarriage surgery [245]. A survey of health facilities in Malawi in 2015 estimated

that the number of cases treated for post-abortion care was over 67,000 (including both miscarriage and induced abortion), with over 15,000 of these cases being late miscarriages [246].

Pregnancy-related infection was estimated to be responsible for 261,000 maternal deaths between 2003 and 2009, with over 99% of these deaths being in low- and middle-income countries [5]. Infection after uterine evacuation procedures to treat miscarriage is reported to occur in 6% of individuals in high-income countries [247-248], and up to 30% of individuals in low-income countries [249]. Pelvic infection is a serious complication of uterine evacuation procedures to treat miscarriage and can result in serious illness and death [250]. It can also have long-term consequences, which can increase rates of ectopic pregnancy and infertility [251]. As well as physical effects, miscarriage can also have considerable emotional and societal implications for individuals and their families, with the consequences of miscarriage lasting far beyond the length of the pregnancy [252-256].

2.2.2 Description of the intervention

Antibiotic prophylaxis can be defined as the administration of "antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications" [257]. Prophylactic antibiotics are given for certain surgical procedures to reduce the risk of infection after surgery, including vacuum aspiration for abortion care [258-260]. For uterine evacuation procedures to treat miscarriage, the administration of prophylactic antibiotics would mean that

individuals are given antibiotics around the time of uterine evacuation even if they are not known to have genital tract infections.

Studies have demonstrated that almost 50% of individuals in some regions are prescribed prophylactic antibiotics for uterine evacuation procedures to treat miscarriage [261], and that prophylactic antibiotics may improve outcomes [250], i.e., a reduction in severity of disease and length of hospital stay. In this review, prophylaxis will be defined as the administration of antibiotics to prevent infection.

A Cochrane Review [262], examined the evidence on antibiotics for incomplete abortion, and, with the inclusion of a single study, [249], concluded there was "not enough evidence to evaluate a policy of routine antibiotic prophylaxis to individuals with incomplete abortion". This review stated the “real and urgent need to find out whether antibiotics should routinely be used in cases of incomplete miscarriages”.

The World Health Organisation (WHO) recommends electric or manual vacuum aspiration as uterine evacuation procedures to treat miscarriage before 12 to 14 weeks [259]. Vacuum aspiration is also called suction curettage or dilatation and suction, and uses a vacuum source to remove pregnancy tissue. Vacuum aspiration does not require electricity and can be used with a hand-held vacuum syringe (manual vacuum aspiration) or electric pump.

Sharp metal curettage to remove pregnancy tissue after dilatation of the cervix (if required) used to be common practice for uterine evacuation to treat miscarriage [263]. A sharp metal curettage (also known as dilatation and curettage) was used to remove the pregnancy tissues from the uterus; however, sharp curettage is associated with a higher incidence of pelvic infection when compared to vacuum aspiration [101] and is no longer recommended due to the increased incidence of such complications and associations with Asherman's syndrome (intrauterine adhesions) [264]. Many clinicians in low-income settings use sharp metal curettage because they are not trained in vacuum aspiration or do not have the necessary equipment to perform vacuum aspiration.

Uterine evacuation procedures to treat miscarriage beyond 12 weeks usually involve pre-procedure cervical dilatation with medications or osmotic dilators, or both [265], and evacuation with a combination of vacuum aspiration and specialised forceps (also known as dilatation and evacuation or D&E). Uterine evacuation procedures to treat miscarriage of more advanced pregnancies can be more complex and associated with greater risk of complications [101]. Uterine evacuation procedures to treat miscarriage up to 12-14 weeks have been reviewed previously [101], indicating that vacuum aspiration is safe, quick to perform, and less painful than sharp curettage, and is recommended for use in the management of incomplete miscarriage, but the findings were based on data from a single study.

Perhaps because of the lack of evidence of effectiveness of prophylactic antibiotics for uterine evacuation procedures to treat miscarriage, there is inconsistency in clinical practice and international guidelines [243, 261, 266, 267]. Some guidelines do not recommend prophylaxis,

reflecting the lack of evidence [243, 267], whereas other guidelines support their use, based on extrapolation of findings from other indications [266]. This review will not address prophylactic antibiotics for medical management of miscarriage.

2.2.3 How the intervention might work

Uterine evacuation procedures to treat miscarriage can introduce pathogens that cause infection when a surgical instrument is inserted through the cervical canal into the uterine cavity to remove the pregnancy tissue [268]. The most common micro-organisms that cause infection in the reproductive tract are enterococci, streptococci, staphylococci, Gram-negative bacilli and anaerobes [269]. When chlamydia and gonococcus exist in the vagina, they can ascend into the uterus during uterine evacuation and cause infection [270].

Antibiotics work by killing existing bacteria (bactericidal) or inhibiting the replication of bacteria (bacteriostatic). The types of antibiotics used prophylactically should be effective against these common micro-organisms and include the following: ampicillin, cephazolin, clindamycin, vancomycin, azithromycin, and the aminoglycosides [268]. Antibiotic prophylaxis before certain operations has been shown to reduce the risk of infections.

There is some evidence to support the use of antibiotic prophylaxis for surgical abortion procedures [174,267]. Current WHO guidance advocates the use of appropriate prophylactic antibiotics for all individuals, before or during the procedure [260,266]. This recommendation is based on a

Cochrane Review of 19 randomised studies showing that prophylactic antibiotics reduce pelvic infection when given for surgical abortion [258].

As the procedures for uterine evacuation for abortion and to treat miscarriage are the same, it can be hypothesised that prophylactic antibiotics could reduce pelvic infection among individuals undergoing uterine evacuation procedures to treat miscarriage. Identifying populations experiencing miscarriage who have not sought an intervention to end their pregnancy can be complicated, particularly in settings where abortion access is limited by legal restrictions. Individuals presenting for medical care to treat miscarriage could be experiencing complications from an incomplete abortion obtained in a safe or unsafe setting. The cause of miscarriage can be unclear, especially in countries where abortion is illegal or access to abortion is heavily restricted. This review aims to estimate the effectiveness of antibiotic prophylaxis among individuals obtaining a uterine evacuation procedure when presenting with a miscarriage, regardless of its cause.

Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage may be effective in reducing maternal death and serious illness caused by infection. Prophylactic antibiotics may play a role in reducing the long-term consequences of pelvic scarring caused by infection, such as ectopic pregnancy and infertility, and may be economically beneficial to the health system as a cost-effective intervention [155].

2.2.4 Why it is important to do this review

Clinical evidence and guidance are clear that antibiotic treatment is needed for individuals experiencing miscarriage with signs and symptoms of infection [271], because of this we will not include studies that evaluate the use of antibiotics in individuals with confirmed or suspected septic miscarriage. However, it is less clear whether antibiotic prophylaxis is effective or necessary at the time of uterine evacuation procedures to treat miscarriage.

This Cochrane Review is an update of the Cochrane Review 'Antibiotics for incomplete abortion' by May 2007 [262], but this review uses the term miscarriage rather than incomplete abortion. Since the Cochrane Review by May 2007, there have been further randomised studies [272-273], including a large, multi-centre, randomised, placebo-controlled study conducted on the use of prophylactic antibiotics before miscarriage treatment with surgical abortion [272].

If antibiotic prophylaxis proves to be ineffective or causes serious adverse events, unnecessary use of antibiotics could be minimised, which is essential given the growing problem of antibiotic resistance. Therefore, the policy, practice and cost implications arising from this review will be important.

2.2.5 Objectives

The objective of this review was to evaluate the effectiveness of routine antibiotic prophylaxis to individuals undergoing uterine evacuation procedures to treat miscarriage.

2.3 Methods

2.4.1. Criteria for considering studies for this review

2.4.1.1. Types of studies

We considered only randomised controlled trials (RCTs) for inclusion in this systematic review.

2.4.1.2. Types of participants

The types of participants were individuals presenting with miscarriage in healthcare facilities, treated with uterine evacuation procedures. There was no gestational age limit. We excluded individuals with signs and symptoms of infection prior to the procedure.

2.4.1.3. Types of interventions

Any prophylactic antibiotic regimen with no antibiotics (placebo or no treatment). Multiple interventions such as blood transfusion, medications for pain relief, or comparisons of different types of surgical miscarriage management in addition to antibiotic treatment, as long as the study groups compared an antibiotic with placebo or no treatment.

2.4.1.4. Types of outcome measures

The primary and secondary outcomes of this review were as follows.

Primary outcomes

1. Uterine infection [274], as defined by the following criteria [275]. The individual has at least two of the following signs or symptoms:

a. Fever (> 38.0 °C).

b. Pain or tenderness (uterine or abdominal, with no other recognised cause); or

c. Purulent drainage from uterus.

2. Adverse effects of treatment

Secondary outcomes

1. Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage
2. Pelvic inflammatory disease (PID)
3. Hospitalisation for treatment of infection

2.4.2. Search methods for identification of studies

The Fertility Regulation Group Information Specialist conducted a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. We carried out translations where necessary. The search strategies for each database are available in **Appendix 2.1.**

2.4.2.1. Electronic searches

The following databases were searched from their inception:

1. Cochrane Central Register of Controlled Trials (CRSWeb): Inception to 8 May 2022
2. MEDLINE ALL (Ovid) 1946 to 6 May 2022
3. Embase.com Inception to 8 May 2022
4. Global Health (Ovid) 1973 to 2022 Week 18
5. Scopus (conference abstracts only) - Inception to 8 May 2022

Grey literature was searched on the following sites:

1. Guttmacher Institute www.guttmacher.org/united-states/abortion
2. International Planned Parenthood Federation www.ippf.org/
3. Ibis Reproductive Health ibisreproductivehealth.org/
4. Individuals on Waves www.individualsonwaves.org/
5. Marie Stopes International www.mariestopes.org/
6. Population Council www.popcouncil.org/
7. Population Services International www.psi.org/
8. Ipas www.ipas.org/

2.4.2.2. Searching other resources

The bibliographies of included studies were checked for any relevant systematic reviews for further references to relevant studies. We contacted experts and organisations in the field to obtain additional information on relevant studies where required.

2.4.3. Data collection and analysis

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth (Cochrane PCG).

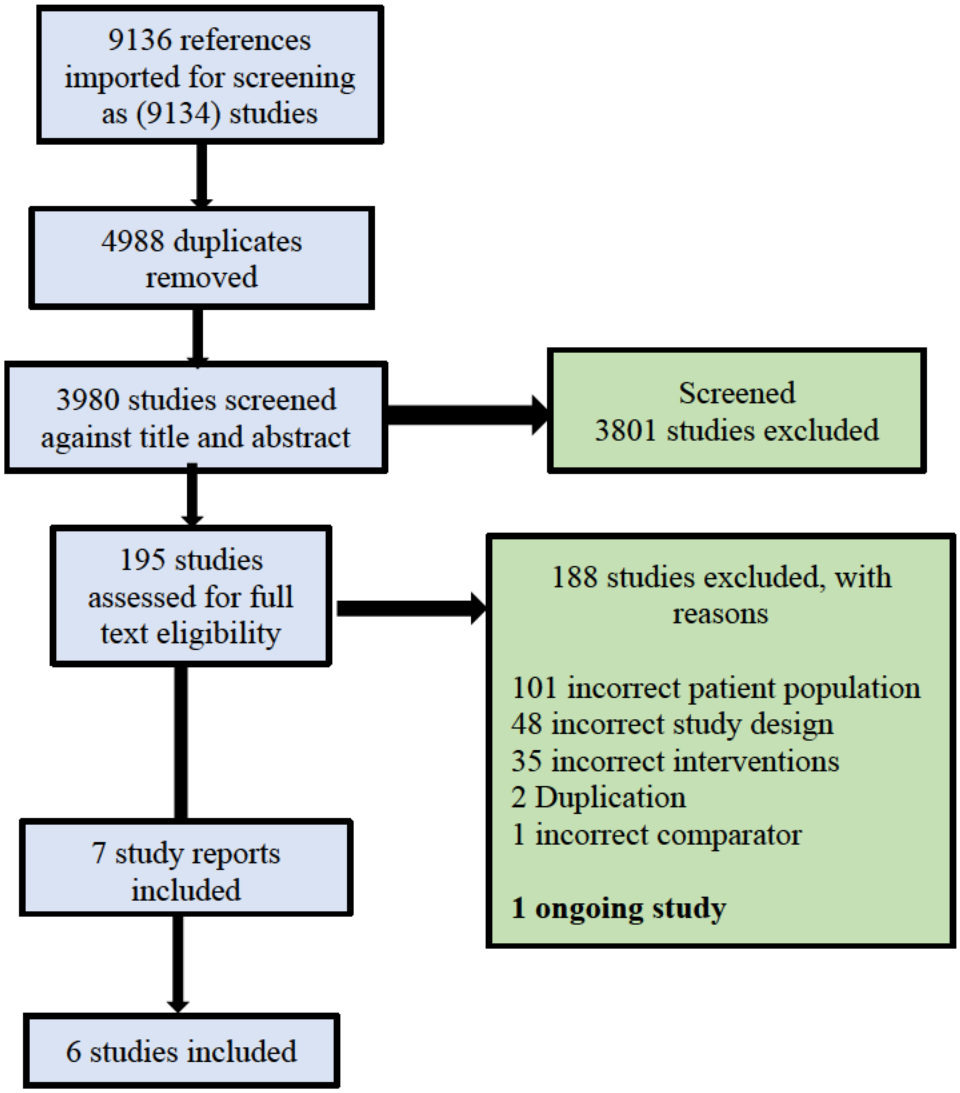
At least two review authors (SI, AA, AW, CM, JC) independently assessed the studies for inclusion in the review, assessed study quality, extracted the data and graded the body of evidence.

2.4.3.1. Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database and removed duplicates. Two review authors (SI, AA) independently screened titles and abstracts for inclusion on a web-based tool Covidence. The full-text study reports or publications were retrieved, and two review authors (SI, AA) independently screened the full texts and identified studies for inclusion and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion or, if required, consulted a third review author (AW, JC). We listed studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table **[Appendix 2.2]**. We collated multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We

also provided any information that could be obtained about ongoing studies. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram **(Fig 2.1).**

Figure 2.1. PRISMA Flow Diagram



2.4.4. Data extraction and management

We used a standard data collection form for study characteristics and outcome data; we piloted the form on at least one study in the review. At least two review authors (SI, AA, CM, JC) independently extracted the following study characteristics from the included studies;

1. Methods: study design, number of study centres, type of study centre, study setting and location, date of study, follow-up;
2. Participants: number, inclusion criteria, exclusion criteria, other relevant characteristics;
3. Interventions: intervention components; dose, route, regime, co-interventions, comparison, compliance;
4. Outcomes: outcomes specified and collected, time points reported;
5. Notes: funding for study, notable conflicts of interest of study authors, ethical approval.

At least two review authors (SI, AA, CM, JC) independently extracted outcome data from included studies. If any of the review authors had been involved in a study that is included in the review, they did not participate in the risk of bias assessment or data extraction (we planned to seek additional support by the central Cochrane team if this was required). If any outcome data were reported in an unusable way, we noted in the 'Characteristics of included studies' table **[Appendix 2.3]**. We resolved disagreements by consensus or by involving a third review author (AW).

2.4.5. Assessment of risk of bias in included studies

Two review authors (SI, AA, CM, JC) independently assessed the risk of bias for key outcomes for results of randomised studies using the Cochrane RoB 2 tool [276], and criteria outlined in

chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [277]. Any disagreement was resolved by discussion or by involving a third review author (AW, JC). We assessed the key outcomes defined in this protocol for risk of bias. We assessed the following domains using answers to signaling questions, with overall judgments derived from the tool.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

An additional domain is included for cluster-randomised studies as outlined in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [278], bias arising from

We planned to identification or recruitment of individual participants within clusters.

include cluster RCTs in our review and use the variants of RoB 2 for cluster-RCTs. This variant would address the following issues with bias specific to cluster-RCTs in addition to those above.

1. Bias arising from the randomisation process
2. Bias arising from the timing of identification and recruitment of participants
3. Bias due to deviations from intended interventions
4. Bias due to missing outcome data
5. Bias in measurement of the outcome

We judged each potential source of bias as high, low, or 'some concerns' and provided a quote from the study report together with a justification for our judgment in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a study author, we noted this in the risk of bias table **[Appendix 2.4]**. We did not exclude studies on the grounds of their risk of bias. When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome. We conducted the review according to the published protocol **[Appendix 2.5]** and reported any deviations from it in the 'Differences between protocol and review' section of the review.

2.4.6. Measures of treatment effect

For dichotomous data, we analysed data based on the numbers of events in each arm of each study to estimate the effect of the intervention using risk ratio together with the appropriate associated 95% confidence interval.

2.4.6.1. Unit of analysis issues

The unit of analysis was each participant recruited into the studies.

2.4.6.2. Dealing with missing data

We planned to contact study authors where necessary in order to verify key study characteristics and to obtain missing outcome data (e.g., when a study was identified as abstract only).

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we performed analyses, as far as possible, on an intention-to-treat basis. That is, we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each study was the number randomised minus any participants whose outcomes were known to be missing.

2.4.7. Assessment of heterogeneity

To evaluate the presence of clinical heterogeneity, we generated descriptive statistics for study characteristics and study population characteristics across all eligible studies.

We conducted a meta-analysis and assessed statistical heterogeneity in each meta-analysis using Tau^2, the I^2 statistic [279], and Chi^2 statistic [280]. We described the clinical diversity and methodological variability of the evidence in the review text and with study tables describing study characteristics including design features, population characteristics, and intervention details.

To assess statistical heterogeneity, we visually inspected forest plots and described the direction and magnitude of effects and the degree of overlap between confidence intervals. We also considered the statistics generated in forest plots that measure statistical heterogeneity. We used the I^2 statistic to quantify inconsistency among the studies in each analysis. We considered the P

value from the Chi^2 test to assess if this heterogeneity was significant ($P < 0.1$). If we identified substantial heterogeneity, we reported this finding and explored possible explanatory factors using our prespecified subgroup analysis.

We used a rough guideline to interpret the I^2 statistic value rather than a simple threshold, and our interpretation has taken into account an understanding that measures of heterogeneity (I^2 statistic and Tau^2) estimated with high uncertainty when the number of studies is small [281].

1. 0% to 40%: heterogeneity might not be important
2. 30% to 60%: may represent moderate heterogeneity*
3. 50% to 90%: may represent substantial heterogeneity*
4. 75% to 100%: considerable heterogeneity*

*The importance of the observed value of the I^2 statistic depends on 1. magnitude and direction of effects, and 2. strength of evidence for heterogeneity (e.g., P value from the Chi^2 test, or a confidence interval for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

2.4.7.1. Assessment of reporting biases

We planned to contact study authors where necessary, asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results. If we

were able to pool more than 10 studies, we planned to create and examine a funnel plot to explore possible publication biases, interpreting the results with caution [282].

2.5. Data synthesis

We only undertook meta-analyses when we felt them to be meaningful, that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

If it was reasonable to assume that each study contributing to the meta-analysis for that outcome was estimating the same underlying treatment effect (i.e., similar interventions, study populations and settings, and similar methods used) we planned to conduct a fixed-effect meta-analysis. If there was clear clinical diversity between studies, which was sufficient to expect that the underlying treatment effects differ between studies, or if we detected substantial statistical heterogeneity (as described above), we planned to use a random-effects meta-analysis. A random-effects meta-analysis assumes that the different studies are estimating an average pooled effect from a distribution of related intervention effects.

2.5.1. Subgroup analysis and investigation of heterogeneity

The effectiveness of antibiotic prophylaxis for uterine evacuation procedures to treat miscarriage could be influenced by several factors. These factors include gestational age at the time of the procedure (pregnancies of a greater gestation may have a higher incidence of pelvic infection due to the complexities involved with the surgical procedure), the type of surgery used (manual vacuum aspiration, suction curettage or sharp curettage); the type of miscarriage (missed or incomplete; incomplete miscarriage may be associated with a higher incidence of pelvic infection when

compared to missed miscarriage), and the legal status of abortion for the study setting (legal, heavily restricted or illegal; studies conducted in settings where abortion is legal may be less likely to include cases of unsafe interventions).

We carried out the following subgroup analyses to compare the effects estimated in studies that differ according to the following characteristics.

1. Gestational weeks at time of procedure (< 12 weeks, ≥ 12 weeks, unclear)
2. Type of surgery (manual vacuum aspiration, suction curettage, sharp curettage, dilation and evacuation)
3. Type of miscarriage (missed miscarriage, incomplete miscarriage)
4. Evidence of unsafe or surgical abortion (no evidence, some evidence)
5. Antibiotic class (tetracyclines, others)
6. Antibiotic regime (short course; < 3 days, longer course > 3 days; [245]
7. Antibiotic route (oral, intravenous)

In studies of individuals that spanned the categories described above (e.g., different types of surgery or type of miscarriage types included in the same study), we clearly stated this in the baseline characteristics, and we stratified the analyses into categories that reflected the majority of participants or included a subgroup category of mixed populations. We conducted interaction tests for subgroup differences and only described the estimates of effect for different strata if there was evidence of an interaction effect.

2.5.2. Sensitivity analysis

For the primary outcomes we performed sensitivity analyses defined a priori to assess the robustness of our conclusions and explored its impact on effect sizes for the following.

1. Restricted the analyses to studies with antibiotics as a single intervention
2. Risk of bias (restricted to low risk of bias studies only): we ranked studies as 'low risk of bias' if they were double-blinded and have allocation concealment and outcome data available for nearly all participants randomised (less than 10% missing). We considered protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses because protocol publication only became widespread in recent years.
3. Use of fixed-effect versus random-effects model

We assessed differences by evaluating the relative effects and assessment of model fit.

2.5.3. Summary of findings and assessment of the certainty of the evidence

We created summary of findings table **[Appendix 2.6]** for the intervention comparison of any prophylactic antibiotic versus no treatment or placebo. The table describes the results for each of the key outcomes defined in this review in accordance with the GRADE approach. These outcomes include pelvic infection and adverse effects of treatment. We also presented the findings from subgroup comparisons testing the effect of different treatment groups (such as antibiotic class and regime) on pelvic infection and adverse effects (e.g., short course of doxycycline versus short course of all other antibiotics).

We planned to include any relevant and important outcomes that we became aware of during the review process and explain the reasons for this is the section 'Differences between protocol and review'. Two review authors independently assess the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias [283]. We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of interventions* [278], and the EPOC worksheets [284], and used GRADEpro GDT software (GRADEpro GDT). We resolved disagreements on certainty ratings by discussion and provided justification for decisions to down- or upgrade the ratings using footnotes in the table and made comments to aid readers' understanding of the review where necessary. We used plain language statements to report these findings in this review [284].

We considered whether there was any additional outcome information that we were not able to incorporate into meta-analyses and noted this in the comments, and stated if it supports or contradicts the information from the meta-analyses.

2.6. Results

2.6.1. Description of studies

2.6.1.1. Results of the search

The search retrieved 9136 articles. 195 studies were potentially eligible and were retrieved in full text. Six studies (7 articles) met our inclusion criteria (see characteristics of included studies). We

excluded 188 studies, and one study was ongoing (see characteristics of excluded studies **[Appendix 2.2]** and characteristics of ongoing studies **[Appendix 2.7]**).

2.6.2. Included studies

2.6.2.1. Study design and setting

Six parallel-design randomised controlled trials (RCTs) were included. Five were single centre studies whilst one was multi-centred. Four studies were conducted in low to low-middle income countries; Thailand [273], Sri Lanka [285], Zimbabwe [249], Malawi, Tanzania, Uganda and Pakistan [272], whilst two were in high income countries; USA [247-248]. All studies were conducted in hospitals that could perform uterine evacuation procedures to treat miscarriage.

2.6.2.2. Participants

The studies included 4371 individuals diagnosed with either incomplete or missed miscarriage. Five studies included individuals who were below 22 weeks gestation. Seeras 1989 did not report gestational age [249] and all studies included individuals without clinical features of infection at the time of inclusion. No study stated whether there was evidence of unsafe abortion in the included population.

2.6.2.3. Interventions

All studies compared antibiotics with either placebo (five studies) [247, 248, 272, 273, 285] or no treatment (one study) [249]. The antibiotic class in four studies were tetracyclines [247, 248,

249,285], one study used a cephalosporin [273], and one study used a combination of tetracycline and nitroimidazole [272].

2.6.2.4. Outcomes

All six studies reported uterine infection, three studies reported on hospitalisation for treatment of infection [247,248, 272] and antibiotic treatment after uterine infection [249, 272,273], but only one study reported on adverse effects [272]. No studies reported on pelvic inflammatory disease.

2.6.2.5. Ongoing studies

One study was ongoing [286], this was a randomised controlled trial that included individuals up to 12 weeks and 6 days gestation with incomplete or missed miscarriage that were having surgical evacuation and were randomised to receive either prophylactic oral doxycycline (single dose of 200 mg) and metronidazole (500 mg) or placebo. The primary outcome of this study was uterine infection within two weeks of surgery.

2.6.3. Excluded studies

187 studies were excluded from the review, for the following reasons: 101 studies did not include individuals requiring uterine evacuation procedure for treatment of miscarriage, 48 studies were not randomised trials, 35 did not include antibiotic prophylaxis as an intervention, 2 studies were duplications and 1 study used an active comparator rather than placebo or no treatment.

2.6.4. Risk of bias in included studies

The risk of bias summary showing the review authors' judgements about each risk of bias item for each included study can be found in **Appendix 2.8.**

2.6.4.1. Bias arising from the randomisation process

Five studies [247, 249, 272, 273, 285] were assessed as low risk of bias from the randomisation process as they used computer randomisation or a random numbers table. One study [248] did not describe the randomisation method used so was assessed as having some concerns for bias. All studies reported adequate allocation concealment using sealed envelopes or treatment packets and all studies reported similar baseline characteristics in each group.

2.6.4.2. Bias due to deviations from intended interventions

Three studies [272,275,285] were assessed as low risk of bias from intended interventions as they blinded participants and personnel to treatment allocation and blinded assessors. These studies used appropriate analysis to estimate the effect of assignment to the intervention. Two studies [247,248] were assessed as high risk of bias as they either did not blind participants or personnel or did not report if blinding was carried out, they did however blind outcome assessors to treatment allocation. Both of the studies assessed as high risk of bias had either a high rate of non-compliance with the intervention or a high loss to follow-up rate, and neither of these studies used appropriate analyses to estimate the effect of assignment to intervention. One study [248] was rated as having some concerns of bias as it was reported as a double-blind but did not state who was blinded, neither did they report whether an appropriate analysis was used to estimate the effect of assignment to intervention.

2.6.4.3. Bias due to missing outcome data

Four studies [249, 272, 273, 285] were assessed as low risk of bias due to missing outcome data as they had less than 10% of missing data. Two studies [247-248] had more than 10% of missing data, neither study conducted sensitivity analyses to account for missing data. One study [248] reviewed the medical records of the individuals lost to follow up within a year of the treatment in an effort to assess outcomes so this study was assessed as having some concerns of bias. The other study was assessed as high risk of bias [247].

2.6.4.4. Risk of bias in measurement of the outcome

All six studies [247,248,249, 272, 273, 285] were assessed as low risk of bias in the measurement of the outcome as the method of measuring the outcome was appropriate in all studies, and it was unlikely that the measurement or ascertainment of the outcome differed between the groups as the outcome assessors in all studies were blinded.

2.6.4.5. Risk of bias in selection of the reported result

Only one study [272] was assessed as low risk of bias in selection of the reported result as it reported prespecified analyses in a published protocol. Five studies [247, 248, 249, 273, 285] were assessed as having some concerns of bias as they did not pre-specify statistical analysis plans in a published protocol, however none of the studies reported the use of multiple eligible outcome measurements or multiple eligible analyses of the data.

2.6.5. Effects of interventions

(a) Comparison of Antibiotics versus Placebo or No Treatment

2.6.5.1. Primary outcomes

Uterine Infection

Based on meta-analysis of six RCTS, there may be little or no difference in uterine infection with prophylactic antibiotic use, but the effect was not precise, and this evidence was assessed to be of low certainty (RR 0.78 95% CI 0.47 to 1.28, 6 RCTs, N = 4,371, I^2 = 50%, low certainty of evidence) **[Table 2.1];[Appendix 2.9].** The illustrative risk of uterine infection following antibiotics was estimated to be 33 per 1000 based on an assumed risk following placebo or no treatment of 42 per 1000. A sensitivity analysis for this outcome resulted in a larger effect that was estimated with greater precision. Both the overall effect and the sensitivity analysis limited to high-quality studies were consistent with a reduction in uterine infection with prophylactic antibiotics.

Adverse Effects of Treatment

A single study reported multiple adverse events [272]. No other studies reported this outcome. There were too few studies to conduct any planned sensitivity analyses.

Vomiting

A single study reported the adverse effect of vomiting of individuals receiving antibiotics and individuals receiving placebo or no treatment (RR 1.20, 95% CI 0.61 to 2.38, 1 RCT, N = 3,404, I^2 = n/a, low certainty of evidence **[Table 2.1]; [Appendix 2.10].** The risk of vomiting following antibiotics is 11 per 1000 and the risk following placebo, or no treatment is 9 per 1000. Antibiotic prophylaxis may increase vomiting slightly, but the evidence is of low certainty.

Diarrhoea

A single study reported the adverse effect of diarrhoea between individuals receiving antibiotics and individuals receiving placebo or no treatment (RR 0.92, 95% CI 0.51 to 1.65, 1 RCT, N = 3,404, I^2 = n/a, low certainty of evidence **[Table 2.1];[Appendix 2.11]**. The risk of diarrhoea following antibiotics is 12 per 1000 and the risk following placebo or no treatment is 13 per 1000. Antibiotic prophylaxis may result in little or no difference in diarrhea, but the evidence is of low certainty.

Allergy

A single study reported the adverse effect of allergy (RR 3.01, 95% CI 0.12 to 73.76, 1 RCT, N = 3,404, I^2 = n/a, very low certainty of evidence **[Table 2.1];[Appendix 2.12]**. The risk of allergy following antibiotics is assumed to be 1 per 1000, there were no events of allergy in the placebo or no treatment group. Antibiotic prophylaxis may increase risk of allergic reaction, but the evidence is very uncertain.

Anaphylaxis

A single study reported the adverse effect of anaphylaxis. No cases of anaphylaxis were reported so meta-analysis was not possible. The evidence is of very low certainty that there is not an effect with prophylactic antibiotics on anaphylaxis.

2.6.5.2. Secondary outcomes

Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage

Meta-analysis of three studies found that prophylactic antibiotics may reduce the need for further antibiotics to treat infection after uterine evacuation procedures for miscarriage (RR 0.94 95% CI 0.54 to 1.64, 3 RCTs, N = 3,574, I^2 = 63% **[Appendix 2.13]**. The risk of antibiotic treatment to treat infection following antibiotics is 62 per 1000 and the risk following placebo or no treatment is 66 per 1000 but the evidence is of very low certainty.

Pelvic inflammatory disease (PID)

No studies were found that included pelvic inflammatory disease as an outcome.

Hospitalisation for treatment of infection

Meta-analysis of three studies found that prophylactic antibiotics likely reduce hospitalisation for treatment of infection after uterine evacuation procedures for miscarriage (RR 0.76, 95% CI 0.40 to 1.46, 3 RCTs, N = 3,859, I^2 = 0% **[Appendix 2.14]**. The risk of hospitalisation for treatment of

infection following antibiotics is 8 per 1000 and the risk following placebo, or no treatment is 11 per 1000. The evidence is of moderate certainty.

2.6.6. Sensitivity analyses

We carried out pre-specified sensitivity analyses by restricting our analyses to studies assessed as low risk of bias [272,273, 285]. When analyses were restricted to include only studies assessed as low risk of bias as described in our protocol [287] (double-blinded with allocation concealment and outcome data available for nearly all participants randomised with less than 10% missing), three placebo-controlled RCTs (N = 3737; 85% of total participants) were included. The risk of uterine infection was reduced with antibiotic prophylaxis when compared to placebo and this evidence was of high certainty (RR 0.57, 95% CI 0.37 to 0.86, I^2 = 0%, n =3737, 3 studies **[Appendix 2.15]**. The risk of uterine infection with low risk of bias studies following antibiotics is 18 per 1000 and the risk following placebo is 32 per 1000. The evidence is of high certainty.

Sensitivity analyses were also performed according to the statistical model (fixed-effect versus random effects model) and the analytic approach would not affect the conclusions of the review (RR 0.77 95% CI 0.58 to 1.03, n =4371, 6 studies, I^2 50%).

Sensitivity analyses were performed according to the statistical model for the sensitivity analysis for the low risk of bias studies (fixed-effect versus random effects model) and the analytic approach would not affect the conclusions of the review (RR 0.56 95% CI 0.37 to 0.85, n =3737, 3 studies, I^2 0%).

All included studies used antibiotics as a single intervention, so no sensitivity analyses were performed.

2.6.6.1. Subgroup analyses

Too few studies were included to carry out the pre-specified subgroup analyses for gestational weeks at time of procedure, antibiotic class, regimen and route **[Appendix 2.16]**. Three pre-specified subgroup analyses (type of surgery, type of miscarriage and evidence of unsafe or surgical abortion) were not conducted because subgroup details were unavailable.

2.7. Discussion

2.7.1. Summary of main results

The main objective of this review was to evaluate the effectiveness of antibiotic prophylaxis in individuals undergoing uterine evacuation procedures to treat miscarriage.

Primary outcomes

When all studies were considered (6 studies, n=4371), the evidence suggested that routine antibiotic prophylaxis may reduce uterine infection among individuals undergoing uterine evacuation procedures to treat miscarriage but the evidence is of low certainty due to risk of bias related to missing outcome data and non-adherence with treatment, as well as imprecision and should therefore be interpreted with caution. A sensitivity analysis based on three trials assessed

to have low risk of bias across domains prespecified in the protocol (n=3737, 85% of total participants), demonstrated a larger effect size with high certainty, resulting in an estimated 43% reduction in the risk of uterine infection rates with antibiotic prophylaxis.

Data were limited with regard to potential adverse effects, as these were reported in a single study only (3404 participants). The evidence suggested there was probably no difference in diarrhoea or vomiting (low certainty), and that antibiotic prophylaxis may increase the risk of allergic reactions including anaphylaxis, but the evidence is very uncertain.

Secondary outcomes

Three studies with a total of 3574 participants found that antibiotic prophylaxis may reduce the need for antibiotics to treat infection after uterine evacuation procedures to treat miscarriage, but this evidence was very uncertain.

Three studies with a total of 3859 participants found that antibiotic prophylaxis probably reduces hospitalisation for treatment of infection and the evidence is of moderate certainty.

Meta-analysis was not conducted for pelvic inflammatory disease as no studies were found that included this as an outcome.

2.7.2. Overall completeness and applicability of evidence

We identified evidence for both of our pre-specified GRADE outcomes. We identified evidence for all but one of our pre-specified secondary outcomes (pelvic inflammatory disease).

The populations were similar across the studies with a similar gestational age at the time of procedure. The surgery type was not reported in all studies, neither was type of miscarriage. The intervention in most studies used antibiotics from the same class and were given in a 'short course' regime, often a one-time dose. The outcome definition of uterine infection varied very little across the included studies and were comparable to the collection of signs and symptoms reported in the CDC definition of uterine infection. The outcome assessment point was assessed at similar time points in the studies (between 1-2 weeks). One of the studies included in the review raises questions when comparing their findings to the other studies. Seeras 1989 [249] had a very high event rate when compared to the event rate of other included studies, it also reports significant issues with treatment compliance ('long course' regime of four times a day for one week). Finally, in settings where unsafe abortion is more common the risk of infection is higher and the benefits of antibiotics could be more pronounced. The studies in this review were conducted in settings with different abortion policy contexts and effects of prophylaxis could vary across settings.

Our review does not answer questions about the clinical importance of the outcome and whether treatment of uterine infections based on symptoms following treatment would be effective for preventing further health complications such as PID or severe infections requiring hospitalisation or intravenous antibiotic treatment.

2.7.3. Quality of the evidence

The quality of the overall evidence for the primary outcome of uterine infection was low, the evidence was downgraded for serious study limitations (due to bias from deviations from intended interventions because of a lack of blinding [247] and a high rate of non-compliance with the intervention [249], as well missing outcome data due to a high loss to follow-up rate [247] as and imprecision. However, the quality of the evidence for the meta-analysis including only studies assessed as low risk of bias, was graded as high, with adequate blinding of participants, personnel and assessors, minimal missing data and appropriate measurement of the outcome. A single study provided the evidence for the outcomes of adverse effects and were graded as high but further downgraded for serious imprecision due to wide confidence intervals (vomiting; low, diarrhoea; low,) and very serious imprecision due to few events and wide confidence intervals (allergy; very low and anaphylaxis; very low).

Most studies were assessed as having low risk of bias arising from the randomisation process and from missing outcome data. All the studies were assessed as having low risk of bias arising from measurement of the outcome as all assessors were blinded. However, only half of the studies were assessed as having low risk of bias arising due to deviations from the intended interventions, because they did not report whether an intention-to-treat analysis was performed. Most studies were assessed as some concerns in bias in selection of the reported result, because a pre-specified analysis plan was not reported. However, publication of a study protocol became common practice after most studies were conducted.

2.7.4. Potential biases in the review process

We performed a systematic search in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist, but we cannot be sure we identified all relevant trials. We pre-published and followed our protocol [287] **[Appendix 2.5].** Some authors of this review (AW, DL, CM) were directly involved within one of the RCTs included in this review [272], however these authors were not involved in study selection, data extraction, or risk of bias assessment of this study.

Due to the small numbers of studies included in this review we were unable to create a funnel plot to formally explore publication bias, so appreciate that the presence of publication bias may positively impact the results.

We were unable to contact study authors when data were missing due to the age of the studies [247-248]. We performed analyses on an intention-to-treat basis. Data from one ongoing study may inform future updates of this review.

2.7.5. Agreements and disagreements with other studies or reviews

The previous review (May 2007) [262] included a single study (Seeras 1989) [249] and found that there was not enough evidence to evaluate a policy of routine antibiotic prophylaxis to individuals undergoing uterine evacuation procedures to treat miscarriage.

A more recent review [288] examined the evidence on prophylactic antibiotics for individuals undergoing surgical procedures for incomplete abortion. The review included 24 RCTs (n= 16,178 individuals) and found that prophylactic antibiotics reduced the risk of genital tract infection (RR 0.72 95% CI 0.58 to 0.90, I^2=49%). The findings of this review cannot be compared to our review, given that his review included both individuals undergoing surgical procedures for abortion and individuals undergoing uterine evacuation procedures to treat miscarriage.

2.8. Authors' conclusions

When all studies were considered, the low certainty evidence for prevention of uterine infection does not offer clear evidence to suggest whether routine antibiotic prophylaxis should be provided to individuals undergoing uterine evacuation procedures to treat miscarriage. Whereas meta-analysis of three well conducted placebo-controlled trials (n=3737), assessed as low risk of bias found a reduction in uterine infection rates with antibiotic prophylaxis.

The chapter concludes that giving routine antibiotics for uterine procedures may have little or no difference in reducing the risk of getting a uterine infection. However, when we only looked at the combined findings from the three high quality studies, we found that giving preventive antibiotics reduces the risk of infection in the uterus after procedures for early pregnancy loss. We also found that preventive antibiotics may reduce future hospitalisation for treatment of infection, but we could not be certain about the impact of the need for 'further' antibiotics to treat infection. I will now proceed to the next stage of maternal infections that is early recognition and management of maternal sepsis.

Chapter 3

EVALUATION OF THE FEASIBILITY OF THE FAST-M MATERNAL SEPSIS INTERVENTION IN PAKISTAN, A PROTOCOL

The previous chapter concluded the section on preventing maternal infections. The next section of this thesis will focus on the early recognition and management of maternal sepsis, mainly through implementation of the FAST-M intervention. Overall, this section will comprise of four chapters.

This chapter details the protocol of the feasibility study of the FAST-M intervention which was implemented at the Liaquat University of Medical Health Sciences (LUMHS), a low resource public sector tertiary hospital located in the Hyderabad district of Pakistan. The facility has intensive care unit, high density care units, operating rooms, labor rooms and blood laboratory for the management of its patients. LUMHS has three obstetrics and gynecology (OBGYN) wards. Each ward has its own Head of Department (HOD) who manages day-to-day operations and processes and there is one Chairperson who oversees all three units. Patients are mainly admitted in wards from labour room which also serves as an emergency triage for these patients. The number of deliveries at LUMHS hospital is estimated at 18,000 per year. Most of the cases from rural areas are referred to the LUMHS hospital as it is located in a central area and is an easy reach for peripheral health facilities.

This chapter will begin by giving a summary of the issue of maternal sepsis in Pakistan, followed by a description of the components that make up the FAST-M bundle intervention. I will then give an overview of the research objectives, the methodology, which describes the study setting and provides a rationale for the design, and then move onto the method of data collection, analysis, and integration.

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Author's contributions: Sheikh Irfan, David Lissauer, Rubina Barolia & Lumaan Sheikh conceptualised the design of the study and creation of data collection tools. David Lissauer, Arri Coomarasamy, Rubina Barolia, James Cheshire, Catherine Dunlop provided feedback on the first draft. Sheikh Irfan & Bakhtawar Khowaja edited and wrote the final draft. The authors read and approved the final manuscript.

3.1. Abstract

Background: Maternal sepsis is a life-threatening condition, defined by organ dysfunction caused by infection during pregnancy, childbirth and the postpartum period. It is estimated to account for between one-tenth and half of all maternal deaths globally. An international stakeholder group, including the World Health Organisation, developed a maternal sepsis management bundle called "FAST-M" for resource-limited settings through a synthesis of evidence and international consensus. The FAST-M treatment bundle consists of five components: Fluids, Antibiotics, **S**ource identification and control, assessment of the need to Transport or Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate). This study aims to adapt the FAST-M intervention and evaluate its feasibility in Pakistan.

Methods: The proposed study is a mixed method, with a before and after design. The study will be conducted in two phases at Liaquat University of Medical and Health Sciences, Hyderabad. In the first phase (formative assessment), we will adapt the bundle care tools for the local context and assess in what circumstances different components of the intervention are likely to be effective, by conducting interviews and a focus group discussion. Qualitative data will be analysed considering a framework method approach using NVivo version 10 (QSR International, Pty Ltd) software. The qualitative results will guide the adaptation of FAST-M intervention in local context. In the second phase, we will evaluate the feasibility of the FAST-M intervention. Quantitative analyses will be done to assess numerous outcomes: process, organisational, clinical,

structural and adverse events with quantitative comparisons made before and after implementation of the bundle. Qualitative analysis will be done to evaluate the outcomes of intervention by conducting FGDs with HCPs involved during the implementation process. This will provide an understanding and validation of quantitative findings.

Discussion: The utilisation of care bundles can facilitate recognition and timely management of maternal sepsis. There is a need to adapt, integrate and optimise a bundled care approach in low-resource settings in Pakistan to minimise the burden of maternal morbidities and mortalities due to sepsis.

3.2. Background

Pregnancy and childbirth-related complications are a major public health concern [267]. Every day approximately 830 women die from preventable causes related to pregnancy and childbirth, and almost one-third of these occur in South Asia [289]. Physiological and immunological variations during pregnancy and the postpartum period predispose women to risks of these complications [290]. About 60% of maternal deaths occur during delivery and the postpartum period [291]. The major complications that account for 80% of all maternal deaths include severe bleeding after childbirth, infections (usually after childbirth), hypertension and unsafe abortion [13].

The World Health Organisation estimates suggest that globally, maternal sepsis accounts for about one-tenth of the maternal deaths around the time of childbirth and is the third most common cause of maternal mortality [292-293]. While the maternal mortality related to sepsis has decreased considerably in high-income countries accounting for 2.1% of the total maternal deaths from the period of 2005 to 2008, the numbers are still high in lower-income countries accounting for up to 15.1% of maternal deaths annually [294]. More recent WHO estimates that were focused specifically on better understanding the contribution of maternal infection to adverse outcomes suggested that up to half of all maternal deaths were actually infection-related [16].

In Pakistan, complications during pregnancy and childbirth are the leading causes of death in women aged 15–45 years, accounting for 20% of all deaths of women of child-bearing age [295]. National figures showed that 15% of maternal deaths are reported due to sepsis [296], and maternal sepsis is established as the 3rd leading cause of maternal mortality [74]. Numerous

determinants have been identified that increase the susceptibility of women to sepsis, which include shortage of resources, basic infrastructure, availability of antibiotics, lower literacy rate, lower socioeconomic class, lack of antenatal care, lack of awareness [297].

There are national sepsis guidelines for Pakistan (SGP) which are designed to aid in the recognition and management of sepsis in adults in the local settings and are modelled on the Surviving Sepsis Campaign (SSC) [298]. However, there is still uncertainty about how best to prevent and treat maternal infections and sepsis and how to optimise the implementation of evidence-based practices in low-resource settings.

Whereas a substantial proportion of the improvements in maternal outcomes in high-income countries was attributed to the prevention and appropriate treatment of maternal sepsis [202]. Early warning scores, modules of educational material in routine healthcare settings, and the bundled approach to sepsis management in high-income countries have been effective in reducing maternal mortalities and morbidities [299]. A more rapid completion of a 3-h bundle of sepsis care and rapid administration of antibiotics were found to be associated with lower risk-adjusted in-hospital mortality ($p < 0.001$) [185]. Despite the improvement of sepsis care in high-income countries, there is still a lack of maternal sepsis-care bundle specific to the maternal population of low-resource settings [292].

The development of a maternal sepsis treatment bundle has been identified as an international "Priority Action" [222]. In collaboration with the WHO Maternal Sepsis Initiative, a Delphi approach was adopted to select contributory components to a maternal sepsis treatment bundle in

low-resource settings [222]. The components selected were as follows: Fluids, Antibiotics, Source identification and control, assessment of the need to Transport/Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate). The treatment bundle was named "FAST-M" as a memorable acronym for both communication and awareness-raising [222].

The FAST-M intervention was implemented in districts of Malawi to evaluate the feasibility of early identification and management of maternal sepsis and demonstrated significant improvements in maternal sepsis care. The components included a (1) Maternal Early Obstetric Warning Signs (MEOWS) chart and FAST-M decision tool, (2) FAST-M treatment bundle and (3) The FAST-M implementation program which consisted of the following: training program, sepsis champions, task shifting, performance dashboards, and data feedback to promote systems level change [300].

Following the implementation of the FAST-M intervention, women were more likely to have a complete set of vital signs monitoring compared with the baseline phase (0/163 [0%] versus 169/252 [67.1%], $P < 0.001$). Improvements in sepsis management were seen across all components of the FAST-M treatment bundle, in particular the proportion of women receiving antibiotics within 1 h (3/12 [25.0%] versus 72/107 [67.3%], $P < 0.004$) [300].

The FAST-M intervention has the capacity to strengthen maternal sepsis care as demonstrated in Malawi. We therefore aim to adapt and evaluate the implementation of the FAST-M intervention to assess improvement in maternal sepsis care in the low-resource setting of Pakistan. A mixed-methods approach will be used to plan the intervention and draw study conclusions.

The following are the study objectives:

Qualitative research objectives

- To adapt FAST-M bundle care tools (MEOWS chart, decision tool, and treatment bundle) to the context of Pakistan
- To understand the barriers and facilitators to these approaches
- To evaluate implementation outcomes of FAST-M intervention in low resource setting of Pakistan

Quantitative research objectives

- To assess whether the use of the FAST-M intervention is feasible in the local healthcare system and improves sepsis care (quantitative comparisons made between before and after implementation of the bundle).

Mixed methods research objectives

- To integrate quantitative and qualitative findings into the FAST-M bundle care tools for adaptation to the local context
- To evaluate implementation outcomes through quantitative and qualitative findings
- To develop insight and in-depth understanding of the quantitative findings through qualitative follow-up with healthcare providers

3.3. Methods and analysis

3.3.1. Study Aim

This study aims to determine whether it is feasible to introduce a complex intervention (including a bundled approach) for maternal sepsis care in the low-resource setting of Pakistan.

3.3.2. Study design

A sequential mixed method intervention design will be used. This two phase-design will start with the qualitative phase to collect data for the adaptation of FAST-M bundle care tools and will be applied to make these tools contextual based. In the first qualitative phase (formative assessment), we will identify healthcare providers and health officials for key informant interviews and the focus group discussion. The healthcare providers and the officials working at the study site with experience in managing sepsis patients will be selected. These individuals will be interviewed to explore ideas and views that will guide the intervention phase.
Data collected from the qualitative phase will be utilised to adapt bundle care tools and plan training programs. This will be then followed by the implementation of contextual-based modified FAST-M tools in the study setting and will allow us to assess the practicality of implementation.

The implementation outcomes will be evaluated using both the quantitative and qualitative methods (summative evaluation) to validate the study findings. Quantitative comparisons will be drawn before and after the implementation to distinguish study outcomes. Focus group

discussions with healthcare providers will provide in-depth qualitative findings regarding implementation outcomes.

Rationale for design

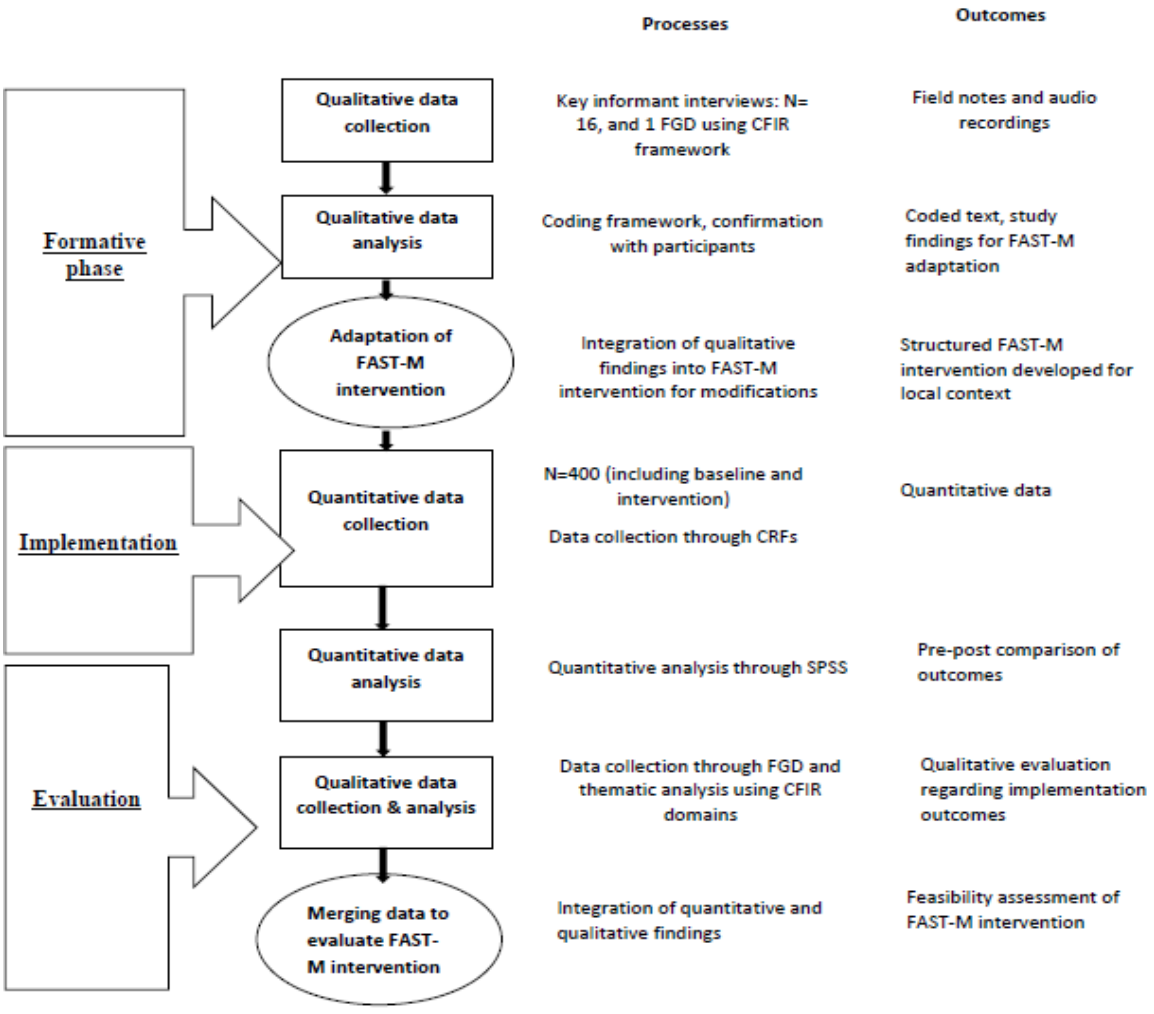
The mixed-methods approach involves qualitative and quantitative data collection, analysis and integration within the same study to provide a better and more comprehensive answer to research questions [300-301]. A sequential mixed-method intervention model will be used to gain insights into the existing local practices in order to adapt the FAST-M intervention and evaluate implementation outcomes of a locally adapted intervention.

The FAST-M intervention is new in Pakistan and its feasibility assessment will require adaptation before implementing it at the study setting. Thus, this study will begin with qualitative and quantitative assessments to understand the existing practices and culture of maternal sepsis care to modify bundle care tools in the context of local setting. This will support the study team to plan and provide useful and practical approach for the intervention. Baseline facility audit tool (quantitative observational data through CRF) will determine existing resources and practices to manage maternal sepsis, resource availability, and infection control infrastructure in the facility, whereas the qualitative approach will explore the views of healthcare providers and their readiness for the intervention, potential challenges and enablers for implementation.

While evaluating the implementation outcomes, qualitative and quantitative data will be combined to validate the study findings. The quantitative data will provide findings on patients'

outcomes through the collection of observational data, and the qualitative findings will help in validating quantitative findings. It will also explore the HCPs' readiness, facilitators, challenges, and reflection on the implementation. Therefore, the feasibility of this complex intervention will be assessed using mixed methods to gather evidence through qualitative and quantitative approaches and confirm our study findings. **Figure 3.1** provides the overview and flow of study using qualitative and quantitative strands.

Fig. 3.1. Overview and flow of study using qualitative and quantitative strands



3.3.3. Study setting

The study will be conducted at the Liaquat University of Medical Health Sciences (LUMHS), which is a public sector tertiary hospital located in the Hyderabad district of Pakistan. The hospital has a total of 3000 beds and 35 departments which serve a large number of mostly underprivileged populations. The hospital provides 24-h emergency cover to patients coming from nearby urban and rural areas. LUMHS has three obstetrics and gynecology units.

The current data from the facility shows that a total of approximately 11,205 patients were admitted to OBGYN units from the period of January to August 2021, and 210/11,205 (1.87 %) women were diagnosed with maternal sepsis. The maternal mortality rate in these units was recorded as 159/11205 (1.4%). Out of these 159 deaths, 45 were due to confirmed maternal sepsis (28.3%). These indicators demonstrate that there is a need for a robust system to early detect and manage maternal sepsis cases in the hospital.

3.3.4. Study Procedures

3.3.4.1. Adaptation phase

For a FAST-M bundle to be effective in Pakistan, it is necessary to identify how best to implement the FAST-M bundle in the context of local settings. In order to adapt this intervention, a systematic method will be taken to understand the nature of existing practices and an appropriate system for characterising the intervention and its components that can make use of this understanding. This constitutes phase 1 of the study.

This formative research (phase 1) will adopt a qualitative research design involving focus group discussion (FGD) and key-informant interviews (KIIs) and a purposive sampling approach. The

aim of group discussion and interviews will be to engage health practitioners, government officials, and other key stakeholders to understand the behavior of existing practices in the study setting for maternal sepsis care, to finalise the FAST-M tools for the context of Pakistan, and to identify various facilitators and barriers that may influence the implementation of the FAST-M intervention. The FGD and KIIs will be conducted using interview guides developed through the use of the Consolidated Framework for Implementation Research (CFIR) [302].

Consolidated Framework for Implementation Research (CFIR)

The CFIR is a commonly used framework to facilitate the implementation of research design, evaluation, and implement evidence-based interventions. It comprises five major domains: (1) intervention characteristics, (2) outer setting, (3) inner setting, (4) characteristics of individuals, and (5) process of implementation. CFIR is categorised as a determinant framework with the objective to understand and explain factors (individual or organisation) that influence implementation outcomes [302]. This framework has been used in a wide range of studies because this flexible framework can be tailored to different settings across multiple contexts [303]. We aim to use the tailored CFIR framework to assess critical barriers and facilitators to implementation that need to be addressed at multiple levels if the FAST-M bundle is to be successfully optimised and adopted in health care practices in Pakistan **(Appendix 3.1).**

The interview guides **(Appendix 3.2)** for KIIs and the FGD have been developed using five major domains of CFIR to identify existing practices for sepsis management. These guides contain questions that will help identify the facilitators and barriers to the implementation of

FAST-M intervention in the study setting. The identification of existing practices for maternal sepsis care and facilitators and barriers in phase 1 will then form the basis of adaptation of tools in local context for feasibility testing of FAST-M intervention in phase 2.

Sampling

Key informant interviews and the FGD will be conducted with:

- HCPs including physicians, nursing staff, healthcare administrators who are associated with maternal sepsis care and management
- HCPs who have worked at the study site for the last 6 months

Fifteen to 20 semi-structured key informant interviews and a focus group discussion are planned in the qualitative phase of the study until data saturation is reached [304].

Data collection

Semi-structured interview guides have been developed to explore healthcare professionals' views and attitudes towards FAST-M intervention and its implementation at their facility. Before beginning the interview, the qualitative researchers will describe the FAST-M bundle components and the patient referral pathway demonstrating the algorithm and summary for utilisation of FAST-M bundle care tools **(Appendix 3.1).**

A free flow of discussion among participants will be encouraged, using probes from these discussions to obtain healthcare professionals' perceptions about the feasibility of the FAST-M intervention. Interviews will be conducted face to face in Urdu and English according to the participants' preference and will be audio recorded following consent from study participants. Interviews and focus group discussions will be conducted by experienced study team members who are also trained, qualitative researchers. Detailed field notes will be also taken during each interview to capture non-verbal language and cues.

All data will be kept confidential for 7 years on password-protected computers and/or locked filing cabinets only accessible to members of the research team. During transcription, audio recordings will be referenced only with an identification number for anonymity of participants, with all identifying information removed before using the software analysis tool.

COVID-19- Standard Operating Procedures (SOPs)

In view of the current COVID-19 pandemic situation, all project-related activities will comply with standard operating procedures (SOPs). The following measures will be taken related to this study: (1) all research staff will be provided with appropriate masks, sanitizers, and/or other applicable Personal protective equipment (PPE) to the field staff; (2) daily mandatory screening for COVID-19 symptoms of all project staff; and (3) KIIs and FGDs will be conducted with social distancing (6 feet) with all participants wearing face coverings.

Data Analysis

Qualitative data gained during formative assessment through individual interviews and FGDs in phase 1 will be audio-recorded, transcribed and analysed using content analysis approach and the inductive analysis methods to determine the facilitators and barriers for implementation of the intervention and will be summarised according to CFIR domains. This will help to understand the important contextual features that are helping or hindering the operationalisation of the FAST-M intervention.

The codes, categories and themes will be developed using NVivo version 10 (QSR International, Pty Ltd) software [305]. The primary team will review the codes and associated themes multiple times to check for potential biases, to ensure they are reflecting participants' words and meanings, and improve the credibility of interpretation of the interviews. Initial findings will be shared with a group of participants to help with interpretation and generate meaning from the data. The FAST-M bundle care tools (MEOWS chart, decision tool, and treatment bundle) will be modified through construal gained from interviews and discussions with healthcare providers.

3.3.4.2. Baseline phase

Following phase 1, a baseline assessment phase of 2 months will be carried out to assess existing resources and practices to prevent and treat maternal sepsis. The case report form (CRF) will be used for assessing baseline resource availability, practitioner's knowledge and infection control infrastructure. Based on the findings from baseline assessments, necessary infrastructure and

training to establish FAST-M decision intervention will be introduced to the study site. The baseline data will later be used to compare if the introduction of the intervention affects clinical practice. This will enable us to compare whether the subsequent introduction of the intervention affects existing practice.

3.3.4.3. Training Program

Multiple full day training sessions by the study team will be delivered to healthcare practitioners working for maternal care and sepsis management at the study site. The interactive sessions will be offered in English and Urdu languages for each healthcare practitioner to understand the practices completely. Any requirement for supplementary educational material such as posters and a study booklet will be determined via feedback from frontline clinical staff and stakeholders on facilitators and barriers to the use of these tools. This will be done using qualitative interviews and focus groups discussion during phase 1.

The training and implementation program is likely to consist of:

- Background information on maternal sepsis, including risk factors, signs and symptoms and the potential consequences if untreated
- Use of the MEOWS chart to track and trigger the recognition of deteriorating patients
- Use of the FAST-M decision tool to recognise and screen for potential study participants at risk of maternal sepsis
- Use of the FAST-M treatment tool to initiate the bundle components
- Guidance around implementing the individual components of the FAST-M bundle

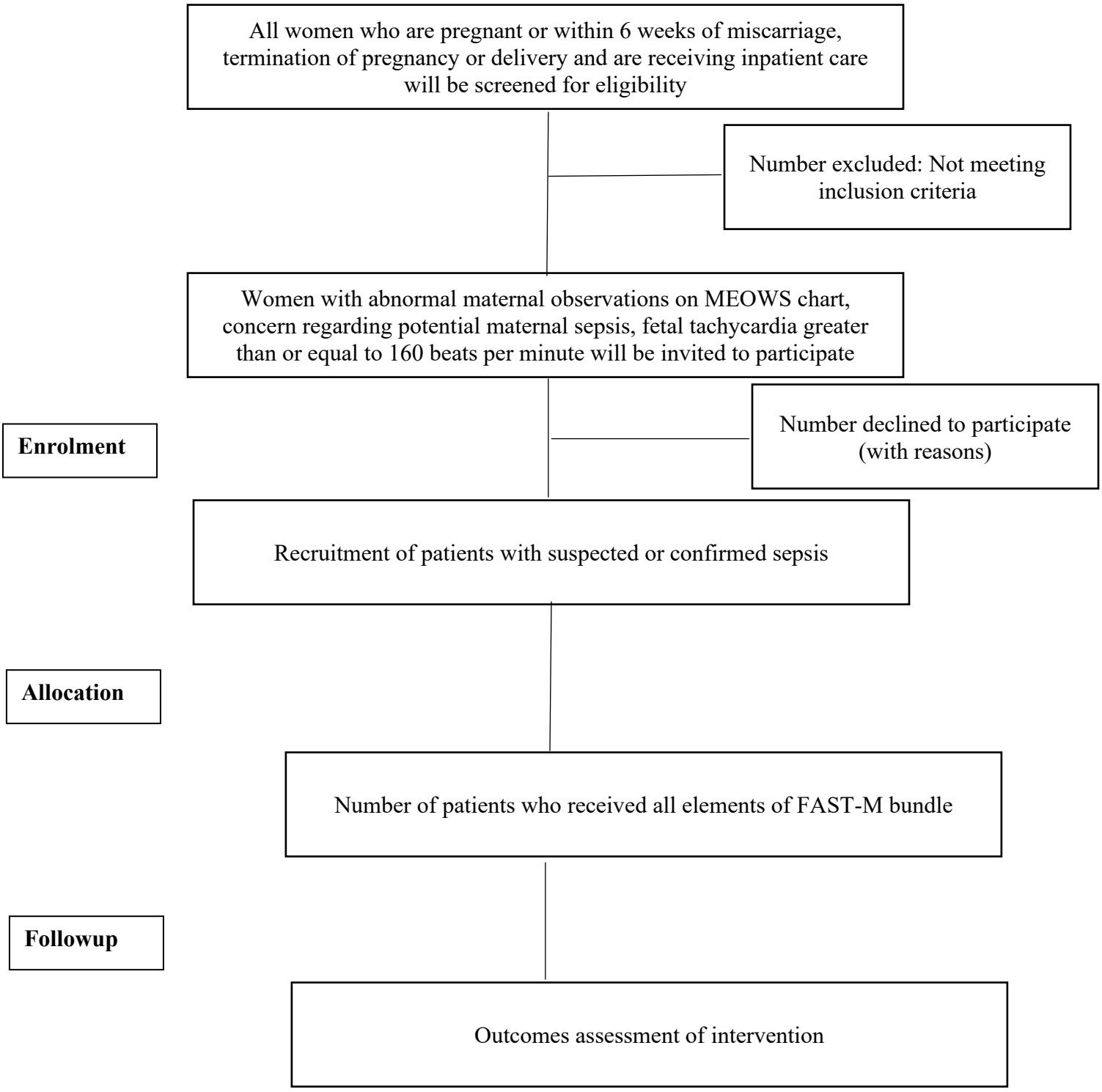
• Use of feedback tools (run chart and dashboard) and approaches the team can use to work together to improve compliance and outcomes

Post-training, an impact survey will be made to measure the extent to which skills and knowledge learned in the program has translated into improved behavior among participants who attended the training program.

3.3.4.4. Intervention phase

At the start of the intervention phase, FAST-M bundle care tools **(Appendix 3.1)** will be introduced including MEOWS chart, FAST-M decision tool, and FAST-M treatment bundle. **Figure 3.2** provide the summary of assessment, enrollment, and intervention.

Figure 3.2. Flow of study



Modified early obstetric warning score

MEOWS stands for Modified Early Obstetric Warning Score (MEOWS) to identify suspected maternal sepsis patients. This tool helps in identifying any early warning scores used to track the physiological parameters of an individual over time onto a chart, with guidance thresholds to trigger clinical action if they become abnormal [306]. The MEOWS chart used during the implementation of the FAST-M intervention in the districts of Malawi will be adapted in the context of Pakistan for the purpose of this feasibility study [300].

The use of obstetric early warning systems (OEWS) in UK maternity units was recommended in the 2007 Confidential Enquiry into Maternal and Child Health (CEMACH) report as an adjunct to reducing maternal morbidity and mortality [306]. MEOWS included in the 2007 UK Confidential Enquiry consisted of scores of respiratory rate, oxygen saturation, temperature, heart rate, blood pressure, assessment of urine, including for proteinuria, color of amniotic fluid, neurological response, pain score, assessment of lochia, and an overall assessment of whether the woman appears well [305]. Clinical action is triggered by a single parameter exceeding a red threshold or any two parameters exceeding a yellow threshold. MEOWs chart has been widely adopted in the UK and internationally [307].

To complete the MEOWS chart, the healthcare providers involved in the study will be trained to record patient observations (heart rate, respiratory rate, blood pressure, conscious level, urine output, and temperature) and fetal heart rate (if applicable) from medical records. These observations will be charted on a MEOWS chart in the inpatient setting.

Decision tool

Abnormal observations (indicated by a single red or two yellow thresholds) will trigger a review by an attending doctor or nurse. This will be agreed locally prior to study commencement. These patients will then be screened for potential sepsis using the FAST-M decision tool. In addition to abnormal maternal observations, cases of suspected sepsis will also be identified using the FAST-M patient pathway when prompted by attending clinician concern regarding potential maternal infection or an increased fetal heart rate greater than or equal to160 beats per minute (in pregnant women).

Patients will be defined as having or are at a higher risk of having sepsis, who will trigger a red flag on the decision tool and will be commenced immediately on the FAST-M treatment bundle pathway. These patients will receive a review from a doctor/nurse as soon as possible, with the bundle initiated within 1 h. Those patients who trigger two yellow flags on the decision tool and have or are at a higher risk of having sepsis require a review from a doctor/nurse within 3 h. All suspected cases will remain in observation for possible development of red flags. Half-hourly (if red trigger) or hourly (if two yellow trigger), observations will be made in the first instance until otherwise specified by an attending clinical decision-maker. Those patients without at least one red or two yellow flags will be considered to have a low risk of sepsis and will be managed according to local guidelines by the screening healthcare practitioner.

FAST-M treatment bundle

Patients managed with the FAST-M treatment bundle will have their treatment recorded on the FAST-M treatment bundle form including documentation of actions completed and any reasons for not completing certain components of the bundle.

The FAST-M treatment bundle consists of the timely consideration of all the following:

- Fluids
- Antibiotics
- Source identification and control
- Assessment of the need to Transport / Transfer to a high level of care
- Ongoing Monitoring (of the mother and neonate)

Sampling

During the intervention phase, patients will be assessed by a healthcare practitioner on the decision to initiate screening for potential maternal sepsis that will be based on the following inclusion criteria:

- Women who are pregnant or within 6 weeks of miscarriage, termination of pregnancy, or delivery
- Abnormal maternal observations triggered on the inpatient MEOWS chart
- Healthcare practitioner's concern regarding potential maternal sepsis
- In pregnant women, fetal tachycardia greater than or equal to160 beats per minute

For enrollment of sepsis cases, we will power to a primary process outcome of "sepsis management compliance". This is defined as "the proportion of patients admitted with features of sepsis who receive appropriate monitoring (full set of vital sign measurements on admission) and antibiotics within 1 h (if required)." This means the notes of all patients with suspected or confirmed sepsis will be reviewed and their data would be collected using study case report forms (CRFs).

Assuming baseline compliance is less than 10%, to detect an increase in compliance to 20%, with an alpha of 0.05, we will require the observation of 199 participants in each phase (baseline and intervention) to achieve a power of 80%. The test statistics used is 1-tailed test. This is adequate precision to allow important increases to be estimated. Allowing for loss to follow-up and missing laboratory results, we will take 210 in each phase, as appropriate to allow the study to have adequate power to detect an increase in compliance. This number of cases will be feasible to collect within 6 months, based on the current rate of sepsis from hospital records of the anticipated site. The flow of participants through the study is presented in **Fig.3. 3**

Fig. 3.3. Flow of participants through the study

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	**Close-out**
TIMEPOINT	$-t_1$	**0**	t_1	t_2
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Baseline data collection	X			
Allocation		X		
INTERVENTION:				
Feasibility of FASTM bundle care tool			⟷	
ASSESSMENTS:				
/proportion of inpatients receiving a full set of vital signs on admission/			X	
/proportion of women with suspected maternal sepsis receiving the full FAST-M bundle/			X	X
/proportion of women with suspected maternal sepsis escalated to senior healthcare practitioners on the basis of abnormal vital signs/			X	X

Data collection

During the intervention phase, data will be collected by a member of the research team who will not be part of the clinical team. Data will be collected using CRFs on various outcomes; structural, clinical, organisational, and any adverse events.

If the patient requires a transfer as part of the FAST-M treatment bundle to any other health facility due to shortage of beds or other resources, the data collector will continue to follow up on the patient's clinical outcomes. The data collection team will keep their study site updated on their performance using this data and will visually display it on run charts and dashboards and work on strategies to improve performance. The data will be maintained in an investigator file to be secured in a locked cabinet. The information recorded on the data collection sheet will be recorded in a database located on a secure server. Quantitative data (data collection on CRFs) will be measured every 2 weeks throughout the intervention phase.

Data analysis

Quantitative analyses will be done to assess numerous outcomes; process, organisational, clinical, structural and adverse events with quantitative comparisons made before and after implementation of the bundle. Quantitative data will be analysed using percentages, means, medians interquartile ranges and 95% confidence intervals, and the change identified over time.

3.3.4.5. Co-interventions for implementation of the intervention

Clinical champions

The local clinical champions and team leaders will be identified during training program. Healthcare practitioners who have been involved in the management of patients with maternal sepsis or infections for at least 6 months and have demonstrated capacity and enthusiasm will be recruited as champions for maternal sepsis intervention as well as key members of the study management group. These champions will be trained to take a lead from different units at the study site and will remain engaged throughout the implementation process. The overarching goal of each champion will be to encourage engagement and compliance with the FAST-M bundle. To achieve this goal, champions at each site will be engaged in a number of key activities: disseminating knowledge, advocating, navigating boundaries, facilitating consensus, arranging meetings with stakeholders, tracking quality indicators, and developing organisational communication strategies and relationships.

Ongoing improvement approaches

Ongoing improvement practices at different units of the study site will be carried out by clinical champions of the respective units. The improvement strategies include: (1) weekly/biweekly training of health care providers on FAST-M tools, (2) display of run charts, dashboards in units to demonstrate the rate of maternal sepsis and outcomes of maternal sepsis cases over time, and (3) meeting with stakeholders for communicating needs and requirements for implementation of the FAST-M intervention. **Table 3.1.** shows the summary of ongoing improvement approaches planned to implement for FAST-M implementation

Table 3.1. Ongoing improvement approaches for FAST-M implementation

Approaches	Planned strategies
Facility-level approaches	Site leadership by project champion Formation of local sepsis committee Formal site launch
Individual-level approaches	Multidisciplinary, scenario-based local training Coaching by local project champion Aide-memoires, posters Paper-based tools (MEOWS chart, decision tool, treatment tool) Task sharing of vital sign measurement
Ongoing improvement approaches	Site-based performance dashboards and run charts Local problem-solving: led by sepsis committee (ongoing quality improvement, ownership, local adaptations, engagement, learning climate, and sustainability)

3.3.4.6. Evaluation phase

We will explore a range of outcomes measurement through quantitative data for maternal sepsis care. Primary process includes (1) the proportion of patients admitted with features of sepsis who received appropriate monitoring (full set of vital sign measurements on admission recorded on MEOWS chart), (2) the proportion of women with suspected maternal sepsis received antibiotics within 1 h (if required), (3) the proportion of women with suspected maternal sepsis receiving the FAST-M treatment bundle (including each bundle component) within 1 h of identification of sepsis. Secondary outcomes will include the following: (1) the proportion of women with suspected maternal sepsis referred to clinical decision-maker on the basis of abnormal vital signs

records and (2) the proportion of women with suspected maternal sepsis receiving a clinical review by a senior clinical decision-maker following their diagnosis.

For qualitative evaluation, two to three follow-up focus group discussions will be conducted with HCPs involved during the process of implementation of the FAST-M intervention. The HCPs will be invited for group discussions from all participating units to share their views and perceptions regarding implementation outcomes. This will provide an opportunity to gain more insights into quantitative findings and explore the observational results in more depth. The interview guides **(Appendix 3.3)** for FGDs have been developed using five major domains of CFIR to evaluate the outcomes and feasibility of the FAST-M intervention. These discussions will be audio-recorded following consent from study participants. Focus group discussions will be conducted by experienced study team members who are also trained, qualitative researchers. Detailed field notes will be also taken during discussions to capture nonverbal language and cues.

Qualitative data gained through FGDs will be transcribed and analysed using thematic analysis approach and the deductive analysis methods. The CFIR domains will be used as themes and constructs as subthemes for the purpose of analysis [302]. The research team will conduct multiple reviews of the transcripts and tapes to familiarise themselves with the data that will be reflexive and interactive. Analysis will begin soon after first FGD is completed and will be continued concurrently with data collection to help determine when new information is no longer being generated. Although we identified the CFIR as the appropriate framework, additional codes may emerge during the familiarisation process to develop from the experiences of participants.

An audit trail will be used to document our decision-making process. The codes, subthemes and themes will be developed using NVivo version 10 (QSR International, Pty Ltd) software [305]. The primary team will review the codes and associated themes multiple times to check for potential biases, to ensure they are reflecting participants' words and meanings, and improve the credibility of the interpretation of the interviews.

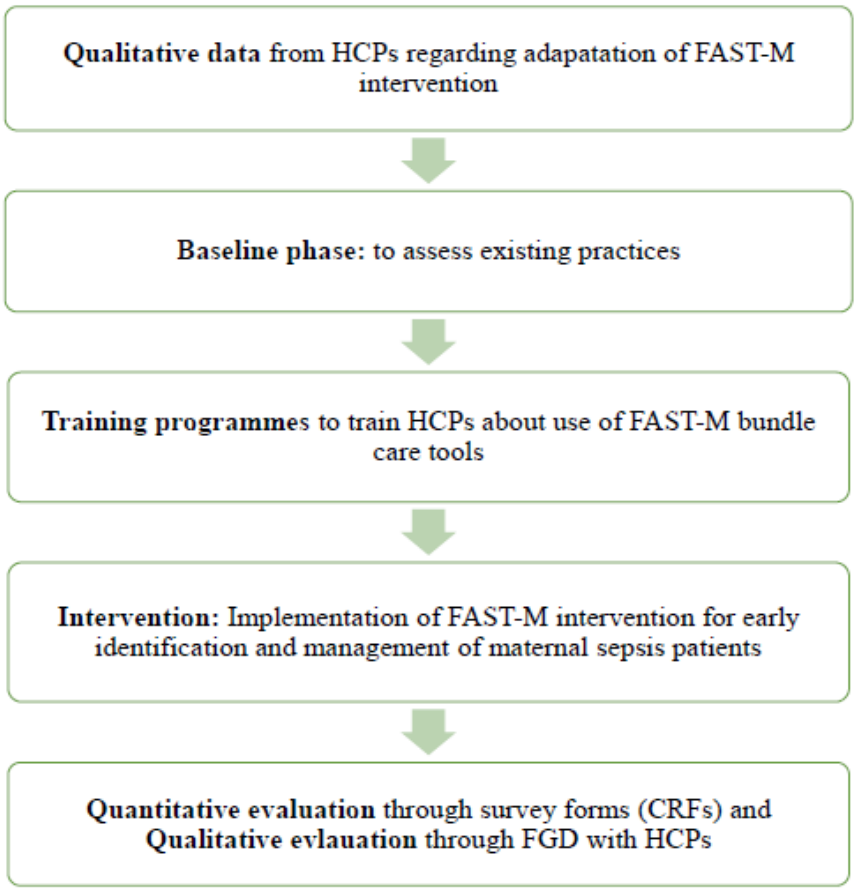
3.3.5. Data integration

The mixed-methods design of the study using both the qualitative and quantitative data will be utilised throughout the study to implement the intervention, determine outcome results, and validate the study findings. This approach will support in explaining and building upon quantitative results through qualitative findings and will provide in-depth data to justify significant study outcomes.

The integration of data will occur at two points. First, when we will adapt the FAST-M intervention by means of combining baseline quantitative data (facility audit tool) findings and qualitative findings to create contextual-based adapted tools. The qualitative data will explore views and perceptions of HCPs to understand observational records. The study team will use the findings from the initial exploratory databases to build into a feature that can be analysed quantitatively. The development of locally adapted tools will base on both quantitative and qualitative data and will increase the content validity of the study.

Second, when reporting evaluation outcomes using qualitative and quantitative results through a joint display. The overall process of implementation and modifications in the inner or outer setting before and after the implementation will be determined through observational findings and personal feedback. The results of this mixed-methods study will be displayed through the CFIR framework. The follow-up on the experiences of HCPs after implementation will help in using actual participant quotes and matching them with the quantitative survey results to explain the study outcomes. **Figure 3.4** displays the complete overview of study procedures and implementation.

Fig. 3.4. Overview of study implementation



3.4. Potential Harms

Fluid resuscitation in patients with sepsis if not managed appropriately can precipitate volume overload and subsequent pulmonary edema. This is a particular concern in patients with preeclampsia. Clear teaching and guidance regarding fluid resuscitation will be provided during the training programs. The participants will be evaluated regarding their understanding of fluid administration through a post-test. When fluid resuscitating patients with suspected maternal sepsis, the decision regarding the rate of fluid administration will be made by the responsible clinician based on clinical examination findings and ongoing monitoring and will be documented in patients' files. The data for fluid administration will be collected through a review of patients' records and all information related to its indication, rate, and duration will be recorded on study CRFs.

3.5. Discussion

Overall, bundle care tools have the potential to enhance improvements in sepsis care [292]. However, the implementation challenges posed by these bundles should be examined, especially in low-resource settings. The FAST-M maternal sepsis intervention has the potential to be used as an integrated strategy for early recognition and management of maternal sepsis in the low resource health settings. This mixed-method study will establish whether it is feasible to implement the FAST-M bundle for early identification and management of maternal sepsis in Pakistan. The long-term vision is that the intervention will be trialled in other settings across Pakistan. A large multi-country interventional trial is also anticipated to ascertain the

effectiveness of the bundle to improve maternal sepsis care and outcomes in other low- and middle-income countries. The study findings will be disseminated to clinicians and key stakeholders to formulate appropriate bundle care tools for sepsis care. This will help reduce the high rate of maternal mortalities caused by sepsis.

Overall, this chapter described the process by which the FAST-M intervention was implemented in a low-resource setting in Pakistan and how its feasibility was evaluated. This protocol serves as a blueprint for the next couple of chapters where the implementation, feasibility and acceptability of the intervention is investigated.

Chapter 4

ADAPTATION OF THE FAST-M MATERNAL SEPSIS INTERVENTION FOR IMPLEMENTATION IN PAKISTAN: A QUALITATIVE EXPLORATORY STUDY

The previous chapter laid the groundwork for the implementation of the FAST-M intervention in a local setting. As stated in the protocol, the study was carried out in two phases. For the first phase, as our research question was descriptive and exploratory, a formative assessment was required, which is what this chapter sets out to achieve.

I will give a detailed explanation of the four overarching themes that were identified through the focus group discussions and key informant interviews by applying an inductive content analysis approach to gather a rich information for the research objective. Furthermore, I will explore the existing gaps in the recognition and management of maternal sepsis and the availability of resources in these low-resource facilities as all these factors determined how efficiently the FAST-M intervention could be implemented.

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Authors' contributions: Sheikh Irfan, David Lissauer, Rubina Barolia & Lumaan Sheikh conceptualised the design of the study and creation of data collection tools. Raheel Sikandar, Raheela Rani, Sehrish Khan assisted in data collection from field site. Sheikh Irfan, Rubina Barolia, Bakhtawar Khowaja & Kubra Rind managed data collection and interpretation. Sheikh Irfan and Bakhtawar Khowaja carried out the analysis and wrote the initial manuscript. All authors provided input during the interpretation of the data and revising of the manuscript. David Lissauer, Arri Coomarasamy, Rubina Barolia, James Cheshire, Catherine Dunlop provided feedback on the first draft. Sheikh Irfan & Bakhtawar Khowaja edited and wrote the final draft. The authors read and approved the final manuscript.

4.1. Abstract

Objective

A maternal sepsis management bundle for resource-limited settings was developed through a synthesis of evidence and international consensus. This bundle, called "FAST-M" consists of: Fluids, Antibiotics, Source control, assessment of the need to Transport/Transfer to a higher level of care and ongoing Monitoring (of the mother and neonate). The study aimed to adapt the FAST-M intervention including the bundle care tools for early identification and management of maternal sepsis in a low resource setting of Pakistan and identify potential facilitators and barriers to its implementation.

Setting

The study was conducted at the Liaquat University of Medical and Health Sciences, which is a tertiary referral public sector hospital in Hyderabad.

Design and Participants

A qualitative exploratory study comprising key-informant interviews and a focus group discussion was conducted with healthcare providers (HCPs) working in the study setting between November 2020 and January 2021, to ascertain the potential facilitators and barriers to the implementation of the FAST-M intervention. Interview guides were developed using the five domains of the Consolidated Framework for Implementation Research: intervention characteristics, outer setting, inner setting, characteristics of the individuals and process of implementation.

Results

Four overarching themes were identified, the hindering factors for implementation of the FAST-M intervention were: (1) Challenges in existing system such as a shortage of resources and lack of quality assurance; and (2) Clinical practice variation that includes lack of sepsis guidelines and documentation; the facilitating factors identified were: (3) HCPs' perceptions about the FAST-M intervention and their positive views about its execution; and (4) Development of HCPs readiness for FAST-M implementation that aided in identifying solutions to potential hindering factors at their clinical setting.

Conclusion

The study has identified potential gaps and probable solutions to the implementation of the FAST-M intervention, with modifications for adaptation in the local context.

4.2. Background

Maternal sepsis is a major contributor to maternal morbidity and mortality worldwide [5]. Maternal sepsis is a life-threatening organ dysfunction caused by a dysregulated host response due to infection during pregnancy, childbirth and in the postpartum period [4,42].

Globally, maternal sepsis accounts for about one tenth of maternal deaths and is the third most common cause of maternal mortality [5, 46]. It was estimated that each year 75,000 maternal deaths occurred in low-income and middle-income countries due to maternal sepsis and approximately 10% of maternal deaths in Africa and Asia occur due to sepsis [41, 46]. The risk of death among women who develop puerperal sepsis was higher in Africa (odds ratio 2.71), Asia (1.91), and Latin America and the Caribbean (2.06) than in developed countries [41].

Led by the WHO and other partners, a global initiative was commenced in 2015, to develop strategies aimed at improving the early recognition and management of maternal sepsis [222]. Strategies to ensure early identification and treatment of sepsis have demonstrated significant improvement in outcomes in high income adult population settings [229] and it was necessary to translate these approaches into the maternity population and make them appropriate for low-resource settings [308]. Yet, there is very limited evidence of the implementation of such approaches specific to maternity care in low-resource settings.

Thus, a maternal sepsis bundle was developed as part of this process to improve the recognition and management of maternal sepsis in a low-resource setting. A modified Delphi approach was adopted to identify components significant to treatment and monitoring in terms of clinical

importance and feasibility in resource-poor settings [222]. The components selected were: **F**luids, **A**ntibiotics, **S**ource control, assessment of the need to **T**ransport/Transfer to a higher level of care and ongoing **M**onitoring (of the mother and neonate). The bundle was named "FAST-M" as a memorable acronym for both communication and awareness-raising [222].

Implementation of the FAST-M intervention across 15 government healthcare facilities in Malawi was found to not only be feasible but also resulted in improved clinical care [300], demonstrating that the intervention could assist in the early identification and management of maternal sepsis in low-resource settings [300]. This is now being tested formally as part of a large cluster-randomised trial across Malawi and Uganda.

In Pakistan, complications during pregnancy and childbirth are the leading causes of death in women, accounting for 20% of all deaths of women of child-bearing age [85, 296, 309]. National figures show that 15% of maternal deaths are reported due to sepsis [309] and maternal sepsis is established as the 3rd leading cause of maternal mortality [310]. Globally, the incidence of puerperal sepsis is 4.4% [69] whereas in Pakistan the incidence is reported to be 10-15% [311].

There are national sepsis guidelines for Pakistan which are designed to aid in the identification and management of sepsis in adults in the local settings and are modeled on the Surviving Sepsis Campaign [312]. However, these are inconsistently applied and lack a comprehensive implementation approach. There is still uncertainty about how best to optimise the implementation of evidence-based practices around maternal sepsis prevention and management in Pakistan.

The absence of routine monitoring in most public facilities in Pakistan during labor and childbirth such as not taking vital signs of women and newborns substantially increases the risk of maternal and newborn morbidity and mortality [313]. It has been evident that the quality of care is poorer in public referral facilities than in primary healthcare facilities [72]. While the FAST-M intervention when implemented in health settings of Malawi has shown improvements in vital signs recording and improved timely identification and management of women with maternal sepsis [300].

It is therefore planned to adapt and implement the FAST-M intervention in Pakistan. However, we recognise that to optimise its use in the Pakistani context requires a robust process of adaptation and re-design prior to its field testing. The implementation of the FAST-M intervention will be highly context specific. Therefore, this study aims to understand the existing sepsis management practices and behaviours to adapt the FAST-M bundle care tools in the local context. In addition, it will assist in the identification of the potential facilitators and barriers to its implementation in a low-resource setting within Pakistan.

This qualitative study was conducted in preparation for the implementation of FAST-M intervention in phase II of the study. The protocol and procedures for phases I and II of this study have been described in detail elsewhere [314]. The study findings obtained in this formative research will aid in the development of feasible methods to improve the processes and implementation of the FAST-M intervention in Pakistan.

4.3. Methods

4.3.1. Study Design

Our methods, grounded in implementation science, aimed to identify the anticipated facilitators and barriers in the implementation of FAST-M intervention at the Liaquat University of Medical Health Sciences (LUMHS), Hyderabad. Implementation research aims to identify the factors that function as barriers and enablers to specific interventions [315]. As our research question is descriptive and exploratory, this formative research adopted a qualitative research design involving both focus group discussion (FGD) and key-informant interviews (KIIs) and a purposive sampling approach.

FGD and KIIs were conducted with health care providers (HCPs) working at the study site using interview guides structured using the Consolidated Framework for Implementation Research (CFIR) [316]. The aim of FGD and KIIs was to engage health practitioners, government officials, and other key stakeholders to understand the behavior of existing practices in the study setting for maternal sepsis care, identify various facilitators and barriers that may influence the implementation of the FAST-M intervention and inform the adaptation of FAST-M bundle care tools and implementation approach according to the local context. Data collection through KIIs and FGD were to ensure data triangulation through different methods ensuring credibility of the study findings. The present study is being stated as per the guidance provided in consolidated criteria for reporting qualitative research.

4.3.2. Consolidated Framework for Implementation Research

The CFIR is a 'meta-theoretical' framework that provides an overarching analysis for implementation [316]. It offers an extensive and standardised list of constructs that allow researchers to identify various variables that are most relevant to a particular intervention [317]. The CFIR consists of five major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals, and the process of implementation. These domains are organised into 39 constructs **(table 4.1).**

Table 4.1. CFIR domains and associated constructs

Domains	Constructs
One: Intervention Characteristic	Intervention Source Evidence Strength and quality Relative Advantage Adaptability Trialability Complexity Design Quality and packaging Cost
Two: Outer Setting	Patient Needs and Resources Cosmopolitanism Peer Pressure External Policies and Incentives
Three: Inner Setting	Structural characteristics Networks & Communication Culture Implementation Climate Tension for change Compatibility Relative priority Organisational incentives and rewards Goals and feedback Learning climate Readiness for implementation Leadership engagement Available resources

	Access to knowledge and information
Four: Characteristics of Individuals	Knowledge and Beliefs about the intervention Self-efficacy Individual stage of change Individual identification with organisation Other personal Attributes
Five: Process	Planning Engaging Opinion leaders Formally appointed internal implementation leaders Champions External change agents Executing Reflecting and evaluating

CFIR has been used in various studies to inform qualitative processes across a range of complex intervention, because this flexible framework can be tailored to different settings across multiple contexts [316-317]. We therefore, used the tailored CFIR framework to understand critical barriers and facilitators to implementation of FAST-M intervention that need to be addressed at multiple levels if the FAST-M intervention is to be successfully optimised, and adopted in healthcare practices in Pakistan.

4.3.3. Study setting

LUMHS is located in Hyderabad district, Pakistan. LUHMS is a referral public sector hospital which serves a large number of mostly underprivileged populations. The hospital offers various facilities for both in-patient and out-patient. The hospital has three obstetrics and gynaecology (OBGYN) units and provides 24 hours emergency cover to patients coming from urban and rural areas of Sindh. It manages a high volume of cases of maternal sepsis every month. The current data from the facility shows that a total of approximately 11205 patients were admitted to

OBGYN units from the period of January to August 2021, and the maternal mortality rate was recorded as 159/11205 (1.4%). Out of these 159 deaths, 45 were due to confirmed maternal sepsis (28.3%). These indicators direct that there is a need for a robust system to early detect and manage maternal sepsis cases in the hospital.

Patient and public involvement

There was no patient or public involvement in setting the research agenda.

4.3.4. Data collection methods and study participants

HCPs working at LUMHS hospital were purposively sampled for KIIs and FGD. The letters of invitation were sent to all HCPs including Doctors (residents and faculty members), staff nurses, and administrators who were involved in the management and treatment of maternal sepsis patients for at least the past 6 months from the time of invitation. All the participants who were approached by the study team agreed to participate in the study. The aim of KIIs and FGD was to explore and understand the behavior of the existing practices and guidelines used in the hospital for sepsis management, and an appropriate system for characterising intervention and its components that can make use of this understanding. KIIs with HCPs were conducted in the meeting room and faculty offices at LUMHS hospital. A FGD was conducted in the seminar room at LUMHS hospital. A trained moderator facilitated the FGD. Interviews were scheduled according to participants' preferences and were audio-recorded following consent from study participants **(Appendix 4.1).**

4.3.4.1. Data collection procedure

A semi-structured interview guide was developed to explore healthcare professionals' views and attitudes towards the FAST-M intervention **(Appendix 4.2),** with a focus on the views on the feasibility of FAST-M implementation among healthcare professionals using five major domains of CFIR: intervention characteristics, outer setting and inner setting, characteristics of the individuals and the process of implementation. The interview guides were tailored considering each category of participants. The research team reviewed the interview guide for content and flow and trialed the guide for the length of time and appropriateness of the questions. Before beginning the interview, the qualitative researchers first described the FAST-M bundle components and the patient referral pathway **(Appendix 4.1)** demonstrating the utilisation of FAST-M bundle care tools. The interview guide underwent subsequent modifications and iterations based on interviews conducted.

A free flow of information was encouraged, using probes from these discussions to obtain healthcare professionals' perceptions about the adaptation and feasibility of the FAST-M intervention. Interviews were conducted face-to-face in Urdu and English (KIIs = 16; FGD =1). The standards of precautions for control of COVID-19 infection were followed during data collection. All study participants were screened before interviews for COVID-19 infection through a series of questions regarding their symptoms. The participants were asked to wear masks at all times during interviews and discussions. The focus group discussion was conducted in a large seminar room to maintain physical distance between participants as a precaution for control of COVID-19 infection.

Interviews and focus group discussion were conducted by RB, SIA, BMHK, and GKR, who are part of the investigating team and are trained in qualitative research. The research questions were based on FAST-M intervention characteristics, outer and inner health care setting, characteristics of the individuals, and the process of implementation. Detailed field notes were taken during each interview to capture non-verbal language and cues. KIIs were conducted for 20- 40 min; FGD was conducted for 50 min and consisted of 12 participants in a group. Data were collected using interview guides developed on five major domains of CFIR: intervention characteristics, outer setting, inner setting, characteristics of the individuals, and the process of implementation. Data were collected and analysed through an iterative process. The data collected through interviews and discussion were carried out until data saturation was achieved and no new information emerged [318]. We defined saturation as the amount of data needed until nothing new information and a meaningful conclusion drawn out about the feasibility of the FAST-M intervention was apparent and redundancy was reached.

4.3.5. Data Analysis

Study data were analysed using a conventional qualitative content analysis approach facilitated by NVivo V.10 (QSR International) software. First, all the audio recordings were translated and transcribed from the local language (Urdu) into English. Transcripts were read several times to develop an interpretation of the participants' views about the feasibility of FAST-M implementation. FGD and KIIs were coded as one data set. Two investigators coded a subset of transcripts independently using separate coding that was then combined to match codes, and agreement by investigators was sought on a coding framework. Codes were formulated inductively from the transcripts related to research questions and CFIR domains. Coding

discrepancies were discussed and resolved to reduce researchers' biases. Codes were then analysed into categories and then the major themes based on the data findings.

The potential barriers and facilitators and modifications in the bundle care tools were identified that were discussed and reviewed by the research team. To ensure the credibility of the research, study data were triangulated by different data sources including doctors, nurses, and administrators and through different data collection methods including FGD and KIIs, to compare alternative perspectives and to assess any inconsistencies. The hospital leadership and a subgroup of clinical care providers were directly contacted and invited to attend an interactive session to hear about the findings and reflect on whether these were considered representative of their existing practices prior to modifying the bundle care tools and adapting the intervention. This respondent's validation process enhanced rigor and established conformability [319].

4.4. Results

In this qualitative study, 1 FGD and 16 KIIs **(table 4.2)** were conducted with HCPs (doctors, nurses, and health administrators), between November 2020 and January 2021who were involved in the management and treatment of maternal sepsis patients. **Tables 4.3 and 4.4** present demographics of study participants. A baseline facility audit was alongside conducted to identify the availability of resources in the facility **(Appendix 4.3).** The survey findings assisted the study team to plan a practical approach for the implementation of the intervention (the audit findings will be recorded elsewhere). The qualitative findings presented in this paper aided the validation of observational findings. This helped the study team to gain feedback and insights from healthcare providers about their existing sepsis guidelines and resource availability. Based on

these findings, the bundle care tools will be modified before implementation and the feasibility assessment.

Table 4.2. Study participants

Focus group discussion with HCPs	Total FGD=1; n=12
Doctors (Medicine); (OBGYN)	n=3; n=5
Nurses (OBGYN); (labor room)	n=1; n=1
Health administrators	n=2
Key informant interviews	Total KIIs= 16; n=16
Doctors (OBGYN); (Operating room); ICU	n=8; n=1; n=2
Nurses (OBGYN)	n= 4
Health administrators	n= 1
FGD, focus group discussion; HCPs, healthcare providers; ICU. Intensive care unit; KII, key informant interviews; OBGYN, obstetrics and gynaecology	

Table 4.3. Demographics of participants in KIs

KIs	N=16
Job Title	
Faculties from obstetrics and gynecology (Professor, Associate &Assistant Professors)	3
Faculties from obstetrics and gynecology (Professor, Associate &Assistant Professors)	1
Registrars, Residents & Medical Officers (OBGYN)	5
Residents & Medical Officers (Family Medicine)	2
Registered nurses	4
Administration staff	1
Working experience in facility	
>10 years	7
> 5 years	6
1- 5 years	3
Gender	
Male	4
Female	12
Role in the hospital	
Administration	2
Leadership	3
Clinical practices	11
KIIs, key informant interviews.	

Table 4.4. Demographics of group participants

FGD participants	N=12
Job Title	
Faculties from obstetrics and gynecology (Professor, Associate &Assistant Professors)	5
Faculties from family medicine (Professor, Associate &Assistant Professors)	3
Registered nurses	2
Administration registrars	2
Working experience in facility	
>10 years	5
> 5 years	5
1- 5 years	2
Gender	
Male	4
Female	8
Role in the hospital	
Administration	2
Leadership	5
Clinical practices	5
FGD, focus group discussion.	

Data analysis revealed four overarching themes: (1) challenges in existing system; (2) clinical practice variation; (3) HCPs' perceptions about FAST-M; and (4) Development of HCPs readiness for FAST-M implementation. **Table 4.5** demonstrates the identified themes and categories.

Table 4.5. Themes and Categories

Themes	Categories
Challenges in existing system	Shortage of HCPs in the hospital
	Lack of adequate resources and quality assurance
Clinical practice variation	Sepsis guidelines and documentation
	Individual care practices and HCP comfort levels
Health care providers' perceptions about FAST-M	Understanding of the FAST-M bundle
	Perceptions about significance of FAST-M
	Identifying solutions to the application of FAST-M
Development of HCPs readiness for FAST-M implementation	Understanding and identifying gaps
	Consensus building for FAST-M implementation

4.4.1. Challenges in existing system

4.4.1.1.Shortage of HCPs in the hospital

A majority of the study participants reported challenges in the existing sepsis management practices. The major challenge reported by HCPs is the increased volume of patients coming to the obstetrics and gynecology inpatient wards and emergency room. The increased number of patients exaggerates the workload on HCPs. The issue of a high patient to doctors' ratio that is 6:1; and a high patient to nurses' ratio that is 20:1 was raised by a majority of study participants. There is a shortage of health workforce considering the influx of patients in the unit which is a hindering factor for provision of quality healthcare services.

"Being a tertiary level hospital, being a civil hospital and the main hospital, we are facing an increase patients flow on daily basis" (KII- Senior Registrar- OBGYN)

"On floor, we have 6 doctors, and you think how many patients are there. Sometimes we have 36 admissions; sometimes we have around 40 admissions. So, you can see for doctors to patients ratio it is around 6:1 and for staff, they are sometimes present and sometimes not" (KII- Senior Registrar)

HCPs identified that there is a considerable shortage of nurses in the hospital for the care of patients. The importance of nurse's role was acknowledged by all the key informants and focus group participants, and they emphasised the shortage of nurses for sepsis management in the hospital as a key challenge, with only one or two nurses assigned to 20 patients in each shift. As it was stated:

"Yes, we are short of staff nurses. Look, if we have around 32 to 40 patients so there is only one nurse for their care or hardly two" (KII- Staff Nurse)

"In the emergency room, we do not have staff nurses available, so the doctor is responsible for maintaining IV line and catheterisation. If there will be staff nurses available in the ER so they can help us with IV line, sending lab investigations and with catheterisation. But this is a bitter truth that we have a shortage of staff. No doubt the staff present in wards does work like they do patient's monitoring, IV medications and follow doctor's instructions" (KII- Admin Registrar)

4.4.1.2.Lack of adequate resources and quality assurance

HCPs, mainly doctors, and nurses working in the hospital, voiced concerns over the scarcity of resources. All HCPs indicated their workplace as a low-resource setting and described private hospitals as having '*more resources than us*'. Despite the disparity in resources, HCPs generally believed they were maximising sepsis management within the limits of what was possible in their unit.

"...this is not a private hospital and unit like that. This is a civil hospital and we have to face many things. Our surroundings are not as favorable as it seems. We have to struggle a lot, and this is the cause of delay in things. But anyways, we are trying our best to manage sepsis cases within our available resources" (KII- Registrar Admin)

A majority of the patients present with complications and require intensive monitoring. There are high dependency units (HDUs) and intensive care units (ICUs) in the hospital for critical

monitoring of the patients though the shortage of spaces in HDU and ICU is a challenge, as reported by the study participants.

"We have monitors available but not according to the patients need. We cannot monitor all the patients and we do it according to the severity of patient's condition. We have only two HDU beds and this is a challenge for us" (KII- Senior Registrar)

"We have 12 surgical and 12 medicine beds in ICUs altogether in LUMHS for all units. We face constraints of getting ICU beds for critical patients" (FGD- HOD)

The OBGYN units have their own set of routines or guidelines that help HCPs organise their practices and influence how and when care is provided. When asked about barriers and enablers in sepsis management, HCPs talked about the lack of awareness of policies that made it difficult to identify and manage sepsis cases. This concern was raised by a few key informants that a number of HCPs working in the facility are unaware of the hospital policies. Though all the key informants noted the presence of policies and guidelines for sepsis management, only a few (6/16) key informants had detailed knowledge about the policies or guidelines related to sepsis management. The other departments in the hospital, for example medical ICU, surgical ICU, labour room, emergency room, and inpatient wards follow different guidelines for sepsis management. This hinders the care given to patients because no unified system or protocol exists in the facility for sepsis management.

Few people know the correct knowledge of sepsis. People should refresh their knowledge and there should be combined meetings of all units, so we have a protocol for CVP lines, high flow oxygen administration and antibiotics. There should be a set vision for this" (KII- Senior Registrar)

It was also reported by health administrator of the facility that the non-performance and non-seriousness of HCPs towards their job responsibilities is an impeding factor in sepsis management and causes frustration and burnout among them.

"Our doctors are in a hurry to quickly complete their work and go, because they have a lot of burden" (KII- Healthcare Administrator)

All HCPs stressed on compromised quality of resources available in the facility. They reported that the quality and efficiency of antibiotics are lacking and there are hurdles in the obtainability of antibiotics. This delays patients' management and the patient care process.

"The most important is the below standard antibiotics provided here" (FGD- Associate Professor OBGYN)

This is honest truth that the antibiotics we get from outside, from a good company, there is a difference in the quality and efficiency. We are not getting good results with antibiotics as we are supposed to" (KII- Senior Registrar)

HCPs also highlighted the constraints faced by the level of patients. The collection and transport of blood samples to laboratories is a complicated process. The patient's samples are transferred to laboratories by the hospital staff at the selected time of the day. If any patient's investigation is required after that fixed set time, it is transferred to laboratory through patients' attendants. Consequently, this delays patients' investigational process.

"We have developed a system that in morning, the ward boy will collect samples from each ward, it goes to university hospital which doesn't charge anything. If any sample is missed and sent

later, we send them through patient's attendants, and they are charged" (KII-Health Administrator)

HCPs also deliberated on patient's ability to afford for lab investigations. Most of the patients coming to the facility belong to the low-income class group considering their socio-economic background. Though LUMHS is a public health facility, and a majority of services are provided in the hospital without charge, there are few investigations for which patients are required to pay fees for services, for example blood culture and serum lactate tests.

"Our patients are poor, and they cannot afford investigations like culture test and serum lactate. They are costly so people are reluctant for these blood tests" (KII- Registrar)

"These investigations should be free for patients. Culture bottles are so expensive, and people are so poor that they go and throw them away" (FGD- Registrar Admin)

4.4.2. Clinical practice Variation

4.4.2.1.Sepsis guidelines and documentation

The interview participants reported that the OBGYN units follow Royal College of Gynaecology (RCOG) guidelines. The RCOG guiding principles provide information about the risk factors of maternal sepsis, the basic vital signs and identification of maternal sepsis, clinical features suggestive of sepsis, investigations to rule out maternal sepsis, and the specific antimicrobial therapy for management [320]. Despite the presence of guidelines in the hospital, the early identification and management of sepsis is a huge struggle.

"MEOWS chart was there in RCOG guidelines, and we used to do that, but as you have these FAST-M tools, we didn't use to do this way. We used to do this very haphazardly" (KII- Assistant Professor)

The **F** in the pneumonic of FAST-M denotes fluid resuscitation. This administration of intravenous fluids can be a key intervention for management of sepsis if it is associated with hypotension, however, rapid fluid administration is more complex in pregnant women if there are other co-existing medical problems such as eclampsia. These concerns and delays in fluid administration in the existing system were identified by HCPs. This delay was because of the HCPs anticipated apprehensions and concerns related to complications of fluid therapy as stated:

"In existing practices, we are giving the antibiotics, but this fluid therapy sometimes gets delayed as we are concerned about the development of pulmonary edema in septic patients after giving fluids" (KII- Registrar)

"Sometimes these gynae people get worried that whether it is sepsis or cardiac issue and whether we should give fluids or not as the patient can have fluid overload" (FGD- Assistant Professor-Medicine)

Most of the study participants stated that they are following similar procedures and guidelines as provided in FAST-M bundle care tools. Yet, they identified a lack of documentation in the existing practices.

"We do not follow the step wise procedure and documentation, but we follow the same thing as we do respiratory rate, BP, GCS and etc." (KII- Fellow-ICU)

4.4.2.2.Individual care practices and HCP comfort levels

There is a hierarchy of doctors in the hospital from senior to junior level based on their qualifications and experience. The hospital units are managed by Professors who are head of department of the units. The upper category in the hierarchy of doctors comprises all the faculty staff including associate professors and assistant professors, the second upper category in the hierarchy covers registrar doctors, who support postgraduate residents and house officers who come for their internship programme following completion of medical training. These all categories of doctors have diverse job roles for the management of patients as stated:

"We have faculties, and we have them on senior level, then we have our Registrars, PGs and HOs, so suppose senior level look for all the patients, do patients rounds and check and advice for the patients. Registrars have their assigned patients' beds. The registrars are assigned according to the number of beds present and occupied. These registrars are accompanied by PGs. Suppose if any registrar is assigned 12 beds, she gets two PGs who can look after 6-6 beds. So, the main people who are on the floor are registrars and PGs who manage patients according to the faculty's advice" (KII- Associate Professor)

Within the hospital, it was observed that HCPs' approach to sepsis management was not consistent. Clinical practice variation refers to patients receiving differing care depending on when, where, and by whom they are being cared for, despite evidence for best practice. One HCP noted that:

"Some doctors send lactate and culture test, and others don't... this may be because of patient's financial affordability. And this variation is also there when we prescribe antibiotics. Every doctor has their own practice" (KII- Registrar)

Some nurses voiced concerns about timely management of patients. HCPs reported that patients monitoring gets delayed due to shortage of staff nurses to monitor the patients. There are less senior and skilled nurses in the unit to identify and assess the criticality of the patient. The novice nurses are inexpert to take care of the patients and they also lack skills towards sepsis care.

"Senior nurse makes the schedule and look after the labor room as well as ward because of their competencies. We have new nurses as well but it is obvious that their understanding and knowledge of the work is less than ours" (KII- Staff nurse)

"We get senior and competent nurses in the morning shift because there is more work in morning shifts" (KII- Senior Registrar)

Unit practice norms, combined with the HCPs' personal comfort, confidence, and skills, inform their practices about sepsis management. HCPs also have varying definitions and criteria for which patients are transferred to ICUs and to sort this process uninterrupted, HODs decide on the eligibility criteria for admission to ICU.

4.4.3. Health care provider's perceptions about FAST-M

4.4.3.1. Understanding of the FAST-M bundle

HCPs reported that they were informed about FAST-M bundle care tools from their head of departments who are keen to test this intervention in their local setting. Some HCPs had more opportunities to learn about the components of FAST-M bundle, but other HCPs specifically staff nurses did not know about the FAST-M tools. While all doctors reported having a baseline

understanding of FAST-M tools and its components including Maternal Early Obstetrics Warning System (MEOWS) chart, decision tool and treatment tool, they expressed the need of additional understanding of FAST-M tools before its implementation. All HCPs recommended providing additional education and training sessions to HCPs to address such gaps.

"Whatever HCPs are doing, they are doing at their own, they are also trained but they are not very well trained, so training will help them to manage patients well according to the guidelines" (KII- OR Doctor)

Healthcare administrators and doctors employed at the hospital displayed their interest in support for implementation of FAST-M intervention, whereas nurses most frequently cited satisfaction with their existing practices.

"Our OBGYN doctors are already providing us the charts for monitoring of cesarean deliveries, for baby's monitoring and there are different charts for monitoring. We are already managing our patients well" (FGD- Nurse)

Majority of the key-informants highlighted positive influences of implementation of FAST-M bundle care tools on existing policies of sepsis management in the hospital as one of them stated:

"There is no current guideline followed in the hospital and this has come as a sort of guideline that can be used for sepsis management" (KII- OR Doctor)

4.4.3.2.Perceptions about significance of FAST-M

HCPs attitudes towards FAST-M implementation were positive and supportive. All HCPs shared positive perceptions about timely sepsis identification and management through classification of

patients using MEOWS chart's triggers as red and yellow flags. The use of colours such as red flags and yellow flags indicating cutoff values facilitates HCPs in identifying and categorising patients. HCPs identified colour demonstration in the MEOWs chart as a major enabler in identification of sepsis patients.

"Now we know that there is a red and yellow flag, and if patient is in severe sepsis we have to send the samples within an hour and have to give antibiotic and fluids as described in the protocol" (KII- Registrar)

"It is very easy because of colors we are getting alert on red and yellow flags. This is very easy and understandable" (KII- Senior Registrar)

HCPs believed that FAST-M tools improve knowledge of HCPs as the tools include everything related to the identification and management of the patients with maternal sepsis. The flow of the tools was appreciated by HCPs and they also stated that this organised flow of FAST-M tools will save time in sepsis management.

"This tool provides specifications about fluid therapy and antibiotics administration with specific time. It has improved our knowledge" (KII- Nurse)

HCPs also indicated the significance of FAST-M tools as being initiated by any healthcare provider including the nurse. There is no requirement of a doctor to initiate the bundle care tools. The staff nurses and even the trainee dispensers, who are available in the unit as helpers to staff nurses, can initiate the MEOWs chart for identification of the cases.

"The good thing I see in this FAST-M is that even the nurse can start this bundle care" (FGD-HOD Gynae)

Generally, most HCPs stated that the FAST-M intervention will help in sharing tasks between HCPs and it will increase the accountability of HCPs to perform their responsibilities

"It should be done because from staff till doctor everybody will be responsible for their work and will document each and every thing. We get tired of emphasising this" (KII- ICU Fellow)

One of the KIs emphasised the quality of this tool as being non-invasive. Patients would easily accept this intervention and HCPs would not hesitate to initiate it. It can be easily accepted and implemented.

"The intervention that has been introduced, it is totally non-invasive and it is the same work that we do in our daily routine, so we will have no problems in its implementation" (KII- ICU Fellow)

All the key-informants and focus group participants articulated patients' benefits through FAST-M implementation. They emphasised that the early identification and management of maternal sepsis through the FAST-M tools may decrease patients' length of stay in the hospital, and eventually decreasing the length of stay would benefit patients in providing physical, economic and psychological advantages. Ultimately, this would help in decreasing maternal morbidities and mortalities in the long run.

"...it will benefit patient that it will help in decreasing the stay of patients and their exposure will be reduced. This will reduce morbidities and mortalities in the long run" (KII- Registrar)

4.4.3.3. Identifying solutions to the application of FAST-M

Some HCPs were doubtful of the practicality of intervention in the prolonged and continuous implementation due to resource restrictions (e.g, quality of available antibiotics, shortage of staffing, shortage of equipment and monitors). The inability to overcome these limitations led to a common attitude that:

"Nothing is sufficient from top to bottom, we try our level best to provide but we do not have monitors, we have hurdles for lab investigations, there are issues of availability of nurses and antibiotics, there are many technical gaps" (KII- Registrar Admin)

All respondents suggested that in order to strengthen the significance of FAST-M intervention for early identification of sepsis, the inclusion of the variable of oxygen saturation in the MEOWS chart, with appropriate cut off values, would be important. This was because pulse oximetry is now available routinely in the unit and may be an important indicator of clinical deterioration. This feedback was consistently given by all HCPs.

"Oxygen saturation is mandatory to include in the MEOWs chart for monitoring of patient" (FGD- Assistant Professor- Medicine)

It was informed through HCPs working in the medicine unit that sepsis guidelines followed in their unit include an addition of steroid therapy and inotrope support for sepsis management.

"You should include support because sometimes when we give fluids and antibiotics, but still patient is not maintaining the blood pressure because most of the times septic patients arrives late, so you should include source plus support in S. so both of the things will be included. Because support is the most important" (FGD- Assistant Professor- Medicine)

All HCPs agreed over the use of ceftriaxone as first choice of antibiotics in FAST-M treatment bundle based on its cost and availability for patients.

"We give Ceftriaxone straight away as it is freely available. We give 2g Ceftriaxone and for those patients whose culture is sent, we wait for their blood culture reports to change antibiotics accordingly. Otherwise, our patient mostly responds to ceftriaxone" (KII- Senior Registrar)

Few participants specified that they use piperacillin/tazobactam and meropenem for management of the confirmed cases of sepsis due to their beneficial results in such patients, yet the patients pay out of pocket for the cost of these antibiotics. Thus, meropenem and piperacillin/tazobactam were proposed as the second choice of antibiotics due to their availability and cost.

"...sometimes when we do not have availability of meropenem so we give ceftriaxone to the patients, which is easily available free of cost for patients" (KII- Senior Registrar)

HCPs also suggested involving nursing interns and trainee dispensers who come for their training and work without wages. The involvement of nursing interns and trainee dispensers would reduce the problem of shortage of staffing in the unit and they would be employed to implement the FAST-M intervention without added investment for human resources.

"We get one or two girls from BScN programmeme, but we can talk to the dean in account and there are many people who can help us with this" (FGD- Health Administrator)

The focus group participants identified the need of increasing awareness which is the key to implementation of the FAST-M intervention. The stakeholders emphasised understanding of

HCPs about the significance of FAST-M bundle care tools as a key to effective implementation in future. One of the group participants suggested:

"We can make big boards and we can involve everyone and give them awareness. And we can provide examples to them that how it was implemented in past in different setting showing good outcomes" (FGD-HOD Gynae)

Moreover, the inclusion of MEOWs charts in patients' Medical Record files of the hospital was emphasised by every group member involved in the discussion.

"We will include MEOWS chart in all patients' files so our doctors can easily record the findings on MEOWS chart which will alert them about patient's condition" (FGD- HOD Gynae)

4.4.4. HCPs readiness for FAST-M implementation

The HCPs readiness towards FAST-M intervention started with the drive of identification of requirements for FAST-M adaptation and concluded with the consensus building of HCPs for its implementation.

4.4.4.1.Understanding and identifying gaps

HCPs acknowledged that successful implementation of the FAST-M intervention would require health care facility to be well-equipped, including both the availability of equipment and trained HCPs. Other key challenges to the successful implementation of FAST-M intervention are related to logistics, including shortage of human resources and inadequate funds for procuring monitors for assessments, antibiotics and lab investigations. One of the most frequent concerns around

FAST-M implementation included the need to train HCPs including doctors, nurses, and auxiliary support staff to enable them to set up and sustain the services. Further, study participants suggested that a multidisciplinary approach would be useful to ensure that all professionals including the team of doctors, nurses, administrators from different units e.g. medicine, intensive care units, labour room, laboratory and operating room are working together for the successful implementation of FAST-M.

"In team, one person should be from administration, to who if we complain related for our hurdles and queries, so he can work on them, one person should be from laboratory, one should be from nursing staff and one should be from doctors, who can take all the things to higher levels and work on them" (KII- Registrar Admin)

HCPs argued that there are high costs associated with the implementation of FAST-M intervention. Providers further explained that high costs of laboratory investigations would be a limiting factor as it would cause additional anxiety of financial burden to the patients. On the other hand, a few health professionals confirmed that costs would not be a major concern if there was buy-in from hospital administration for the patient's requirements. HCPs mentioned that the initial investments may be higher for procuring required equipment like monitors and apparatus required for monitoring of patients.

"Ceftriaxone is easily available in our hospital, but we are not sure about its quality. But for the critical patients if we see any red flags, we can arrange their requirements from our donations. In our unit, we are doing this for critical patients" (FGD-HOD-Gynae)

4.4.4.2.Consensus building for FAST-M implementation

The focus group participants displayed readiness for implementation of FAST-M interventiom in their local context by developing consensus on resolutions and approaches to the perceived challenges they could encounter during the implementation. The focus group discussion provided the opportunity to reflect on the anticipated challenges and how they may be able to successfully implement in their setting with the available resources. HCPs decided to implement FAST-M intervention in their setting, and they also acknowledged the importance of a training programme for HCPs to implement FAST-M bundle care tools in their setting. It was recognised that the FAST-M protocol comprises similar practices but in an organised and structured way and was well-regarded by all HCPs. They valued the implication of FAST-M intervention as stated:

"We are already doing these all things except documentation so it will be easy to apply. You know the guidelines, you have got an algorithm then it would be difficult to miss any patient. So it's a very good thing and this can be implemented. We have everything but there should be training and if you give that it would be easy to implement: (FGD- Associate Professor-Medicine)

4.5. Discussion

Our findings revealed several potential facilitators for the uptake of FAST-M intervention. Firstly, the HCPs had highly favorable perceptions regarding the use of FAST-M bundle care tools. The major advantage identified was illustration of coloured codes in the MEOWs chart such as red and yellow flags that assist in categorisation of patients according to severity of their symptoms. The early identification of patients with maternal sepsis through MEOWs chart facilitates timely management of patients using decision and treatment tools.

Evolving morbidity can be difficult to recognise in the obstetric population because of the normal changes in peripartum physiology [321]. Delays in recognition of patient deterioration and initiation of treatment lead to worse outcomes in maternal populations [321]. Early Warning Systems (EWS) have been used since 1999 in the general patient population to identify clinical deterioration [188], though the Maternal Early Obstetric Warning System (MEOWS) has been promoted with the aim to reduce maternal morbidity and mortality and improve clinical outcomes [195]. The FAST-M intervention comprises different components for the recognition and management of maternal sepsis.

During the development of the FAST-M bundle through a modified Delphi process, oxygen saturation was mostly perceived as of reasonable importance. Though, the feasibility of implementing this element in low-resource settings limited its usefulness due to the non-availability of pulse oximeters at that time in many low-resource settings [222]. However, considering the outbreak of COVID-19 infection and the availability of pulse oximeters at the study site, it was recommended to include oxygen saturation in the MEOWs chart to determine patient's clinical condition. The inclusion of oxygen saturation in the MEOWs chart is considered important based on the existing sepsis management practices of the facility. Moreover, the element of oxygen saturation is a significant indicator in the identification of patients' clinical conditions. Therefore, the supplementary element of oxygen saturation has been added to the bundle care tools prior to its implementation **(Appendix 4.4).**

The MEOWS chart in the FAST-M intervention tracks physiological parameters and evolving morbidity and once a predetermined threshold reaches, it triggers evaluation by a HCP [195]. The healthcare professional determines further evaluation, treatment, or intervention as necessary through the use of decision tool and treatment bundle [322]. The systematic approach for screening and management of maternal sepsis patients through the FAST-M intervention supports its implementation in the low-resource setting in Pakistan.

All HCPs acknowledged the FAST-M bundle care tools as easy to use as they do not require any invasive procedures to identify suspected maternal sepsis cases and trigger appropriate actions. Second, the HCPs deliberated about long-term improvement in patient's health outcomes through the use of FAST-M intervention such as the decrease in length of patients' stay at the hospital, and improvement in maternal morbidities and mortalities overall.

Our study findings identified that the shortage of HCPs hindered many aspects of sepsis care delivery and may be a critical barrier to any intervention. As the hospital provides free of charge care to patients, there is a high influx of patients in the facility. This high volume of patients' increases workload on HCPs and eventually the shortage of healthcare workers is associated with adverse patient outcomes and comprised quality in patient care [323]. Therefore, all the study participants suggested involving nursing interns, trainee dispensers, and other available human resources to reduce doctors' and nurses' workload through shared responsibilities and employing a task-sharing approach. The approach of task sharing of specialists with trained non-specialist workers has provided positive outcomes in the improvement of patient care, reduced morbidity and mortality rates, and cost-effectiveness [323].

Accordingly, a training programmeme has been planned as part of the implementation of the FAST-M intervention so all HCPs have the required knowledge to manage sepsis cases according to the FAST-M approach, making practice uniform across teams in the facility and ensuring the sustainability of FAST-M intervention as a long-term benefit for patients.

The source identification denoted as ‘S’ in the FAST-M bundle requires a detailed history and examination to identify the infection source along with the targeted further investigations. The training programmeme will provide an opportunity to improve this aspect, including the significance of taking a detailed history and examination and documenting them. This is very important to provide quality care and to help HCPs to plan a patient’s treatment to maintain the continuum of care [324].

The FAST-M implementation in districts of Malawi provided useful example of effective implementation where champions played a significant role in implementing FAST-M intervention, and their contribution for intervention provided day-to-day oversight of healthcare practitioners’ practice [300]. Our study findings suggest that the clinical practice variations among HCPs is a potential major hindering factor in implementation of FAST-M intervention, and yet we decided to select maternal sepsis champions. These champions could potentially standardise the practices for the management of maternal sepsis in all the departments managing such cases. To continue to strengthen the implementation of this intervention, champions will be selected during training programme based on the consensus of HCPs involved in the training of FAST-M intervention.

Moreover, the HCPs were concerned about the compromised quality of available resources such as antibiotics and laboratory investigations which voiced their uncertainty to support FAST-M intervention. They felt that the hospital's environment and the quality of available resources did not support patients' clinical management. It was identified that the hospital system set for laboratory investigations is lengthy and time-consuming.

While the quality of health services within the clinical setting is imperative to provide effective care to the patients [325]. Study findings also suggest that the treatment cost adds to the financial burden of patients and leads to the discontinuation of medical treatment [326]. Thus, the practicability of intervention depends on the facility environment, availability of resources and its affordability for implementation and the readiness of 'healthcare administrators' who are accountable for provision of healthcare supplies. The role of healthcare administrators in upgrading the system is quite significant to avoid barriers to implementation. Hence, the healthcare administrators provided assurance for provision of supplies and resources as a stance to reduce maternal sepsis rate at their healthcare setting and will be fully included in the implementation process, including the training and champion network.

Some specialists raised consideration of broadening the bundle to include more comprehensive sepsis care including consideration of steroid therapy and inotrope support. As part of the adaptation process, this issue was fully discussed with a range of local and international experts from the gynecology and intensive care fields and it was decided that these aspects would be most appropriate only for specialist doctors, normally in an ICU environment, so would not be

suitable for inclusion in the first response bundle. However, the management of patients using steroids would be emphasised during the training programme to delineate its role in the management of COVID-19 as a distinct situation from other bacterial causes of maternal sepsis to ensure rational and evidence based steroid use.

Antibiotics administration is one of the easily available, free of cost and important components of FAST-M treatment bundle for sepsis management. The FAST-M treatment bundle applied in the earlier study conducted in Malawi [300] was therefore of the important. We explored healthcare providers' views regarding use of antibiotics in their local setting for treatment of maternal sepsis. It was identified that Ceftriaxone is easily available free of cost to patients and it provides positive results in treatment of sepsis. Thus, it was agreed to use ceftriaxone as first choice of antibiotics in FAST-M treatment bundle. Moreover, it was also acknowledged that piperacillin/tazobactam and meropenem are used for treatment of confirmed sepsis cases due to the current understanding of the organisms responsible for maternal sepsis and the antimicrobial resistance patterns. Though patients pay out of pocket for the cost of these antibiotics. Thus, m\eropenem and piperacillin/tazobactam were proposed as the second choice of antibiotics due to their availability and cost. The Malawian version of FAST-M treatment bundle was therefore modified for locally appropriate antibiotic guidelines **(Appendix 4.4).**

The importance of an explicit sepsis care policy was discovered during interviews and FGD to assist in standardising infection regulations in the hospital. It was identified that the FAST-M intervention can serve as a guiding policy to provide evidence-based information to support

clinical decision-making. Therefore, a unified system of FAST-M intervention for sepsis care in the facility for maternal patients can serve as a standard tool for maternal sepsis management. The major strength of this study is the use of CFIR that guided the researchers' focus, starting with observations and documenting from a broad health systems and programme implementation perspective, becoming more specific in the later performed interviews and FGD. Moreover, participation of HCPs from several levels to ask their feedback on the research question, and by interviewing HCPs about their experiences helped in gaining better insights about their practices and perceptions.

The study also has some limitations. First, the study focused only on the perspective of the HCPs who were involved in the management and treatment of maternal sepsis patients; therefore, the sample size was limited and important perspectives from patients and their families could have been missed. Secondly, the intervention would be implemented in only one study setting in Pakistan at this time. However, it is notable that this site serves a diverse population from the urban and rural areas of the province of Sindh. The FAST-M tools were specifically adapted according to the existing sepsis practices of the current study setting. Future studies to explore feasibility of FAST-M bundle would require adaptation prior to implementing in other low-resource settings of Pakistan.

We believe that it is possible to implement the FAST-M intervention in low-resource settings of Pakistan and we recommend several strategies to address the challenges facilities may face in their local context. The hospital, leadership and HCPs require collaboration to work as a multidisciplinary team to advance sepsis management practices and understand its implications.

This could be achieved through development and dissemination of FAST-M intervention as a sepsis management guideline in the facility.

The distribution of supportive resources to provide education to all HCPs including doctors, nurses and healthcare administrators about FAST-M tools is required to increase knowledge and awareness of FAST-M bundle. Also, facilities will require selected champions for implementation of the FAST-M intervention.

Overall, bundle care tools have the potential to enhance improvements in sepsis care. However, the implementation challenges posed by these bundles should be examined, especially in low-resource settings, where facilities and services have not yet flourished.

We identified facilitators and barriers for implementation of this intervention from only one of the facilities in Pakistan selected as our study site. Future research is needed to understand how implementation of this adapted FAST-M intervention works when implemented as part of care, and to rigorously evaluate its effectiveness and key implementation outcomes such as the sustainability of the intervention.

4.6. Conclusion

The FAST-M maternal sepsis bundle has the potential to be used as an integrated strategy for early recognition and management of maternal sepsis in low resource health settings in Pakistan. We found several barriers and facilitators for its implementation and suggested key adaptations to the intervention which we perceive will help address these barriers.

Based on this formative research, the FAST-M tools and implementation approach in their adapted format will be implemented in the selected health facility and mixed-methods research conducted to assess the feasibility of implementing these adapted tools as part of the health care system in Pakistan.

This exploratory study found that the FAST-M bundle has the potential to be implemented in its adapted form. An inductive analysis approach provided rich information to plan subsequent phase, training programmes and modify the intervention according to local context using the vast evidence gained by interviewing and discussing with a number of participants. Having these discussions helped in making decisions pertaining to the adaptation of FAST-M intervention. For instance, the recommendations for the inclusion of steroids and inotropic support in FAST-M bundle were consulted with local and international health experts and the consensus was that these components are not suitable to be included in a first-response bundle. These findings were imperative as they assisted in the next phase of this study, the implementation of the FAST-M intervention.

Chapter Five

EARLY RECOGNITION AND MANAGEMENT OF MATERNAL SEPSIS IN PAKISTAN: A FEASIBILITY STUDY OF THE IMPLEMENTATION OF THE FAST-M INTERVENTION

Continuing from the findings in the previous chapter, which provided evidence for the potential the adapted FAST-M intervention had for successful implementation in the local setting, this chapter leads into the next phase: the feasibility of the intervention. The feasibility was assessed by comparing the study outcomes between baseline and intervention phase using quantitative methods. In this chapter, I describe the methodology and study setting/design, the data collection and analysis process, report on the findings and discuss their implications in the local setting.

Submitted paper

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Authors contributions: Sheikh Irfan and David Lissauer designed the study processes. Raheel Sikandar, Fahmida Parveen, Nazia Memon and Sehrish Khan provided support in data collection. Amir Raza, Sheikh Irfan Ghulam Kubra, Bakhtawar Khowaja, Arshia Jehangir and Daayl Mirza carried out the data analysis and interpretation. Sheikh Irfan, Ghulam Kubra, Amir Raza, and Bakhtawar Khowaja took the lead in writing the manuscript. Arri Coomarasamy, David Lissauer, Catherine Dunlop, James Cheshire, Lumaan Sheikh, Raheel Sikandar, Rubina Barolia, Sadia Shakoor, Sarah Saleem, Fahmida Parveen reviewed the manuscript and provided feedback.

5.1. Abstract

Objective: Maternal sepsis is the 3rd leading cause of maternal mortality globally. This study aimed to determine feasibility of FAST-M (**F**luids, **A**ntibiotics, **S**ource identification and treatment, **T**ransfer, and **M**onitoring) intervention for early identification and management of maternal sepsis in Pakistan. The FAST-M intervention consists of maternal sepsis screening tools, treatment bundle and implementation program.

Design and setting: A feasibility study with before and after design was conducted in women with suspected maternal sepsis admitted at the LUMHS hospital Hyderabad. The study outcomes were compared between baseline and intervention phase. In the baseline phase (2 months), the existing sepsis care practices were recorded, followed by a training program for healthcare providers on the application of FAST-M tools. These tools were implemented in the intervention phase (4 months) to assess any change in clinical practices compared to the baseline phase.

Results: During the FAST-M implementation, 439 women were included in the study. 242/439 were suspected maternal infection cases, and 138/242 were women with suspected maternal sepsis. The FAST-M bundle was implemented in women with suspected maternal sepsis. Following the FAST-M intervention, significant changes were observed. Improvements were seen in the monitoring of oxygen saturation measurements [25.5% vs 100%; difference: 74%; 95% CI:68.4%-80.5% p<0.01], fetal heart rate assessment [58% vs100%; difference:42.0%; 95%CI: 33.7% to 50.3%; p=<0.01], and measurement of urine output [76.5% vs 100%; difference 23.5%; 95%CI: 17.6% to 29.4%; p<0.01]). Women with suspected maternal sepsis

received all components of the treatment bundle within one hour of sepsis recognition [0% vs70.5%; difference 70.5%; 95%CI: 60.4% to 80.6%; p<0.01].

Conclusion: Implementation of the FAST-M intervention was feasible and significantly improved the quality of maternal sepsis care, including enhanced early identification and management of maternal sepsis.

5.2. Introduction

Maternal sepsis is ‘a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the post-partum period [42]. Worldwide, it’s the 3rd most common cause of maternal mortality and represents around 11% of maternal deaths [5]. Pregnant patients and those that have recently delivered are more susceptible to maternal infections that can rapidly progress towards sepsis [50,126]. The maternal mortality caused by maternal infections has been reported to be higher in Low- and Middle-income countries (LMICs) than High-Income countries (HICs) i.e., 10.7% in LMICS vs 4.7% in HICs [5].

Modelling studies, based on currently available data, observed that globally around 17000 maternal deaths per year may be attributed to maternal sepsis and other maternal infections (MSMI) [16,327]. Approximately 5.7 million women suffered complications of maternal sepsis globally in 2017 [58]. Annually, 99% of the 302,000 maternal deaths occurred in LMICs [8], with the highest rates reported in Africa and Asia [328]. The reported maternal mortality ratio (MMR) in Pakistan is 186 per 100,000 live births in 2020 [329], and sepsis ranked as the 3rd leading cause of maternal deaths (16.3%) [43] following haemorrhage, and eclampsia [5].

Improving maternal outcome is critical in Pakistan, which failed to achieve Millennium Development Goals (MDGs) 4 and 5 [330]. Pakistan is now signatory to goal 3 of the Sustainable Development Goal (SDG) which aims to reduce maternal mortality to 70/100,000 by 2030 [7].

Whilst the country shows significant improvements in some health indicators [331], the rate of reduction in infant and maternal mortality is low to achieve these indicators in given time [332].

Maternal sepsis has been recognised as a global health priority, and attempts were made to reduce its burden, particularly in LMICs [333]. In 2015, the Global maternal and neonatal sepsis initiative was introduced by the WHO and other partners to design strategies that could help in improving the recognition and management of maternal and neonatal sepsis in low-resource settings [333-335]. This initiative aimed to develop and test the effective strategies to prevent, detect, and manage the maternal and neonatal deaths caused by sepsis [334]. This included the key recommendation to develop a sepsis care bundle specific to maternal population.

The use of these care bundles in the management of sepsis has been found to reduce mortality and improve patient outcomes in high-income countries [209,336]. Most notably, the surviving sepsis campaign (SSC) bundles [215,337], as well as the UK Sepsis Trusts' Sepsis 6 bundle [338] have been widely used [336]. Despite this, there was no sepsis care bundle in particular for the maternal population which can be implemented efficiently in low-resource settings [203,339-340].

To address this, a care bundle for treatment of maternal sepsis in low resource settings was developed by an international health expert panel [222]. The bundle was named “FAST-M” and selected components were Fluids, Antibiotics, Source identification and control, Transfer to an appropriate level of care, and ongoing Monitoring of mother and neonate” [222]. The

implementation of FAST-M intervention was not only found to be feasible in government healthcare facilities in Malawi but also resulted in improved clinical care [300]. The intervention consists of maternal sepsis screening tools, treatment bundle and implementation program.

In Pakistan, despite existence of national sepsis guidelines (SGP), their uptake remains low especially for obstetric patients [312]. Additionally, there is uncertainty that the existing evidence-based approach to prevent, recognise, and treat maternal sepsis is effective and implementable in a low-resource setting. It was, therefore, planned to determine the feasibility of the FAST-M intervention in the local setting before recommending its implementation at scale. The study protocol and procedures have been described in Chapter 3 of this thesis and published elsewhere [341].

To optimise the use of the FAST-M intervention in Pakistan, a qualitative study described in Chapter 4 of this thesis was conducted to understand the existing sepsis management practices/behaviours, and to identify potential gaps and resource availability in the local setting [342]. Based on the qualitative findings and availability of resources in the facility, the FAST-M bundle care tools which were used in Malawi **[Appendix 3.1]** were modified to plan a practical approach for the implementation of the intervention in our local context. This study aimed to determine whether the FAST-M intervention is feasible to introduce for the early detection and management of maternal sepsis in a low-resource setting in Pakistan. We hypothesise that the FAST-M intervention in this adapted form could be successfully implemented and would then improve maternal sepsis care, including its early recognition and management.

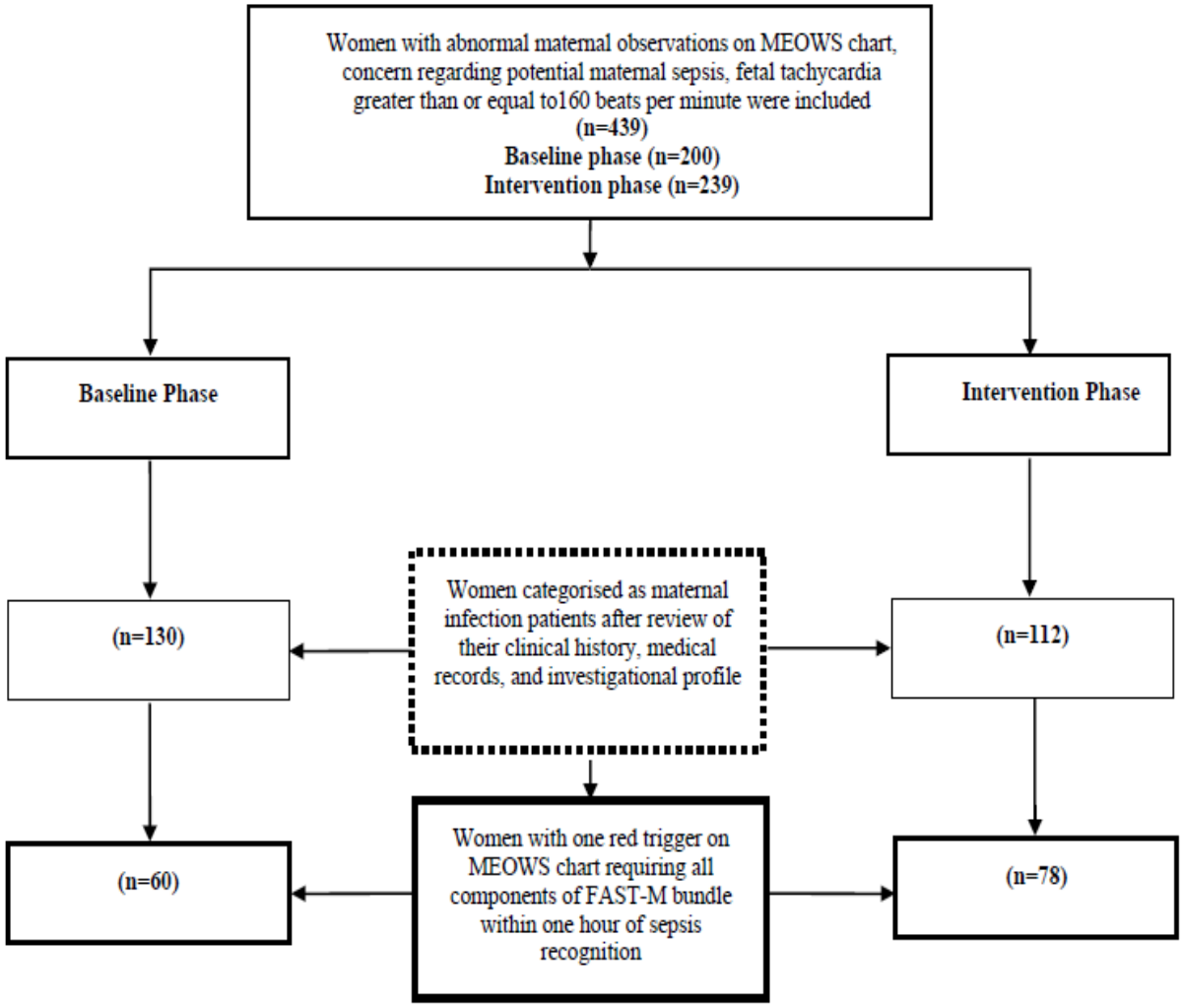
5.3.Methods

A prospective feasibility study with a before and after design was conducted at the Liaquat University of Medical and Health Sciences, (LUMHS) Hyderabad, Pakistan from the period of June 2021 to December 2021. Women admitted to obstetrics and gynecology units of the facility, who were pregnant, or within 6 weeks of miscarriage, ectopic pregnancy, termination of pregnancy, or delivery were considered eligible for this study. These eligible patients were monitored on MEOWS chart during their inpatient admission. Those who had abnormal maternal observations, or healthcare practitioner's concern regarding potential maternal infection, or pregnant women with a fetal tachycardia greater than or equal to 160 beats per minute were included in the study. There were no exclusion criteria for the study.

In the baseline phase, data were collected from facility record using CRF1 (facility audit form) to assess available resources for sepsis management and overall maternal outcomes in last six months **[Appendix 4.3].** Data of patients who were meeting eligibility criteria **(Fig 5.1.)** were recorded on CRF 2 and CRF 3 to assess existing practices for management of maternal sepsis **[Appendices 5.1 & 5.2].** Following this, the intervention phase was carried out. At first, HCPs were trained on the use of FAST-M bundle care tools (MEOWS chart, decision tool and treatment bundle) **[Appendix 4.4]** to early identify and manage sepsis patients. The HCPs training was an ongoing process throughout the implementation of intervention. The FAST-M bundle care tools were then implemented in intervention phase in the facility and data of patients

meeting the eligibility criteria were recorded using CRF 2 and CRF 3 **[Appendices 5.1 & 5.2].** The flow of study participants has been demonstrated in **Fig 5.1.**

Figure 5.1: Flow of participants through the study



Comparisons were made between baseline and intervention phase to assess any change in time and frequency of vital signs monitoring (on MEOWS chart) of patients, and application of all

components of FAST-M bundle care tools **[Appendix 4.4]** within an hour of sepsis recognition. Maternal outcomes (sepsis rate and related mortality) were also compared between baseline and intervention phase.

5.3.1. Intervention:

The planned intervention consisted of 3 components:

1. Maternal sepsis screening tools
2. FAST-M treatment bundle
3. FAST-M implementation Programme

5.3.1.1. Component 1- Maternal sepsis screening tools

Maternal sepsis screening tools included the Modified Early Obstetric Warning Scores chart (MEOWS) and the FAST-M decision tool **[Appendix 3.1]**. MEOWS is the tool adapted by Malawi study based on an early warning score approach and simplified from the approach adopted in UK hospitals [340].

The MEOWS chart used in FAST-M implementation in the districts of Malawi [300] was adapted in the context of Pakistan for this study **[Appendix 4.4]**. The oxygen saturation component was incorporated in the modified MEOWS chart based on the scope of existing practices and the significance of this indicator in the identification of patient's clinical condition.

In the intervention period, eligible patients who had abnormal observations (indicated by a single red or two yellow flags) on MEOWS chart screened for potential sepsis using the FAST-M decision tool **[Appendix 4.4]**. Those who developed a red trigger on the MEOWS chart received an immediate clinical review. FAST-M treatment bundle was initiated within an hour on clinician's judgment on suspicion of sepsis and continued until advised to end the treatment.

Those patients who triggered two yellow flags on the MEOWS chart and were thought to have possible infection were reviewed within three hours. All suspected cases (those without red or two yellow triggers, were still considered for having a risk of sepsis and remained under observation for possible development of red or yellow triggers), these patients were monitored on the MEOWS chart hourly throughout the day and were managed as per local guidelines.

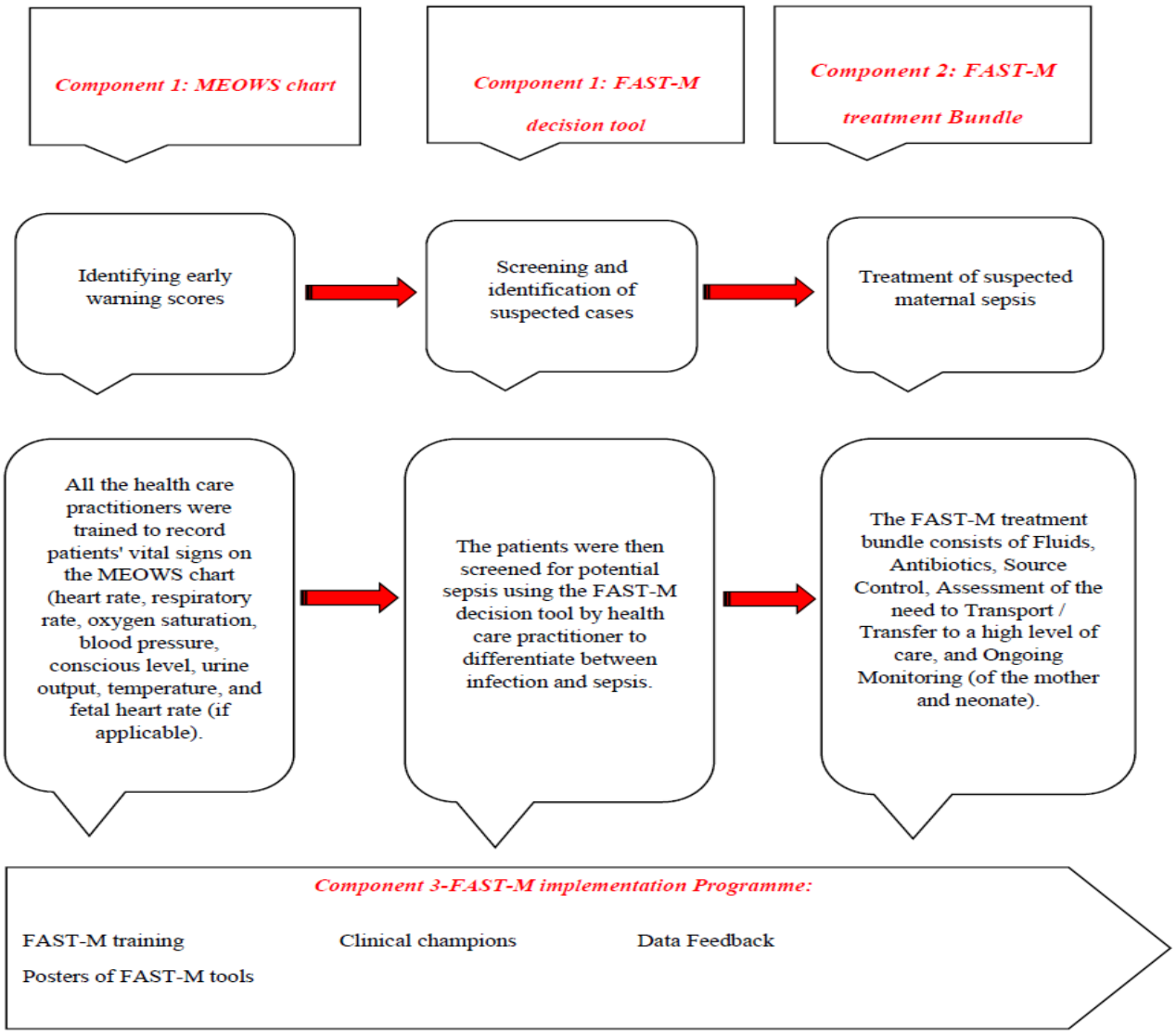
5.3.1.2. Component 2-FAST-M Treatment Bundle

The FAST-M treatment bundle was also adapted in the context of this study. The first and second-line antibiotic therapy guidelines were modified as per the local context during the adaptation phase **(Appendix 4.4)** [342]. Patients with suspected sepsis were commenced immediately on the FAST-M treatment bundle. Each patient's treatment was recorded on the treatment bundle, along with any actions taken and any reasons for not completing certain elements.

5.3.1.3. Component 3-FAST-M implementation Programme

The implementation program **(Figure 5.2)** consisted of the FAST-M training, selection of clinical champions, and feedback achieved from data collected during the baseline phase, and through the facility audit form [**Appendix 4.3**].

Figure 5.2: Components of FAST-M intervention



The two-day training sessions were delivered by health care experts after the completion of the baseline phase, and before the implementation of the FAST-M bundle intervention. The training session started with classroom-based instruction on the FAST-M intervention followed by interactive sessions used as a strategy for hands-on training of healthcare providers on the FAST-M tools. Follow-up training sessions were also conducted every 2 weeks by the local team leads during the implementation of the FAST-M bundle intervention.

Health care practitioners including doctors and nurses (n= 40) working in obstetrics and gynecology units, internal medicine, operating rooms, emergency, and intensive care units of LUMHS hospital were trained to record patients' vital signs on the MEOWS chart (heart rate, respiratory rate, oxygen saturation, blood pressure, conscious level, urine output, temperature, and fetal heart rate (if applicable). These observations were then charted on a MEOWS chart in the inpatient setting and then inserted into the patient's files.

The local clinical champions and team leaders were identified during training programs and trained to take the lead in implementation of the FAST-M intervention at the study site and remained engaged throughout the implementation process. These champions were selected from different hospital departments primarily involved in the management of maternal sepsis patient including obstetrics and gynecology units, emergency department, internal medicine, and intensive care unit. The selected champions included doctors and nurses.

The overarching goal of each champion was to encourage engagement and compliance with the FAST-M bundle. To achieve this goal, champions at each unit were engaged in several key activities that included disseminating knowledge, advocating, navigating boundaries, facilitating consensus, arranging meetings with stakeholders, tracking quality indicators, and developing organisational communication strategies and relationships. The patient records collected were also counter-checked by the clinical champions of the assigned units. These champions also helped the study team in the identification of patients with suspected sepsis and their enrolment in the study.

In addition, training certificates were distributed among the participants. Moreover, FAST-M tools (MEOWS chart, decision, and treatment tool) were displayed in the form of posters throughout all the units involved in the management of maternal sepsis and implementation of FAST-M intervention.

5.3.2. Study Period:

The study comprised a baseline period of two months in which usual practices to detect and treat maternal sepsis existing locally were assessed. The FAST-M training was conducted on the completion of the baseline period. Following training, an intervention period of four months was commenced to assess any change in practice.

5.3.3. Outcomes:

5.3.3.1. Primary process outcomes included

1) The proportion of patients admitted with indications of sepsis, who received appropriate monitoring (full set of vital sign measurements on admission recorded on MEOWS chart).

2) The proportion of women with suspected maternal sepsis receiving the FAST-M treatment bundle (including each bundle component) within 1 hour of identification of sepsis.

5.3.3.2. Secondary outcomes included

1) Rate of vital signs with complete recording of MEOWS chart components [heart rate, respiratory rate, oxygen saturation, blood pressure, mental state, urine output, temperature, and fetal heart rate (in pregnant women)].

2) Rate of application of FAST-M Bundle components [Fluids, Antibiotics, source identification (identified clinically) and control, assessment of the need to transport/ transfer to a high level of care, and ongoing monitoring (of the mother and neonate)].

3) Rate of maternal morbidity and mortality after FAST-M intervention.

5.3.4. Data Collection:

Quantitative data for this feasibility study was collected by a senior research assistant (SRA) on the facility record CRF 1 **[Appendix 4.3.]**, and patient notes including the MEOWS charts, FAST-M decision, and treatment tools onto the relevant paper-based CRFs 2 & 3 **[Appendices 5.1 & 5.2]** following patient consent **[Appendix 5.3].** Data were composed of various outcomes; structural, clinical, organisation, and any adverse events. The data were maintained in an

investigator file to be secured in a locked cabinet. Anonymised and deidentified patients' information recorded on the data collection sheet were recorded in a database located on a secure server.

During the study, biweekly monitoring of the study site was undertaken by the research coordinator, to observe practice, collect feedback and provide updates on the study site's performance, and evaluate any additional training requirements.

5.3.5. Statistical Analysis:

Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Corporation, Armonk, NY, USA) and STATA 14 computer software (Stata Corporation, Texas USA) was used for data processing and statistical analysis. Data were reported in frequency and percentages for categorical observations. A Chi-square test for independence was used to compare components of FAST-M bundle between phases (baseline and intervention). The Chi-square test for trend (P trend) was used to observe the performance during the intervention phase. Statistical significance was determined at $P \leq 0.05$.

Patient and public involvement

Patients were not involved in the design of this study. The FAST-M intervention was implemented on the enrolled patients however, they were not invited to comment on the study design, interpret the results or contribute to writing or editing of this document for accuracy of

findings. Hospital staff participated in the implementation but were not involved in the analysis of findings.

5.4. Results

Vital signs monitoring assessment: 439 women were included in the study (200 in baseline and 239 in the intervention phase), with vital signs recorded on admission **[Table 5.1]**. 242/439 were cases of suspected maternal infection, and 138/242 were women with suspected maternal sepsis. **Figure 5.1** provides the summary of the screening, and enrolment of the study participants.

Table 5.1. Patient's assessment of vital signs on admission (n=439)

Vital Sign	Baseline n=200	Intervention n=239	P-Value
Respiratory rate	194(97%)	239(100%)	0.009
Oxygen Saturations	51(25.5%)	239(100%)	0.0005
Temperature	195(97.5%)	239(100%)	0.019
Heart rate	194(97%)	238(99.6%)	0.051
Systolic BP	196(98%)	239(100%)	0.042
Diastolic BP	196(98%)	239(100%)	0.042
Urine output	153(76.5%)	239(100%)	0.0005
Mental State	196(98%)	238(99.6%)	0.182
Fetal heart rate (in pregnant woman) *	80 (58%)	123 (100%)	0.0005

*For FHR the denominator is 138 in baseline and 123 in the intervention phase.

Following the FAST-M implementation, significant improvements were seen in the assessment of oxygen saturations in the intervention phase compared to the baseline phase [Difference: 74%; 95%CI:68.4%-80.5% p<0.01], fetal heart rate assessment [Difference:42.02%; 95%CI: 33.7% to 50.28%; p=<0.01], measurement of urine output [Difference 23.5%; 95%CI: 17.6% to 29.4%; p<0.01]. Temperature, respiratory rate, heart rate, and blood pressure were measured in 97% of the cases in the baseline phase but showed an increase of almost 3% in the intervention phase [Difference 2.5% 95%CI: 0.34% to 4.66%; p≤0.05]. No significant difference was found in the assessment of mental status in the intervention phase when compared to the baseline phase [Difference 1.6%; 95%CI: -0.52% to 3.7%; p=0.18] **[Appendix 5.4]**.

Baseline characteristics of women with suspected maternal sepsis: 242 women were identified by the FAST-M decision tool as fulfilling the criteria for suspected maternal infection, of which 65% (130/200) women were during the baseline and 46.9% (112/239) during the intervention phase. Out of 242 women with maternal infections, 138 (57%) were identified with suspected maternal sepsis. Sixty of 138 (46.2%) were during the baseline phase and 78 of 112 (69.6%) were observed during the intervention phase.

Fifty percent of women were of gestational age >28 weeks and 46% were in the post-natal period. Blood pressure (62.3%), respiratory rate (59.4%), and heart rate (50.7%) were the most common abnormal trigger followed by temperature (43%), appearance (41%), mental status (27%), and urine output (6%) **[Appendix 5.5].** The most common source of infection found was respiratory (31%), chorioamnionitis (15%), and urinary tract (11%) **[Appendix 5.5]. Appendix**

5.6 represents the various laboratory investigations carried out for the identification of source of infection in suspected maternal sepsis patients.

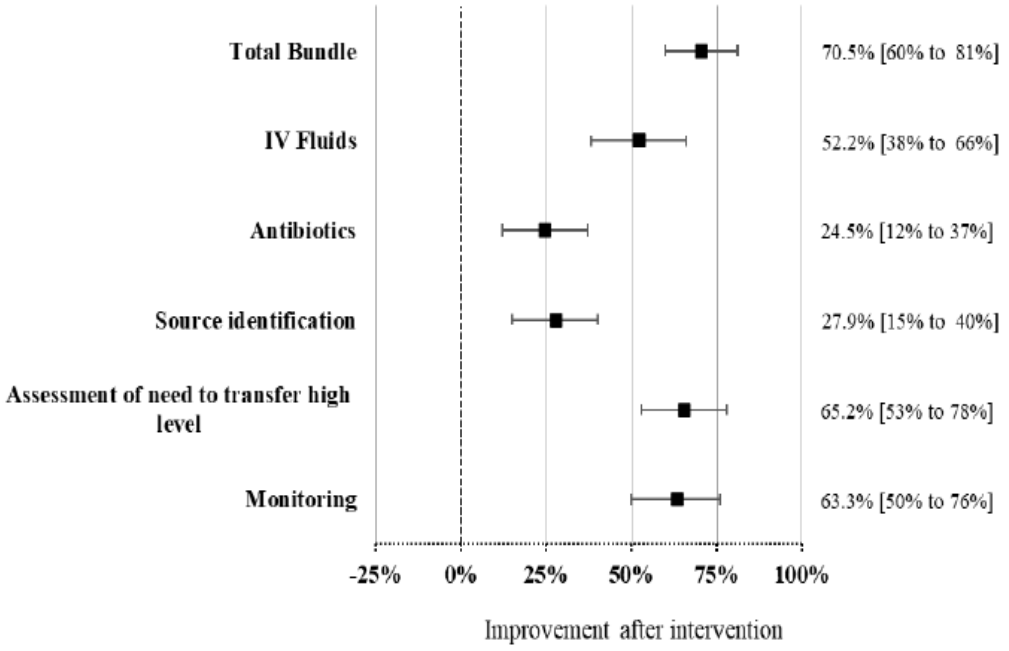
Compliance with the FAST-M treatment bundle within 1 hour: Women with suspected maternal sepsis received all the components of the FAST-M treatment bundle, with the goal of treatment within 1 hour. The mean start time of the FAST-M treatment bundle was 30.67±15.18 minutes for fluid, 26.43±13.45 for Antibiotic, 53±12.72 minutes for sources of identification, 19.62±16.26 assessment of the need to transfer high level and 54.43±10.1 for monitoring. Compliance improved following the intervention, as compared to the baseline [70.5%; 95%CI: 60.4% to 80.6%; $p<0.01$] **(Table 5.2).**

Table 5.2. Completion of FAST-M bundle within 1 hour of recognition of maternal sepsis

	Baseline	Intervention	Intervention over time				P-Value	P-trend
	(n=60)	FAST-M (n=78)	Month 1 (n=29)	Month 2 (n=18)	Month 3 (n=17)	Month 4 (n=14)		
Total Bundle	**0(0%)**	**55(70.5%)**	**20(69%)**	**9(50%)**	**15(88.2%)**	**11(78.6%)**	**0.0005**	**0.2069**
Fluids	21(35%)	68(87.2%)	24(82.8%)	17(94.4%)	15(88.2%)	12(85.7%)	0.0005	0.7516
Antibiotics	43(71.7%)	75(96.2%)	27(93.1%)	18(100%)	16(94.1%)	14(100%)	0.0001	0.3979
Source identification	41(68.3%)	75(96.2%)	28(96.6%)	17(94.4%)	17(100%)	13(92.9%)	0.0005	0.8405
Assessment of need to transfer high level	7(11.7%)	60(76.9%)	22(75.9%)	10(55.6%)	16(94.1%)	12(85.7%)	0.0005	0.1739
Monitoring	12(20%)	65(83.3%)	24(82.8%)	10(55.6%)	17(100%)	14(100%)	0.0005	0.0384

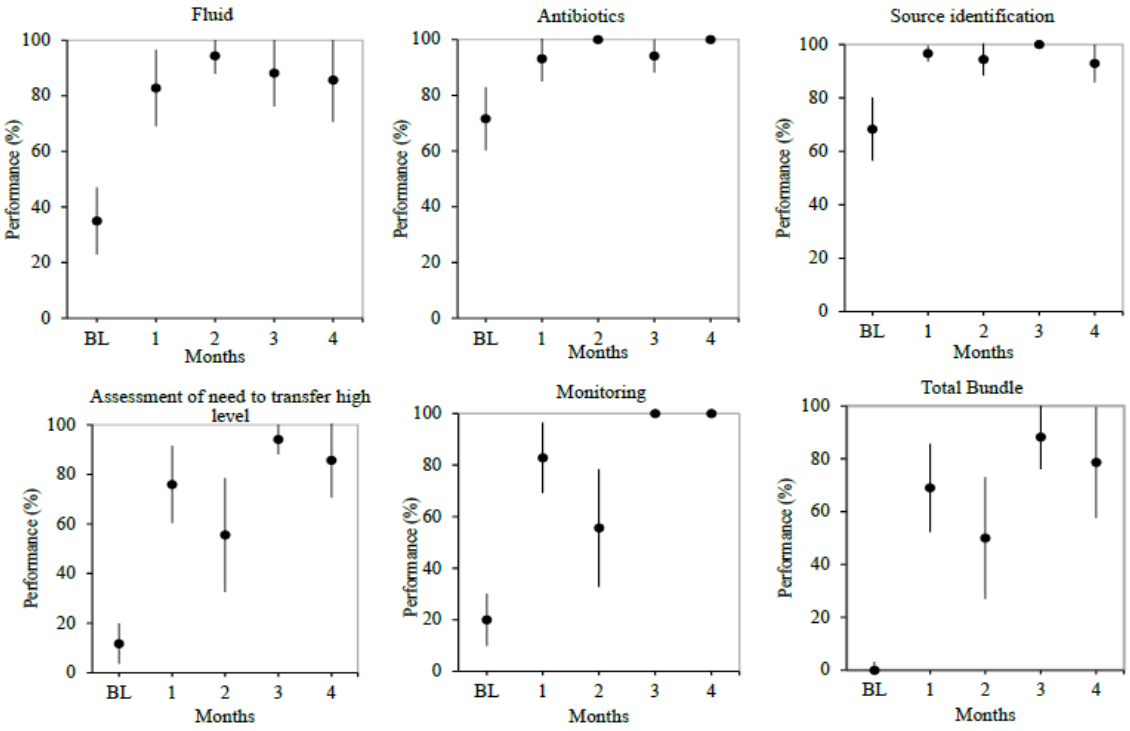
Improvements in management of sepsis cases were seen in all FAST-M bundle components, women were more likely to get IV fluids [52.2%; 95%CI: 38% to 66.3% ; p<0.01], antibiotics [24.5%; 95%CI: 12.3% to 36.6% ;p<0.001], source identification [27.8%; 95%CI: 15.3% to 40.3%; p<0.01], assessment of need to transfer required to high level care [65.3%; 95%CI: 52.8% to 77.6% ;p<0.01], and ongoing monitoring [63.3% ; 95%CI: 50.3% to 76.4%; p<0.01] within an hour of suspected sepsis identification compared to the baseline phase **[Figure 5.3]**.

Figure 5.3. Completion of FAST-M bundle within one hour of recognition of maternal infection



The improvements in the management of women with suspected maternal sepsis were maintained throughout the intervention, with no significant decline in performance over time (P trend value >0.05) **[Figure 5.4]**.

Figure 5.4. Completion of FAST-M bundle within one hour of recognition of maternal sepsis according to timepoint



Maternal Outcomes: The facility data shows 80 (28.6%) deaths due to maternal sepsis out of total 279 total maternal deaths recorded from the period of January to December 2021 **(Appendix 5.7)**. A 9.4% decline in the sepsis related maternal mortality was observed: 52/159 (32.7%) in the month of January-June and 28/120 (23.3%) during the July-December 2021 (p-value=0.087).

5.5. Discussion

The implementation of the FAST-M intervention was feasible, and effective in early identification, and management of maternal sepsis at the study setting. Although the patients were monitored for their vital signs on admission during the baseline phase, there was high compliance with all monitoring components after the intervention, with significant increase in compliance with completion of the MEOWS charts. Following the intervention, women with suspected sepsis were more likely to receive all the critical early interventions needed to treat maternal sepsis. There was high and sustained compliance during the post-interventional observation period with completion of the FAST-M treatment bundle within an hour once maternal sepsis was suspected.

The use of the MEOWS chart has been related to improved health outcomes and has been shown to predict severe maternal morbidity and mortality. Though there is limited evidence on its feasibility and impact on outcomes in low resource settings [343]. The present study confirms the applicability of the MEOWS chart in a low resource setting in Pakistan. However, this chart can only be useful if a comprehensive set of observations is collected consistently. Any missing or irregular observations decreases the ability to identify the patients at risk [299,343]. In the present study, we found that with the combined use of the MEOWS chart along with health care provider training, resulted in improvement in the monitoring of vital signs after the implementation of the FAST-M intervention.

Early detection of sepsis patients is critical for prompt treatment and improved maternal outcomes [50,298,343]. Research indicates that early warning scores accompanied by a clear

escalation policy guide the healthcare providers on the need for additional action to optimise patient care [344]. The decision tool used guided the health care providers on when to proceed with treating the patient as having suspected sepsis and initiating the FAST-M bundle [300]. The present study shows the FAST-M decision tool along with the MEOWS chart guided health care providers in appropriate screening and identification of women with suspected sepsis and assisted in making timely decisions for such cases.

The study was not powered to demonstrate reductions in maternal mortality or severe morbidity, but due to the critical importance of this outcome it was pre-specified as a secondary outcome. Following intervention, we observed a 9.4% decline in mortality of maternal sepsis patients, which suggests that the early identification of the sepsis patients and their timely management may as hoped lead to improved clinical outcomes. This finding is consistent with evidence from high income countries where the use of sepsis care bundles for the immediate treatment of sepsis has been demonstrated in large observational and interventional studies to reduce mortality and improve patient's condition [209,336].

Fluid administration is considered an important part of early sepsis management [222,345]. The restoration of organ perfusion is an important goal of maternal sepsis treatment and fluid resuscitation should seek to restore organ perfusion while maintaining hemodynamic stability. We observed a significant improvement in timely fluid administration once the FAST-M bundle was implemented.

Antibiotics are considered the cornerstone of sepsis treatment and timely antibiotic administration has proved to improve patient outcomes and reduce mortality [345-346]. It is possible that the 24.5 percent increase in the present study in timely initiation of antibiotic administration may have led to the improved clinical outcomes of women with suspected maternal sepsis. In Malawi, 42.3% improvement was seen in intravenous antibiotics administration within an hour of sepsis detection, from a relatively low baseline performance of 25% [300].

Research suggests that the patient's history along with the complete clinical examination is often sufficient for the identification of the source of infection [347]. If the source is not immediately clear, further investigations are required [347]. Source identification was improved by 27.8% after FAST-M implementation in the study setting. Similar findings were reported in Malawi, where source identification improved by 18.2% within an hour of sepsis detection after FAST-M intervention [300].

Amongst patients receiving treatment for maternal sepsis, the need for transfer to a higher level of care should be considered, and the decision on a patient's transfer made by a senior clinician as part of their review [347]. In Malawi, 43.9% improvement was seen in the consideration of transfer to the high level of care after the FAST-M intervention implementation [300]. The assessment of need to transfer was improved by 65.3% within an hour of sepsis detection in the intervention period in the study setting.

Overall, following the FAST-M intervention, more women were monitored and screened for maternal sepsis, and the complete FAST-M treatment bundle was administered within an hour in

70.5% of women with suspected sepsis. This resulted in improvement in the clinical outcomes of women with suspected maternal sepsis. The study findings demonstrate that the FAST-M intervention was feasible and improved the quality of care and clinical outcomes when implemented in the context of a large government hospital in Pakistan.

The strength of our research is that it is the first feasibility study conducted for the assessment of a maternal sepsis care bundle in a low-resource setting within Pakistan. This approach provided the opportunity to analyse practical, and operational factors for introducing the FAST-M intervention in the local setting.

However, the study has several limitations. Our research design does not account for possible temporal effects, hence is exposed to possible selection and reporting bias [348]. Although a before and after design couldn't identify the cause-and-effect relationship, this was the practical approach for determining the feasibility of the FAST-M intervention locally.

Although the intervention was found to be feasible, we recognise that the intervention period was short. A further assessment period is required to examine how well the FAST-M intervention is sustained and if it becomes normalised as a routine part of clinical care in the longer term. It is also important to understand in detail the process of implementation and fully understand the acceptability, and barriers and facilitators to implementation and how this was influenced by the context. This additional information has been collected via an embedded qualitative study and will be presented in next chapter.

Some of the referred patients in the baseline phase were observed to be already on fluid and antibiotics before admission to the hospital, which could have limited the ability of a before and after comparison, though it was only 9.4% (13/138) of patients in the baseline phase who were noted to have already received fluids and antibiotics. Additionally, the health care providers might have been more compliant with the FAST-M intervention, and the outcomes of this study, therefore better than one would see if such an intervention was rolled out at scale due to the close monitoring of the site during the conduct of the study.

5.6. Conclusion

Implementation of the FAST-M intervention was feasible and significantly improved the quality of maternal sepsis care, including enhanced early identification and management of maternal sepsis.

The study determined that, although with limitations, the FAST-M intervention was effectively implemented in LUMHS hospital, albeit for a short period of time. There was a marked improvement in not only the quality of maternal sepsis care but also in its early identification. The study found there was high compliance with all components of the FAST-M bundle hence demonstrating the feasibility of the intervention and showing it can be implemented effectively in the local setting.

Chapter Six

EVALUATION OF THE FEASIBILITY OF THE FAST-M MATERNAL SEPSIS INTERVENTION IN PAKISTAN

Following on from the previous chapter which concluded that the FAST-M intervention was effective during its short intervention period, this chapter will further evaluate implementation outcomes, the barriers and facilitators that were faced during implementation via a qualitative study. The tailored CFIR framework was used to assess whether the FAST-M intervention can be successfully optimised and integrated in other healthcare practices in Pakistan. A deductive thematic analysis approach provided a focus to gather relevant data using the predetermined themes.

I will describe the process of data collection that was done through focus group discussion. The five central themes that emerged from these discussions will then be presented.

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Authors contributions: Sheikh Irfan and David Lissauer designed the study and its processes. Sheikh Irfan, Bakhtawar Khowaja, Rubina Barolia Ghulam Kubra carried out the data analysis and interpretation. Sheikh Irfan, Bakhtawar Khowaja, Pammla Petrucka, Rubina Barolia took the lead in writing the manuscript, Arshia Jehangir, Fahmida Parveen, James Cheshire, Catherine Dunlop, Arri Coomarasamy, Lumaan Sheikh and David Lissauer reviewed the manuscript and provided feedback.

6.1. Abstract

Introduction

The World Health Organization and partners developed and evaluated a maternity-specific sepsis care bundle called 'FAST-M' for low-resource settings. However, this bundle has not yet been studied in Asia. Our study sought to evaluate the perceptions of healthcare providers about the implementation of the FAST-M intervention in Pakistan.

Materials and Methods

The study was conducted at a public sector hospital in Hyderabad. We conducted three focus group discussions with healthcare providers including doctors, nurses, and healthcare administrators (n=22) who implemented the FAST-M intervention. The Consolidated Framework for Implementation Research was used as a guiding framework for data collection and analysis. The data were analyzed using a thematic analysis approach and deductive methods.

Results

Five overarching themes emerged: (I) *FAST-M intervention and its significance* including HCPs believing in the advantages of using the intervention to improve clinical practices; (II) *Influence of outer and inner settings* including non-availability of resources in the facility for sepsis care; (III) *HCPs perceptions about sustainability*, which were positive (IV) *Integration into the clinical setting* including HCPs views on the existing gaps, for example, shortage of HCPs and communication gaps, and their recommendations to improve these; and (V) *Outcomes of the intervention* including improved clinical processes and outcomes using the FAST-M intervention.

Significant improvement in patient monitoring and FAST-M bundle completion within an hour of diagnosis of sepsis was reported by the HCPs.

Conclusions

The healthcare providers' views were positive about the intervention, its outcomes, and long-term sustainability. The qualitative data provided findings on the acceptability of the overall implementation processes to support subsequent scaling up of the intervention.

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6.2. Introduction

Maternal sepsis is the third leading cause of preventable pregnancy-related deaths worldwide [293]. It is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period [334]. Undetected or poorly managed maternal infections can lead to maternal sepsis, death, disability, and other adverse outcomes [349]. The World Health Organization (WHO) estimates that the global prevalence of maternal sepsis from 2010 to 2016 was 4.4% [16]. The incidence of maternal sepsis in high-income countries is 9–49/ 100 000 deliveries [16], however, in low- and middle-income countries (LMIC), the incidence of maternal sepsis is unidentified due to underreported cases [16]. Despite advancements in healthcare service delivery in the last century, maternal sepsis remains a significant contributor to maternal mortality [334].

Reducing maternal mortality is a priority action in achieving the Sustainable Development Goals (SDGs) through 2030 [350] and gained attention in the United Nations Global Strategy for Women's, Children's, and Adolescents' Health in 2015 [13]. Yet, the efforts and strategies to address Sustainable Development Goal 3.1 of *reducing the global maternal mortality ratio to less than 70 per 100 000 live births* [350] have disproportionally focused on the top two maternal mortality issues, i.e., hemorrhage and hypertensive disorders [13]. Despite maternal sepsis being the 3rd most common cause and a contributing factor in half of the maternal deaths, it has received far less attention [200].

The high maternal mortality rate from maternal sepsis is related to delays in the detection of sepsis cases and their timely management [351]. The prevention, early identification, and

adequate management of maternal sepsis will decrease the maternal mortality burden [351]. The burden of maternal mortality from sepsis predominantly falls on LMICs. [200]. The World Health Assembly (WHA) adopted a resolution in 2017 to improve the prevention, diagnosis, and management of sepsis [312]. In response, the WHO and other partners launched the 'Global Maternal and Neonatal Sepsis Initiative' with the objective to develop and test effective strategies to prevent, detect and successfully manage maternal sepsis [352].

Following this initiative, an evidence-based modified Delphi process was conducted to develop the first maternity-specific sepsis care bundle for use in low-resource settings [222]. The final elements included in the bundle were fluids, antibiotics, source identification and control, transport, and monitoring of the mother and the newborn [222], abbreviated as **FAST-M** for ease of healthcare providers' (HCPs) recall. The FAST-M intervention was implemented in Malawi and improved the recognition and management of maternal sepsis patients [300]. The FAST-M intervention included i) the modified early obstetric warning score (MEOWS) chart and FAST-M decision tool for identifying maternal sepsis cases, ii) the FAST-M treatment bundle to manage and treat maternal sepsis (Appendix 4.4), and iii) the FAST-M implementation program to train HCPs on using the FAST-M tools and integrate the bundled approach into daily practice [300].

The maternal mortality rate (MMR) in Pakistan was reported as 186 deaths/100,000 live births in 2020 [82]. National figures show that maternal sepsis is the third leading cause of maternal mortality [77]. There are national sepsis guidelines for Pakistan (SGP) that are designed to aid in the identification and management of sepsis in adults in the local settings and are modeled on the

Surviving Sepsis Campaign (SSC) [353]. However, these guidelines lack a comprehensive implementation approach for pregnant or recently pregnant populations.

Hence a feasibility study was conducted to assess whether it is feasible to implement the FAST-M intervention for maternal sepsis care in Pakistan [314]. This paper presents the qualitative part of the FAST-M evaluation in Pakistan.

6.2. Materials and Methods

6.2.1. Study Design

A two-phase mixed method intervention design was used. This two phase-design began with the adaptation phase. In phase 1 (adaptation), the FAST-M intervention was modified according to the local context before implementation in the study setting. The HCPs provided views on modifications in the bundle care tools according to their local context and a baseline facility survey was conducted to assess the availability of the facility's resources (quantitative data). The findings of phase 1 have been published as a separate record [354].

Based on the findings of phase 1, two-day training sessions were arranged and delivered by health care experts before the implementation of the FAST-M bundle intervention. The training session provided classroom-based instructions on the FAST-M intervention followed by interactive sessions used as a strategy for hands-on training of healthcare providers on the FAST-M tools. Health care practitioners including doctors and nurses (n= 40) working in obstetrics and gynecology units, internal medicine, operating rooms, emergency, and intensive care units of

LUMHS hospital were trained to record patients' vital signs on the MEOWS chart. Clinicians were also trained on using the FAST-M decision tool, and the health experts provided training on the appropriate administration and the use of treatment bundle elements.

The local clinical champions and team leaders were also identified during training programs and were trained to take the lead in implementation of the FAST-M intervention at the study site and remained engaged throughout the implementation process. These champions were selected from different departments primarily involved in the management of maternal sepsis patients. The selected champions included doctors. The overarching goal of each champion was to encourage engagement and compliance with the FAST-M bundle.

In phase 2, the feasibility assessment of the adapted FAST-M intervention was conducted through quantitative assessments for before-after implementation outcomes (the findings will be detailed elsewhere).

While the quantitative findings (in phase 2) reflected an improvement in early detection and management of maternal sepsis cases through the use of intervention, these could not explain '*what'* the HCPs experiences were in implementing this innovative approach in their health setting, or '*how well'* this intervention was integrated into their existing setup. We, therefore, conducted a qualitative study of HCPs and health administrators views and experiences post-implementation, with the objectives of understanding how useful they found this intervention for improving patients and clinical outcomes and what their views were on the overall

implementation process. We conducted focus group discussions (FGDs) with HCPs and administrative individuals who were involved in the implementation of the FAST-M intervention. Fig 6.1 provides the summary of the study processes.

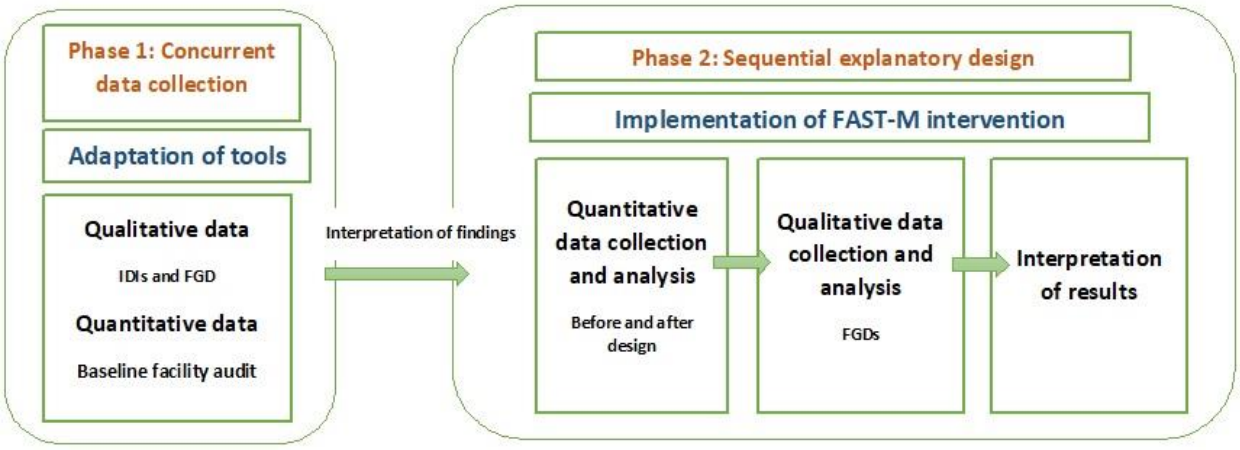
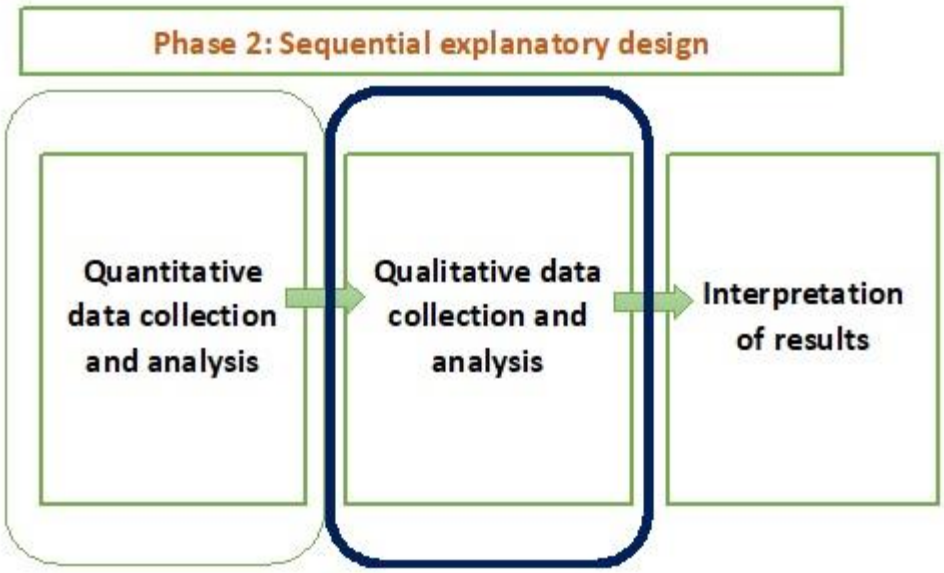


Fig 6.1: Flowchart displaying study processes

Phase 2 determined the feasibility of the adapted FAST-M intervention in a low-resource setting in Pakistan through before and after implementation outcomes (QUAN). For the latter portion of the study (Phase 2), we used a qualitative approach [355] (Fig 2.) to elicit healthcare professionals experiences, thoughts, and opinions on implementation outcomes such as its usefulness, and long-term sustainability of the intervention (QUAL). The exploration of their perceptions throughout this qualitative work (Fig 6.2.) sought to help us to better understand the individuals' experiences of the intervention.

Fig 6.2: Phase 2 of the FAST-M intervention study



6.2.2. Study setting

Liaquat University of Medical Health Sciences (LUMHS) is in the Hyderabad district of the province of Sindh, Pakistan. LUMHS is a 1300 bed tertiary referral public sector hospital that serves a large number of primarily underprivileged populations and the hospital's funding has been allocated from the provincial sector government budget.

The hospital offers both in-patient and out-patient services including three Obstetrics and Gynecology (OBGYN) units and the provision of 24 hours emergency coverage to patients coming from urban and rural areas of Sindh. It manages a high volume of cases of maternal sepsis every month.

The facility data shows that the case facility rate of sepsis in pregnant and recently pregnancy women was high 80/370 (21.6%) from January to December 2021 affirming the need for a robust system for early detection and management of maternal sepsis cases in the hospital.

The HCPs from different units and departments, such as the emergency, OBGYN, internal medicine, and intensive care units, were involved from the beginning of this study to plan and design the conduct of the study. These departments primarily deal with maternal sepsis patients, therefore we decided to have views of providers from all the units and not to limit it to only OBGYN. The FAST-M intervention was implemented in all these specified units to compare the before and after outcomes in clinical care and patients' outcomes.

6.2.3. Ethics approval

Ethical approval for this study was obtained from the LUMHS hospital [REC/-886, 4-87], Aga Khan University Ethical Review Committee [2019-2061-7102], and National Bioethics Committee [515/20].

6.2.4. Research team

This qualitative study was conducted to evaluate the FAST-M implementation by a multi-disciplinary research team with proficiency in OBGYN (DL, SI, RS, LS, AC, JC, CD, FP), and qualitative research in the area of perinatal health (RB, SI, BK, GK, PP).

6.2.5. Sample and recruitment

HCPs, including doctors, nurses, and healthcare administrators, who were involved in the implementation of the FAST-M intervention were purposively recruited and were invited by a study team member to take part in the focus group discussion to provide their views and feedback about the intervention and its implementation outcomes. Participants were eligible to participate if they were working in areas/departments of the hospital that implemented the FAST-M intervention such as OBGYN, emergency, internal medicine, and intensive care units. Discussions were scheduled at the study site and were audio-recorded following written consent from study participants [Appendix 4.1].

Three separate FGDs were conducted with groups of 1) junior doctors; 2) nurses; and 3) senior faculties and administrators, who were involved in the process of implementation. We conducted three FGDs during phase 2 based on our observations and experiences gained from the qualitative study conducted during phase 1(adaptation).

In phase 1, all healthcare providers were invited to participate from different disciplines and levels in a single group discussion. However, the combined FGD impeded the views of junior doctors and nurses due to hesitancy and reverence from senior doctors, which resulted in limited feedback. Therefore, in phase 2 we conducted separate group discussions which provided an opportunity to gain more insights and their views on implementation and explore observational results in more depth.

There were 6 to 10 participants in each FGD to have equal representation from each group. Data were collected until the point of saturation was achieved in each discussion [318], which ensured that no new findings arose from the discussions, thereby allowing participants, who indicated an interest in the opportunity, to share their thoughts and opinions openly.

6.2.6. Data Collection

FGDs were conducted and moderated in a local language (Urdu) by qualitative researchers and study team members (RB, SI, BK). A semi-structured interview guide was developed by the research team [supplemental file 3] and reflected the five major domains of the Consolidated Framework for Implementation Research (CFIR) (Table 6.1) [302], to evaluate the outcomes of FAST-M implementation and understand participants views on its utility.

Table 6.1: CFIR domains and associated constructs

Domains	Constructs
One: Intervention Characteristic	Intervention Source Evidence Strength and quality Relative Advantage Adaptability Trialability Complexity Design Quality and packaging Cost
Two: Outer Setting	Patient Needs and Resources Cosmopolitanism Peer Pressure External Policies and Incentives
Three: Inner Setting	Structural characteristics Networks & Communication Culture Implementation Climate Tension for change Compatibility Relative priority Organizational incentives and rewards Goals and feedback Learning climate Readiness for implementation Leadership engagement Available resources Access to knowledge and information
Four: Characteristics of Individuals	Knowledge and Beliefs about the intervention Self-efficacy Individual stage of change Individual identification with organization Other personal Attributes
Five: Process and outcomes	Planning Engaging Opinion leaders Formally appointed internal implementation leaders Champions External change agents Executing Reflecting and evaluating

CFIR has been used in various studies to inform qualitative processes across a range of complex interventions because this flexible framework can be tailored to different settings across multiple contexts [317]. We, therefore, used the tailored CFIR framework to understand the process of implementation of the FAST-M intervention in an entirely novel/different setting and to evaluate its outcomes.

The interview guide was iteratively reviewed and refined through the course of the study in order to ensure that, as the breadth of the responses are gathered, we could explore depth and relevance in later FGDs. FGDs lasted between 30 and 60 minutes, were recorded with permission, and transcribed verbatim. Detailed field notes were also taken during discussions to capture the non-verbal language and participants' cues.

6.2.7. Data analysis

Qualitative data gained through FGDs were transcribed in local language (Urdu) and then translated in English language by interpreters for the purpose of analysis. Data were analysed using a thematic analysis approach and deductive analysis methods [356]. The CFIR domains were used as themes and constructs as subthemes [302]. The research team conducted multiple reflexive and iterative reviews of the transcripts and tapes to familiarize themselves with the data. The analysis began soon after the first FGD and continued until we gathered information from all the three FGDs.

An audit trail was used to document our decision-making process. Data were searched for information relating to CFIR domains and constructs. Five domains and their constructs of the CFIR framework were used to guide data coding, data analysis, and reporting of the findings. A qualitative thematic analysis approach was adopted, and codes were formulated deductively from the transcripts. CFIR domains were used as predefined themes, and the constructs were used as subthemes using NVivo™ version 10 (QSR International, Pty Ltd) software [357].

A codebook was developed based on the predefined themes. Additional codes on organizational systems and policies, and sustainability of the intervention that were not part of the constructs listed in the tailored CFIR, yet providing important information on the evaluation of the FAST-M intervention were added in the codebook under predefined themes where possible. Three qualitative researchers first reviewed the codes and associated themes individually, and then all the team members reviewed the codebook together to check for potential biases and to ensure the credibility of the findings, to reflect participants' words and meanings. The detailed thematic map was developed after consensus of all team members.

6.3. Results

Three separate FGDs were conducted with HCPs and administrators, including one with junior doctors, such as postgraduate trainees and residents; a second with nurses; and the third with senior faculty members, consultant obstetricians and health administrators (Tables 6.2, 6.3 & 6.4). Participants were approached by the study team from all the eligible units where FAST-M intervention was implemented, yet doctors and nurses from only OBGYN units and ICU agreed to take part in the group discussions as most of the patients during the intervention phase were

enrolled from these units. Hospital administrators were also involved in a group discussion to have their experiences shared from the administration viewpoint.

Table 6.2: Focus group discussion with doctors

FGD participants	**N=7**
Job Title	
Residents	2
Postgraduate trainees	2
Registrars	1
Senior Registrars	2
Working experience in facility	
> 5 years	3
1- 5 years	4
Clinical areas	
Obstetrics and gynecology	5
ICU	2
Gender	
Male	2
Female	5

Table 6.3: Focus group discussion with registered nurses

FGD participants	**N=6**
Clinical areas	
Obstetrics and Gynecology	5
ICU	1
Working experience in facility	
> 5 years	1
1- 5 years	5
Gender	
Male	1
Female	5

Table 6.4: FGD with faculties and administrators

FGD participants	**N=9**
Job Title	
Obstetricians	6
Health care administrators	2
ICU director	1
Working experience in facility	
11 years and above	5
6-10 years	2
1- 5 years	2
Gender	
Male	2
Female	7
Role in the hospital	
Administration	2
Leadership	3
Clinical practices	4

Five overarching themes were developed using the CFIR domains: (I) FAST-M intervention and its characteristics; (II) Influence of outer and inner settings; (III) HCPs perceptions for implementation of FAST-M intervention; (IV) Integration into the clinical setting; and (V) Outcomes of intervention. Table 6.5 demonstrates the identified themes, subthemes & participants' quotes.

Table 6.5: Themes and Subthemes

Themes	Subthemes	Illustrative Quotes
FAST-M intervention and its significance	Advantages of FAST-M intervention	*"FAST-M intervention helped in identifying sepsis but also the other comorbidities"*
	Evidence, strength, and quality of intervention	*"Maternal mortality and morbidity due to sepsis have reduced"*
Influence of outer and inner settings	Resources for patient care	*"Antibiotics and other things are manageable but the real problem we face is lab tests"*
	Healthcare providers communication and their job roles	*"There is a lack of communication between doctors and nurses"*
	Seasonal variations and patient influx	*"We have also noticed seasonal variation, in hot seasons sepsis is more in comparison to winters, in winters we get fewer sepsis patients"*
HCPs perceptions for implementation of FAST-M intervention	Sustainability of intervention	*"FAST-M is the guideline for sepsis and this should be enforced for sustainability"*
	Implementation of FAST-M intervention	"*Patients are recovering now. Now we are able to recognize the patient's problem"*
Integration into the clinical setting	Reflection and Evaluation	"*We got a line of treatment and management plan. This was very effective strategy"*
	HCPs Recommendations	"*Nurses can also be clinical champions"*
Outcomes of intervention	Improved clinical outcomes	"*The patients' outcomes are positive"*
	Improvement in clinical processes	"*This intervention is improving clinical outcomes"*

6.3.1. FAST-M intervention and its significance

6.3.1.1.Advantages of the FAST-M intervention

HCPs attitudes towards the FAST-M implementation were positive and supportive. All HCPs shared positive perceptions of using the MEOWS chart for timely identification of not only sepsis

patients, but also other high-risk patients. They acknowledged that the use of red and yellow flags as triggers on the MEOWS chart facilitated HCPs in identifying and categorizing patients as low or high risk according to given cutoff values. Due to the absence of a triage system in the facility, all the obstetrics and gynecology patients initially present to the labor room at the time of admission. The MEOWS chart served as a triage screening tool for the initial assessment and monitoring of patients and helped in possible diagnoses through complete patient assessment, as stated:

> *"Using MEOWS chart, we did not only recognize the sepsis patients but also other comorbidities like post-partum eclampsia and those patients who were deteriorating with post-partum hemorrhage, so this helped in identifying directly the sepsis but also the other comorbidities on admission". (Obstetrician-1)*

All HCPs were supportive of the use of the MEOWS chart in their routine practices as it helped them improve the initial patient assessments considering all important parameters. The improvement in initial assessments through MEOWS chart recordings was observed during the intervention phase. Whereas the FGD participants reported their perception of a substantial improvement in overall patient monitoring.

> *"What used to be there was when it was very obvious that this is sepsis only then we used to pick up that case, but now it's not like that. The difference you can say that if we take from 100, it used to be 20 so now you can say 60 by using this MEOWs chart (Obstetrician-3)*

HCPs believed that the FAST-M screening tools (i.e., MEOWS chart and the decision tool) augmented the decision-making abilities of both senior and junior clinicians. The early recognition facilitated the early management of patients.

> *"Our postgraduate trainees have also started picking sepsis cases. Previously, we used to just manage those patients who were detected cases of sepsis on admission but now we have started picking the new cases using the decision tool" (ICU director)*

.

The FAST-M intervention served as a unified system for the patient assessment and management of both suspected and confirmed maternal sepsis patients. The HCPs were supported through the management plan and each component in the treatment bundle guided their treatment approach for sepsis patients.

> *"The FAST-M treatment bundle gives details on the management plan and this has helped a lot in the treatment of patients that how much fluids are recommended; which antibiotic should be given and what tests to be done" (Postgraduate trainee-2)*

HCPs were trained to use the FAST-M bundle care tools prior to its implementation following the baseline phase which helped them in applying these tools in their existing practices. The FGD participants believed that more women with maternal sepsis received the overall FAST-M bundle components within an hour during the intervention phase in comparison to the baseline phase. This finding was confirmed by the following quotes:

> *"Because we have started picking up sepsis patients on time, we administer fluids and antibiotics within one hour of the identification of those patients. The blood tests are also sent earlier now to rule out the cause of infection immediately" (Postgraduate trainee-1)*

"Patient management time is crucial to saving their lives. Now we have become more vigilant with administrating fluids and antibiotics on time. (Obstetrician-1)

It was noted that the training programs conducted for FAST-M implementation were beneficial in improving HCPs knowledge on the use of bundle components. 'Fluids' which is the first component of the treatment bundle were routinely administered in the facility to patients. However, HCPs lacked guidance on fluids administration and were reluctant to administer them to patients with co-morbidities such as cardiac disease and pre-eclampsia. The health experts and obstetricians guided instructions to HCPs on appropriate fluids administration in such patients during the training programs. This helped HCPs in proper fluids administration and its monitoring, considering the guidelines provided in the treatment tool.

"We give fluids to all patients who are scheduled for C-section, those who are kept NPO, or if we think they are dehydrated. But this FAST-M has helped us with the proper timelines and measurements to give the fluids" (Obstetrician-2)

"The problem that we were facing initially before this intervention was that we were not clear with the idea of providing fluids to patients with cardiac disease or those who had some other complications such as pre-eclampsia but now we are clear on the dose, and we have set some guidelines on fluids administration. Now without wasting any time, our doctors whoever is on duty provide fluids and antibiotics to patients and send their blood tests immediately, and then monitor those patients frequently (Obstetrician- 2)

'Antibiotics' is the second component of the treatment tool. Instruction on the recommended antibiotics with appropriate dosages was given to HCPs during FAST-M training workshops by

experts. This strategy improved the correct and more frequent antibiotics administration during the intervention phase and was acknowledged by HCPs:

> *"The antibiotics guidelines such as first line and second line antibiotics streamlined our practices. We used to give antibiotics previously as well to most of our patients, but this first line and second line of antibiotics provided us with a clear direction. Previously, we used to give 1g ceftriaxone BD which was not effective but as it is documented in the treatment tool to give 2g ceftriaxone as stat dose within one hour to maternal sepsis patients and now we are observing its effectiveness" (Obstetrician-3)*

To identify the source of infection, the treatment tool guides in taking the patient's history, performing clinical examinations, and routine investigations to rule out the cause and treat it appropriately. Although the practices of clinical history taking and examination were very well performed in their existing setup, some gaps were identified in routine blood tests. This deficit was considered during the training and resulted in improved testing during the intervention phase and complete patient management on the basis of the findings. This finding was also confirmed by one of the group participants:

> *We didn't use to send serum lactate but now we send for suspected sepsis case and from that, we get an idea that this is high-risk patient and then we monitor them accordingly" (Postgraduate trainee II)*

The challenge of the delay in patient transport to high-level care was due to the shortage of beds in ICU, and the excessive documentation required at the time of transport as highlighted by the participants during the training programs. The attending health administrators agreed with the

suggestion of increasing the number of high-density units within the wards to overcome delays in high-level care. They agreed on transfer of critical sepsis patients as a priority with only necessary patient information required at the time of transport to ICUs. There were considerable improvements seen in timely transportation and the frequent monitoring of maternal sepsis patients during the intervention phase as stated:

> *"The patients' transportation time has now improved; we transfer critical patients immediately to ICU and then do all the documentation, paper and file work" (Nurse- 2)*
>
> *"Now we have this MEOWS chart in each patient file, so we frequently monitor them and record the findings and see the variations in all parameters over time" (Obstetrician-1)*

6.3.1.2.Evidence, strength, and quality of intervention

All HCPs acknowledged the intervention's quality and strength for the implementation of evidence-based and timely management of sepsis cases. The FAST-M intervention supported the improvement of existing clinical practices and improved clinical outcomes.

> *"The quality of this FAST-M is that it provides us with the actions that has to be performed according to the guided timeframes such as the patient is going in this direction then he has to get management in 1 hour if the patient has yellow flags, then we can wait so everything is so aligned and systematic that it improves the patient care." (Postgraduate trainee-II)*

In the baseline phase, patients were assessed and monitored on their routine vitals monitoring chart but a few important parameters, such as oxygen saturation, urine output, and fetal heart rate, were missed due to inadequate documentation which delayed patient management. Therefore, the importance of initial patient assessment and the significance of all the parameters to recognize early warning signs were stressed in training workshops. The HCPs were also provided hands-on training on monitoring early warning signs during FAST-M training workshops using different patient scenarios [17]. This effort improved patient monitoring during the intervention phase, as stated:

> *"Now it's easier by monitoring through MEOWS chart, we get an idea of how many yellow or red flags are there and in what line is that patient falling. So, this tells us how to rapidly assess and manage" (Obstetrician-2)*

The FAST-M intervention also empowered junior doctors in the decision-making process and assisted in the timely management of patients as indicated by HCPs.

> *"All the junior doctors, let's say 4 or 5 people on duty, we clearly define them that this is your patient and you have to monitor this patient and you have to record their vital signs, and wherever you get yellow or red trigger you have to inform. From this, it has become easier to identify and manage earlier and this is very clear that you must give bundle elements. Any resident doctor can easily do that, so the first thing is this. We used to give these treatment components to patients previously as well, but we were not giving them within one hour. Second, they are aware that this patient is sick, so they do the next steps themselves (Senior Registrar- I)*

6.3.2. Influence of inner and outer setting

6.3.2.1.Resources for patient care

Almost all HCPs indicated the shortage of nurses in the facility that serves as a major barrier to patient care. The dearth of nurses increases the workload of doctors and compromises the quality of care provided to patients. This challenge was one of the major findings during the adaptation phase and, to overcome this barrier, the FAST-M training programs provided teachings on task-sharing between doctors and nurses. The sharing and distribution of clinical responsibilities were therefore employed during the intervention phase.

> *"Our doctors monitor vitals such as oxygen saturation, and BP themselves. We do medications for all patients. We look after 20 patients, the admitted patients, this is the main problem. But our doctors help us with monitoring vital signs and all other tasks. (Nurse -1)*

The treatment bundle components, such as fluids and antibiotics, were readily available in the facility as confirmed by HCPs, but for the component of source identification and treatment, there remained challenges in laboratory investigations, such as blood culture tests. HCPs expressed that the laboratory lacked the ability to perform blood cultures for anaerobic organisms and retained products of conception (RPOCs) which hindered decision-making on the patient's treatment regime. However, improvement was still seen in the blood cultures in suspected sepsis patients during the intervention phase.

"There are no cultures for anaerobes and RPOCs if that would be available it would have helped us a lot" (Senior Registrar -I)

"We have started sending the blood cultures for sepsis patients now, but still the mechanism of sending those to the lab is problematic" (Obstetrician- 2)

6.3.2.2.Healthcare providers communication and job roles

Almost all HCPs identified lack of communication as a major barrier to FAST-M implementation. This finding was also identified during the adaptation phase and was addressed in training workshops to strengthen interprofessional communication. The communication strategies were discussed through interactive sessions and the probable solutions were identified for improvement. However, this challenge is associated with the organizational culture and will take time to change.

"There is a lack of communication, it's improving but still requires improvement. As we are working in wards, our communication with our colleagues, doctors, postgraduate trainees, and administrators was very poor, few systems have improved, and few have to improve but this needs to be communicated and needs more improvement" (Nurse 3)

Moreover, a lack of trust by doctors in nurses to perform patient assessments and monitoring was expressed during the discussion. Doctors were not content with nurses performing routine tasks which caused overburdening of doctors' responsibilities.

"Monitoring is the responsibility of staff nurses; this is their work, but we can't rely on them, and we can't trust them. If they monitor anyone's blood pressure, many a time this has happened that they record something on a chart and when we monitored, we noticed

that diastolic BP is very high, how can we rely on it? Similarly, if we count heart rate it is 102 and if they do it records 72" (Postgraduate trainee-1)

On the contrary, nurses believed that they are not responsible for patient monitoring, and this is only 'the doctors' duty because there were more doctors than nurses available in the facility.

"Doctors do these duties on their wish because there are 3 doctors assigned to a single bed, one registrar, one postgraduate trainee and a house officer they do every recording themselves" (Nurse-5)

6.3.2.3.Seasonal variation and patient influx

The effects of seasonal variation on patient influx were evident through the observational findings recorded during the baseline and intervention phases. The baseline data were collected from June to August (summer in Pakistan) and the patient admission records were 5500 patients in all OBGYN units of the study setting per month. The intervention phase was implemented from August to December (autumn and winter) and the admission records 3200 patients admitted to OBGYN units per month.

The HCPs, who worked as clinical champions, shared their views on variation in patient influx according to seasonal differences. They believed that the patient volume during the summer season was high in comparison to the winter season and this might be the reason for receiving more septic patients during summers. This could be due to difficulties in the accessibility of rural women to the city area in winters as most of the patients who visit LUMHS hospital are from

rural areas. These important insights can add to interpretation of our observational results as the intervention period for this study was mostly spread over winter months.

"We have also noticed seasonal variation, in hot seasons sepsis is more in comparison to winters, in winters we get fewer sepsis patients" (Obstetrician- 2)

"We get less flow of patients in the winter season, and this is the reason we have less rate of sepsis patients" (Resident doctor-1)

6.3.3. HCP perceptions for implementation of FAST-M intervention

6.3.3.1.Sustainability of intervention

All HCPs provided positive views regarding the long-term sustainability of FAST-M intervention. The components of the FAST-M intervention were already used in the setting; however, the intervention provided a systematic approach for patient care. Hence, HCPs were optimistic about the long-term sustainability of this intervention.

> *"Every implementation requires a protocol. We know that we have to do NVD then we have to maintain the partograph. Similarly, this is the guideline for sepsis, and this should be enforced that this is a sepsis bundle. We are doing this for the first time, but these are guidelines for sepsis, which we have to implement accordingly. As we must follow partogram during delivery and no matter how busy we are we know we have to follow that so similarly this should be applied for sepsis patients and should be attached with their files. Every individual should know that they need to manage sepsis patients this way. They will remember these and will do it on tips like other guidelines" (Postgraduate trainee-2)*

The participants indicated the intent of a long-term uptake and implementation of this intervention in order to enhance future care practices and potential adoption as the protocol for all sepsis patients.

> *"This is improving outcomes and then definitely this will be standard protocol in the later years and will be part of patient management in entire hospital" (HOD-OBGYN)*

The clinicians and health administrators supported the idea of long-term sustainability and they guaranteed the inclusion of bundle care in patients files. As some of the practitioners working at the study setting were also providing private services at other facilities, it was suggested by the administrators that this might help in disseminating the awareness of this useful intervention in the care of patients.

> *"Our doctors are running their private clinics. They do NVDs and c-sections at other facilities too. Many postgraduate trainees who are trained here will go and will serve in big reputed hospitals. I believe if we have trained them on this, we have completed the major step of dissemination already" (Healthcare administrator)*

6.3.3.2.Preparedness and readiness for implementation

As part of this study, HCPs from all participating units were trained before the actual implementation of the intervention. The study team conducted multiple-day training sessions as planned and described in the protocol to provide awareness and knowledge about the intervention [354]. However, due to the rotational duties of HCPs, all of them were not able to attend the

sessions. The HCPs, who didn't attend the training sessions, were not aware of the intervention and they were later trained by the clinical champions selected from their units.

> *"The champions you selected trained everyone and not only postgraduate trainees. All HCPs were taught on FAST-M bundle care tools" (Registrar- I)*

The focus group participants expressed readiness for long term implementation of the FAST-M intervention in their setting as it improved patient outcomes and provided them with guidelines for patient care.

> *"These all things were previously as well but they were not done stepwise. We used to do vital signs but there was no concept of red and yellow triggers, so we were unaware of what is going on but now on the basis of these charts, even in ICU, we use the MEOWS chart to see patients' conditions" (Nurse-5)*
>
> *"Patients are recovering now. Now we can recognize the patient's problem. Previously we were unable to identify what is their problem but now they are given proper treatment" (Postgraduate trainee-2)*

6.3.4. Integration into the clinical setting

6.3.4.1. Reflection and Evaluation

The FAST-M intervention was very well integrated into the study setting and all participants provided positive views about the process of implementation. The role of champions was highlighted as they played a lead role in several key activities (i.e., disseminating knowledge,

advocating, arranging meetings with stakeholders, tracking quality indicators, and developing organizational communication strategies and relationships).

> *"The champions who were selected used to teach and train everyone and used to promote this. They used to check those tools in files and we also made sure that these tools are available in files. We were very much involved, and we also benefited from this thing, not only sepsis but there are many other high-risk patients who are picked and managed on time. We got a line of treatment and a management plan. This was a very effective strategy" (Resident doctor-2)*

The MEOWS chart assisted HCPs to assess patient's health conditions and decide on their management and frequency of monitoring based on improvement or deterioration of clinical parameters listed and their related cutoff values. Based on the beneficial outcomes of the inclusion of the MEOWS chart, the hospital administration decided to include the MEOWS chart in patient files as their routine practice, as stated:

> *"The MEOWS chart has helped a lot in improving patients' outcomes and the hospital administration has accepted our request to include these charts in every patient's file with other routine documents. These charts will be included from the time patient will be admitted to the hospital so this will help us in doing their initial assessments and frequent monitoring later" (HOD- OBGYN)*

FAST-M tools (i.e., MEOWS chart, decision, and treatment tool) were also displayed through posters in all the units involved in the management of maternal sepsis and implementation of the

FAST-M intervention. HCPs supported displaying posters stating these visuals improved awareness, knowledge, and dissemination of sepsis management.

> *"Sometimes by looking at these posters we get a clue of patients conditions and discuss among ourselves even if we are not assigned on that patient" (Nurse-4)*

6.3.4.2.HCP recommendations

During the process of implementation, HCPs identified certain difficulties, such as lack of HCPs awareness and training, and lack of nurses' empowerment. They provided their views on reducing these gaps to strengthen the quality of patient care and the long-term sustainability of the intervention. The senior obstetricians advised improving awareness of HCPs and especially nurses as they could play a major part in patient monitoring.

> *"If there would be refreshers and training held after every two months then this would work more effectively" (Obstetrician-4)*
>
> *"We need improvement and I suggest providing awareness sessions to nurses especially as they could initiate the monitoring whenever doctors are busy or unavailable" (HOD-OBGYN)*

During the training workshops, HCPs selected as clinical champions showed their willingness for voluntary involvement in the FAST-M implementation. All HCPs who showed commitment to becoming champions were doctors. Therefore, the FGD participants recommended empowering nurses by providing them with a primary role in operationalizing this intervention. She suggested

selecting a champion or a team leader from nurses, so they could recognize and accept their role and feel empowered to engage in these efforts.

> *"As you have selected FAST-M champions for doctors similarly nurses can be made champions and this way they will be made accountable for their performance" (HOD-OBGYN)*

6.3.5. Outcomes of intervention

6.3.5.1. Improved clinical outcomes

All focus group participants discussed improved patient outcomes through the use of the FAST-M intervention. A decline in maternal mortality due to sepsis was observed after implementation of the FAST-M intervention. This was an unexpected finding as the study was not powered for such an important outcome. Interestingly, this finding was though also confirmed to be consistent with the perceptions of HCPs:

> *"Maternal mortality due to sepsis have reduced because of intervening this IV fluid and antibiotics within an hour, the patients' outcome is positive" (Health administrator 1)*
>
> *"Maternal mortality and morbidity in our unit due to sepsis have reduced because of timely administration of fluids and antibiotics in an hour" (Resident doctor I)*

However, the finding can only indicate a trend, and this needs to be verified in a larger sample. Even though, the intervention not only benefited patients who were diagnosed with sepsis, but it helped improve overall patient care.

"Now a greater number of patients are diagnosed who may remain undiagnosed, now only one sign we get, and we manage them. It's a red eye-opener for us. As immediately we get the red signal that this patient has got one red sign in MEOWS then we manage that patient" (Postgraduate trainee-2)

6.3.5.2.Improvement in clinical practices

The HCPs increased compliance with timely approach to patient monitoring showed significant difference during the baseline and the intervention phase in monitoring and recording of parameters such as fetal heart rate in pregnant women urine output and oxygen saturations. The intervention improved patient monitoring as indicated by HCPs.

"Now we monitor every patient using this MEOWS chart even if she is not a sepsis patient. This help us in monitoring patients' conditions for the time they are admitted in our wards" (Postgraduate trainee-II)

The HCPs also verbalized on the significant improvement in seeing the investigational profile of patients to decide on the appropriate treatment regime. The significant increase in laboratory investigations supported clinicians in making timely decisions, as reported:

"One of the important pieces of evidence to start any therapy or treatment is to know patients' labs. This FAST-M intervention has helped us in improving lab investigations that are required for patients' treatments (Resident doctor-II)

The healthcare administrators were enthusiastic on inclusion of FAST-M bundle care tools in their existing practices as they observed the overall improvement in clinical practices not only of the sepsis patients but with other maternal issues. One of the administrators stated:

> "*The amount of improvement these tools have demonstrated is significant. We have got a lot of patients with infections due to home births, untrained skilled workers, poverty, negligence of healthcare and many other factors. This will provide us a way to improve our practice and I will really urge to include these in our patients' files so they don't get delayed in getting care" (Healthcare Administrator)*

The FAST-M intervention improved in early identification of not only sepsis but other complicated patients, and guided on the management of patients. This helped all the healthcare workers working if different setting to work on a standard protocol. The people working in HDUs, and ICUs were also benefited through the use of these bundle care tools as stated:

> *"We have a different protocol for managing sepsis patients. We get patients with severe sepsis so we have to start inotropes and steroid therapy when they are in late stage but yes, the administration of fluids, antibiotics and source control and continuous monitoring is even required whether if patients is in early or late stage of sepsis, and so it has helped us to keep a strict eye on monitoring of patients so we can manage them accordingly." (ICU director)*

6.4. Discussion

Our findings revealed that the FGDs participants views on the FAST-M intervention were positive, and they believed that the FAST-M intervention supported improving patients' clinical outcomes.

The MEOWS chart was used as a triage screening tool for patients' initial assessments during the intervention phase. A considerable improvement was seen in the monitoring of vital signs through the observational records, yet HCPs and administrators provided their insights, and they found the MEOWS chart as a useful tool for patient screening and predicting maternal morbidity. A similar finding was reported in a study conducted in a tertiary public hospital in Malawi. The HCPs and managers found a locally adapted early warning screening tool as an enabler to routine screening for infectious morbidities and triaging the sickest patients for priority treatment [358].

Prior to the implementation of this intervention, the patients' vital signs were manually recorded in their files. However, the MEOWS chart was introduced in the units where FAST-M intervention was implemented and proved to improve clinical practices. Hence, the hospital administration decided to include MEOWS charts in patients' files in all facilities for monitoring maternal patients.

The decision tool aided in the decision-making of patients who had signs and symptoms of sepsis and were detected through the MEOWS chart. The use of the FAST-M decision tool supported the clinicians to identify suspected maternal sepsis cases and directed them to make more accurate patient diagnoses. Similar findings were seen when the FAST-M intervention was

implemented in Malawi. The FAST-M decision tool helped clinical decision-makers to differentiate maternal sepsis cases from other complications thereby facilitating earlier and appropriate patient management [300].

The HCPs were supportive of the treatment bundle components as they helped improve patients' clinical conditions through timely administration. The clinical practices, such as fluid and antibiotics administration, source identification and treatment, transport, and monitoring, were already part of the existing care setup, but the FAST-M intervention provided guidance on the recommendations and guidelines for use of each component. The appropriate use of each bundle component within a recommended timeframe was found to be effective in maternal sepsis management. Similar findings were recorded when the FAST-M bundle was implemented in Malawi [300].

The FAST-M training programs helped HCPs in appropriate patient monitoring and their management. HCPs provided constructive views on the FAST-M training programs as it helped them streamline their clinical processes and discover strategies to improve the quality of patient care. The hands-on training on FAST-M tools helped them in understanding the appropriate actions that need to be followed in different situations. The training programs enabled HCPs to achieve significant improvement through their problem-solving strategies such as task sharing and strengthening the transport system of the critical patients as evidenced by their feedback obtained from group discussions.

The HCPs provided views on the challenges that were faced during the implementation such as shortage of nurses, lack of interprofessional communication, and complex mechanisms for transport of blood samples for a few important tests to the laboratory to determine the source of infection. However, similar challenges were reported during the adaptation phase. Yet, healthcare administrators provided their contribution in facilitating the transport mechanism of patients during the intervention phase. There were more HDUs built in within the OBGYN units to ease the complex process of patient's transport to high level of care. Though, we believe that the long-term implementation of these strategies depends upon the organizational structure, preference of people working there and the institutional culture. Research evidence suggests that bringing innovation into the organization is a complex and time taking process and depends on the organization's structure and its problem-solving strategies [359].

The involvement of healthcare administrators and key stakeholders in the adaptation phase also helped in instilling and implementing the idea of task sharing during the intervention phase. Task sharing has been a longstanding strategy in health systems and health settings and has proved to improve clinical practices and outcomes [360]. The approach of task sharing of specialists with trained non-specialist workers has provided positive outcomes in the improvement of patient care, reduced morbidity and mortality rates, and cost-effectiveness [361].

During phase 1, it was proposed to involve nursing interns, trainee dispensers and other available human resources to reduce doctors and nurses' workload [314]. Since the intervention was conducted during the period when the COVID-19 pandemic was at its peak, most of the healthcare workers were involved in services such as telemedicine, vaccinations, and data

collection of infected patients (COVID-19). Therefore, the suggestion of involving other human resources other than hospital assigned doctors and nurses was not implemented during the intervention phase. However, all the participants favored the idea of involving non-designated healthcare workers such as trainee nurses, intern nurses and other paramedics to ease their workload and assured to implement this model in their health system as a long-term work.

The participants acknowledged the benefits of co-interventions, such as the selection of clinical champions and posters demonstrating the FAST-M tools played an important part in the dissemination of knowledge about the FAST-M intervention. The active role of champions improved the patients and clinical outcomes through continuous monitoring and ongoing evaluations. Literature provides positive accounts of monitoring and evaluation, especially in healthcare developments, such as the development of a novel health information project in a health setting [362]. As the FAST-M intervention is implemented for the first time in an entirely new setting, continuous monitoring and evaluations by the senior trained healthcare professionals are necessary to support its establishment and normalisation into practice so it is sustainable in the long term.

The HCPs and administrators also supported sustainability and long-term implementation of the FAST-M intervention. HCPs believed that the healthcare administrator's role could further strengthen the use of the bundle approach. They also empowered healthcare providers working in other facilities to uptake this approach and further disseminate awareness of its use.

The major strength of this study is the use of CFIR which guided the researchers' focus and provided a predefined framework for the analysis of findings. The CFIR framework helped us in reflecting the five major domains [317] to evaluate the study outcomes and understand HCPs' views on the effectiveness of FAST-M intervention (Table 6.6). The CFIR framework also guided us in understanding the processes required for its implementation in an entirely new setting. Moreover, three separate focus group discussions with different groups of HCPs and health administrators that helped us in gaining their views and experiences to have better insights and knowledge regarding the process of implementation from each level.

The study also has some limitations. First, the study focused only on the perspectives of HCPs and administrators who were involved in the implementation of the FAST-M intervention. The focus on their perspectives might have let us miss the perspectives of patients and their families. Lastly, the intervention was implemented in only one study setting in Pakistan at this time. However, it is noted that this site serves a diverse population from the urban and rural areas of the province of Sindh.

We believe that the FAST-M intervention is feasible for use in the low-resource settings of Pakistan, and we recommend several strategies to address the challenges that were encountered during the implementation. The organisational leadership and HCPs require collaboration to work as a multidisciplinary team. The organizational structure and culture require modifications to strengthen HCPs linkages and relationships, which may be catalyzed through the empowerment of nurses and junior doctors who are important in the continuum of care.

The distribution of supportive resources to provide continuous education to doctors, nurses, and healthcare administrators about sepsis care is required to increase knowledge and awareness of sepsis care approaches. Also, facilities will require selected team leaders for the ongoing monitoring and evaluation of health indicators.

We have identified the feasibility of this intervention in one facility in Pakistan selected as our study site. The FAST-M tools had been previously adapted to ensure they were appropriate for the existing sepsis practices and circumstances of the current study setting. These findings show that this adaptation had been successful. If the FAST-M intervention is going to continue to expand to be used in other contrasting countries, we would recommend that a similar adaptation process should again be undertaken to ensure it is optimized for the new context. Future research is also needed to understand the feasibility of this intervention at the primary and secondary levels of care to reduce the delays in patient care for those patients who are referred from these facilities.

6.5. Conclusion

The FAST-M intervention has the potential to be used as an integrated approach for early recognition and management of maternal sepsis in low-resource health settings in Pakistan. The HCPs and health administrators' views and experiences from this study were encouraging in the implementation of the intervention and its relative outcomes. This paper provided qualitative findings on the outcomes of the FAST-M intervention and provided us with rich data to validate and explore our previously reported process and clinical outcomes and provide important information to support subsequent refinement and scaling of the intervention.

Table 6.6. Integration of qualitative and quantitative findings using CFIR domains and constructs

INTERVENTION CHARACTERISTIC		
Identified constructs	**Quantitative data**	**Selected quotations from qualitative data**
Evidence, Strength and Quality	Significant improvements were seen in monitoring of oxygen saturation [Difference: 74%; 95%CI:68.4%-80.5% p<0.01], fetal heart rate assessment [Difference: 42.02%; 95%CI: 33.7% to 50.28%; p=<0.01], and urine output [Difference: 23.5%; 95%CI: 17.6% to 29.4%; p<0.01] following the FAST-M intervention.	*The difference in monitoring you can say that if we take from 100, it used to be 20 so now you can say 60 by using this MEOWs chart (Obstetrician-3)* *"Patients are recovering now. Previously we were unable to identify what is their problem but now they are given proper treatment" (Postgraduate trainee-2)*
Complexity	Out of 239 screened women for the study, 112 (49.6%) were confirmed as maternal infection cases using the sepsis screening tools.	*"Our postgraduate trainees have also started picking sepsis cases. Previously, we used to just manage those patients who were detected cases of sepsis on admission but now we have started picking the new cases using the decision tool" (ICU director)*
Relative Advantage	The before-after outcomes observational record revealed that more women with maternal sepsis received the overall FAST-M bundle components within an hour during the intervention phase in comparison to the baseline phase [70.5%; (95%CI: 60.4% to 80.6%); p<0.01].	*"Now we have become more vigilant with administrating fluids and antibiotics on time. (Obstetrician-1)* *"Because we have started picking up sepsis patients on time, we administer fluids and antibiotics within one hour of the identification of those patients" (PG-1)*
Adaptability	FAST-M implementation improved fluid administration (35% vs 87.2%) and antibiotic administration (71.7% vs 96.2%).	*"FAST-M has helped us with the proper timelines and measurements to give the fluids" (Obstetrician-2)* *Previously, we used to give 1g ceftriaxone BD which was not effective but as it is documented in the treatment tool to give 2g ceftriaxone as stat dose within one hour to maternal sepsis patients and now we are observing its effectiveness" (Obstetrician-3)*
OUTER AND INNER SETTING		
Identified constructs	**Quantitative data**	**Selected quotations from qualitative data**
Patient Needs and Resources	There was an improvement in lab investigations specifically blood cultures for suspected sepsis patients during the intervention phase [45% (baseline) vs. 86% (intervention)].	*"We have started sending the blood cultures for sepsis patients now" (Obstetrician- 2)*
Structural Characteristics	The inpatient records during the baseline data (summer) presented 5500 women/ month admitted in all OBGYN units, whereas the admission records during winters showed 3200 women admitted to OBGYN units per month.	*"We get less flow of patients in the winter season, and this is the reason we have less rate of sepsis patients" (Resident doctor-1)*
Network and Communication	The strategies such as task sharing and strengthening of the transport system for	*"The patients' transportation time has now improved; we transfer critical patients immediately to ICU and then do all the*

	critical patients was implied during the intervention phase	*documentation, paper and file work" (Nurse- 2)* *"We look after 20 patients, the admitted patients, this is the main problem. But our doctors help us with monitoring vital signs and all other tasks. (Nurse -1)*
PROCESS		
Identified constructs	**Quantitative data**	**Selected quotations from qualitative data**
Planning, Engaging and Executing	To improve the source identification and control of infected patients, there was an improvement in the testing of suspected patients during the intervention phase (92% vs 100%) and complete patient management on the basis of the findings (41% vs 75%).	*We didn't use to send serum lactate but now we send for suspected sepsis case and from that, we get an idea that this is high-risk patient and then we monitor them accordingly" (PG II)*
Champions	There were considerable improvements seen in timely transportation (7% vs 60%) and the frequent monitoring of maternal sepsis patients during the intervention phase (12% vs 65%) as stated:	*"The patients' transportation time has now improved" (Nurse- 2)* *"Now we have this MEOWS chart in each patient file, so we frequently monitor them and record the findings and see the variations in all parameters over time" (Obstetrician-1)*
OUTCOMES		
Identified constructs	**Quantitative data**	**Selected quotations from qualitative data**
Reflecting and Evaluating	A decline in the sepsis related maternal mortality [32.7% vs. 23.3%; difference 9.4%; 95%CI: -11.45 to 19.9%; p=0.087] was observed after implementation of the FAST-M intervention.	*"Maternal mortality due to sepsis have reduced because of intervening fluid and antibiotics within an hour, the patients' outcome is positive" (Health administrator 1)* *"Maternal mortality and morbidity in our unit due to sepsis have reduced because of timely administration of fluids and antibiotics in an hour" (Resident doctor I)*
Engaging	The HCPs increased compliance with timely approach to patient monitoring showed significant difference during the baseline and the intervention phase in monitoring and recoding of parameters such as fetal heart rate in pregnant women (58% vs 100%), urine output (76.5% vs 100%) and oxygen saturations (25.5% vs 100%).	*"Now we monitor every patient using this MEOWS chart even if she is not a sepsis patient. This help us in monitoring patients' conditions for the time they are admitted in our wards" (Postgraduate trainee-II)*

This chapter provides further support to the quantitative findings that came out of the implementation process in Chapter 5 and reiterates the FAST-M intervention's feasibility in Pakistan. Strategies have been provided to overcome the challenges that were faced during implementation and these final evaluation findings provide more information to aid in future refinement and scaling of the intervention.

Chapter seven

DISCUSSION

7.1.Overview of thesis

The prevention, timely recognition, and rapid management of sepsis are major factors for curtailing related mortality and morbidity, as emulated in the World Health Assembly 2017 resolution on sepsis [122]. Considerable interventions, including appropriate antibiotics usage, trigger tools, and patient-care bundles enhance monitoring and lessen infection-related severe morbidity and deaths, both in the obstetric [343-346] and general population [347]. Nevertheless, data as to how effectively these interventions are implemented and how sepsis in obstetric population is detected and treated in healthcare facilities are limited. This information is vital for reduction of preventable infection related severe maternal morbidities and deaths, and for the application of quality improvement programmes. Consequently, the purpose of this PhD research was two-fold: firstly, to better understand prevention of maternal infections and secondly to seek to improve the early recognition, and management of maternal sepsis in a low resource health care setting.

The burden of maternal infection and sepsis in low- and middle-income countries was discussed, and the background to this research was explained **(Chapter 1).** The prevention of maternal infections was addressed by a systematic review conducted to evaluate the effectiveness of routine antibiotic prophylaxis for women undergoing uterine evacuation procedures to treat a miscarriage **(Chapter 2).** The background, methods and methodology to "Evaluation of the FAST-M maternal sepsis intervention in Pakistan" feasibility study was explained **(Chapter 3)**, Adaptation work (phase 1) discussed **(Chapters 4)**, before-after implementation (phase 2) quantitative results presented **(Chapters 5)**, qualitative results (phase 2) presented **(Chapters 6)** and discussed **(Chapter 5 & 6)**.

7.2. Purpose of this chapter

This chapter aims to summarise and conclude this research. The summary of findings, strengths and limitations are acknowledged and discussed for all the objectives and sub objectives outlined. The chapter also describes how the results of this research will inform future public and clinical health practice and research.

7.2.1. Objective 1: To evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage.

Infection is a serious consequence of uterine evacuation procedures to treat miscarriage and can result in serious illness and death [250]. Clinical evidence and guidance are clear that antibiotic treatment is needed for individuals experiencing miscarriage with signs and symptoms of infection [271]. However, it is less clear whether antibiotic prophylaxis is effective or necessary at the time of uterine evacuation procedures to treat miscarriage for individuals without signs and symptoms of infection prior to the procedure.

Given that miscarriage surgery is common and infective complications are frequent and serious, contributing to the high numbers of preventable maternal deaths around the world, prophylactic antibiotics, may offer a simple and affordable intervention to reduce maternal death and disability. A systematic review was conducted to synthesise the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage **(Chapter 2)**.

When all studies were considered, the low certainty evidence for prevention of uterine infection does not offer clear evidence to suggest whether routine antibiotic prophylaxis should be provided to individuals undergoing uterine evacuation procedures to treat miscarriage in settings where it is not known if the clinical presentation is a result of unsafe abortion practices. It is important to note that the quality of the evidence included was seriously affected by poor follow up and high non-compliance to antibiotic prophylaxis.

However, when trials assessed as low risk of bias only were meta-analysed (which includes 85% of the total participants), there was a reduction in uterine infection rates with antibiotic prophylaxis. This result suggests that the use of antibiotic prophylaxis reduces uterine infection in individuals undergoing uterine evacuation procedures to treat miscarriage. Moreover, both the overall and the meta-analysis of high-quality studies were consistent with a reduction in uterine infection with prophylactic antibiotics. Whereas it remains unclear whether the practice would lead to significant benefits over providing antibiotics only to those patients who are symptomatic of infection. It is also unclear if this type of prophylaxis has adverse consequences or longer-term harm.

Given the findings from the evidence assessed as being of low risk of bias, policymakers, clinicians and service users together may wish to weigh the well-established side effects of antibiotic treatment against the potentially significant short- and long-term impact that uterine infections can have [360-363].

There is uncertainty around the best antibiotic(s), route of administration and regime to give for prophylaxis for uterine evacuation procedures to treat miscarriage. The majority of trials in our review gave a tetracycline either alone or in combination (five out of six trials) orally (four out of six trials) and gave it for a short course of less than three days (five out of six trials). Therefore, there is uncertainty regarding how other antibiotics, given by different routes (e.g., intravenously), in different regimes (e.g., long course of three days or more) may compare. Likewise, there are too few studies on this topic to conduct stratified analyses, resulting in uncertainties around the effect that gestational age, type of miscarriage and type of surgery has on antibiotic prophylaxis for individuals undergoing uterine evacuation procedures to treat miscarriage.

Future randomised controlled trials (RCT), if conducted, should adhere to CONSORT guidelines, with adequate allocation concealment techniques and blinding to reduce selection and performance bias. They should measure and report the relevant core outcome sets whenever available, to enhance comparability across trials, and reduce heterogeneity of outcome and reporting bias. Future trials should have a pre-specified analysis plan and include an analysis to estimate the effect of assignment to the intervention (such as an intention-to-treat analysis) as well as sensitivity analyses to account for missing data.

Our findings from this review confirms that antibiotic prophylaxis appears beneficial in reduction of infection in women having miscarriage surgery. The meta-analysis includes the latest evidence on prophylactic antibiotics to reduce pelvic infection in women having miscarriage surgery. Our findings are useful in developing evidence-based guidelines and could inform future practice

particularly in Pakistan and other LMIC's, where there is widespread variation in use of antimicrobial prophylaxis in the event of miscarriage. However, increasing antimicrobial resistance, constrained economic resources and healthcare costs for antibiotics merits careful review.

7.2.2. Objective 2: Evaluation of the FAST-M maternal sepsis intervention for early recognition, and management of maternal sepsis in low resource health care setting in Pakistan

The implementation of the FAST-M intervention was ascertained as feasible, and effective in early identification, and management of maternal sepsis at the study setting in Pakistan. In low-resource settings, the lack of screening processes and resources can be an obstacle to the early detection and treatment of maternal sepsis [364-365]. Use of sepsis screening tools have been suggested to decrease the time required to start treatment [366-367]. It was observed, that whilst the Royal College of Obstetricians and Gynaecologist guidelines (RCOG) were recommended for patient management and treatment at the LUMHS hospital, there was no standardised chart for the recording of patients' vital signs. Instead, the vital signs were directly recorded into the patient's file.

The MEOWS chart used in the Malawian settings [300], was adapted before its implementation in Pakistan based on health care providers' suggestions during the adaptation phase of the study. Consequently, the health care providers were trained on an adapted MEOWS chart for regular recording of a full set of vital signs to screen patients who are at risk of developing sepsis, including the recording of oxygen saturations. There was high compliance with all monitoring

components after the intervention, with significant increase in compliance with completion of the MEOWS charts. A large improvement in the reliability of routine oxygen saturation recording following the intervention showed that this component was a feasible addition in the Pakistan context. An earlier study in Malawi on FAST-M intervention showed that the use of the MEOWS chart along with staff training led to the improvement in vital signs monitoring [300].

The FAST-M screening tools in Malawi facilitated the identification of maternal sepsis patients and guided health care staff to escalate management plans. Patients were more likely to receive a clinical review by the senior decision-maker based on the diagnosis of suspected maternal sepsis [300]. The present study shows that it was also true in the Pakistan context where the FAST-M decision tool along with the MEOWS chart guided health care providers in appropriate screening and identification of women with suspected sepsis and assisted in making timely decisions for such cases.

It's been reported that each part of the care bundle should be completed to reach the desired result, and failure to complete any of the components may have an impact on the overall patient outcome [368]. The bundle care tools we used guided health care providers with a recommended fluid administration approach and to cautiously reassess the patient's hemodynamic condition between fluid boluses, through clinical examination and monitoring of the patient's vital signs. This sought to avoid overloading the patient which can actually worsen sepsis outcomes [369-370].

The restoration of organ perfusion is an important goal of maternal sepsis treatment and fluid resuscitation should seek to restore organ perfusion while maintaining hemodynamic stability [368]. However, the benefits and risks of intensive early goal-guided fluid resuscitation have been the subject of intensive research [344-346, 371-373]. Higher volume of fluids in patients with sepsis and septic shock has been associated with harm, although a meta-analysis showed that the quality of evidence was very low. The CLASSIC pilot study showed that a restrictive fluid therapy was feasible in the ICU setting and it improve the mortality outcomes in the restrictive group, although not significantly [374].

Fluid management in patients with maternal sepsis and pre-eclampsia is challenging due to the increased risk of pulmonary oedema and must therefore be particularly cautiously managed by healthcare professionals [368]. During the FAST-M implementation, clear teaching and guidance were provided to the health care providers for proper fluid administration in pre-eclamptic or eclamptic patients.

The risk of death from sepsis increases with each hour of antibiotic delay (OR 1.04 per hour; 95 percent CI 1.03–1.06; p 0.001) [299]. As a result, empiric broad-spectrum antibiotics should be given as early as possible, and it is normally suggested that clinicians should aim to provide this where possible within 1 hour of sepsis detection. [184,299].

In LUMHS hospital, we modified the antibiotic therapy before implementation of the FAST-M treatment bundle intervention through a baseline audit survey and an adaptation phase to have HCPs views on the antibiotics recommendations. Ceftriaxone was selected as the first line of

antibiotic therapy, due to its low cost, and availability in the facility. Piperacillin/tazobactam and meropenem were included as second line therapy in the treatment bundle due to high levels of antibiotic resistance in this population, and their easy availability in the study setting making these the health care providers preference. **(Appendix 4.4)**. It's expected that significant improvement in timely initiation of antibiotic administration in the present study may have led to the improved clinical outcomes suspected maternal sepsis patients.

In the baseline phase, it was observed that clinicians had reservations to advise additional tests to identify the source of infection due to the logistics of undertaking these investigations in the facility and potential additional costs to be incurred by the patients. Considering this, the health care providers were given guidance during the training sessions regarding the significance of further investigations if the source is not initially clear with the clinical history and examination. Consequently, an increase was seen in measurements of blood culture, imaging (abdominal, and chest), urine and other blood tests in the intervention phase of the study [**Appendix 5.6].**

The assessment of need to transfer was significantly improved in the intervention period in the study setting. It was observed that LUMHS being the only tertiary referral public sector hospital in the area, its high dependency units (HDUs) and intensive care units (ICUs) were often fully occupied due to the high patient numbers and their needs. This led to the delay in transfer of women with maternal sepsis to higher levels of care. During the training programme, the importance of assessment of a patient for transfer was highlighted, and emphasis was made on expediting this process to ensure it was completed within an hour of sepsis detection if their vital signs were not improving after initial sepsis treatment.

The FAST-M training programmes helped HCPs with appropriate patient monitoring and their timely management. Earlies studies have also found a decrease of in-hospital mortality by 2–3% and decrease length of stay specifically training in teams for the early recognition, diagnosis, and treatment of patients with suspected or diagnosed sepsis [202-203]. “Sepsis rapid response team” supports in aiding the correct treatment measures and resource utilisation [203]. The teaching on appropriate use of each bundle component within a recommended timeframe was found to be effective in maternal sepsis management. The bundle components were taught by a team of experts in related areas, which helped HCPs in developing specific facility guidelines for fluid and antibiotic administration, specific tests for source identification, and transport of patients to high care units according to the priority of care needed.

The favorable results of this study have motivated HCPs to continue the application of the MEOWS chart in every obstetric patient and FAST-M bundle care tools for all cases of maternal infection. Hence, the hospital administration decided to include MEOWS chart along with other FAST-M tools in patients’ files of OBGYN units for monitoring all maternal patients and early recognition and management of maternal sepsis which is considered as a major achievement of this study.

The HCPs believed that the healthcare administrator's role could further strengthen the use of the bundle approach by empowering nurses and other available health care staff to uptake this approach and further disseminate awareness of its use.

We found when translating the FAST-M tools from Malawi to Pakistan some modification in the intervention were needed to ensure they were optimised for the local context and available resources. In LMIC, despite the high burden of sepsis, and though the need for advancement and assessment of evidence-based approaches to clinical care tailored to local context have been acknowledged, comparatively limited studies have addressed this gap in evidence to date [378-381]. Additionally, the result of studies till date have been a bit contradictory, which have further highlighted the necessity of adaptation of evidence and contextualising of clinical protocol.

FAST-M has the potential to be used as an integrative approach for early recognition and management of maternal sepsis in low resource settings of Pakistan and other LMICs. Although, there is a need for further/additional work to bring improvement in execution and assessment of the effect of this intervention on clinical care and outcomes. However, these efforts are unlikely to be sufficient alone, to address the high burden of sepsis mortality in LMIC, if lack of resources are not addressed properly [126].

To be able to begin timely care, the adjusted bundles should ideally be applicable within community-based healthcare settings in addition to only hospital settings, as this is where patients mostly present in LMICs [382]. To maximise coverage and improve sustainability, the adjustment process should be rigorous with wider involvement of practitioners delivering care in

such setting, alongside the input of patients, and be based on a realistic assessment of the available resources [382].

In Malawi, the FAST-M bundle implementation was shown to improve the screening, diagnosis and management of maternal sepsis [300], but it did not in that study demonstrate a reduction in maternal mortality, so our mortality reduction finding in Pakistan is particularly important owing to high rate of sepsis related maternal deaths in the country [82]. However, the finding can only indicate a trend as our selected study design cannot account for temporal trends and is disposed to risk of bias which may have contributed to this finding. This needs to be verified in a larger sample with a different study design. Although, a before-and-after design was considered as more practical approach to allow the fast and effective conduct of the study as part of the implementation process, future studies seeking to determine the effectiveness of intervention should use a cluster randomised design to reduce risks of bias.

Following the intervention, an additional qualitative evaluation was carried adopting CFIR framework to seek the perceptions of healthcare providers about the implementation of the FAST-M intervention in Pakistan (presented in Chapter 6). The CFIR framework helped us in reflecting the five major domains [316] to evaluate the study outcomes and understand HCPs' views on the effectiveness of FAST-M intervention (**Table 6.6)**. This is an important strength of this work.

Overall, the HCPs views and experiences from this study were encouraging in the implementation of the intervention and its relative outcomes. This additional evaluation provided qualitative findings on the outcomes of the FAST-M intervention and provided us with rich data to validate and explore our previously reported process and clinical outcomes and provide important information to support subsequent refinement and scaling of the intervention (**Table 6.6**)

Even though the intervention not only benefited patients who were diagnosed with sepsis, it helped improve overall patient care. The findings of this study have led to an optimised set of interventions, which means we are well placed for a further large-scale intervention trial. Also, this study adds further weight to Malawi work demonstrating the feasibility of the FAST-M bundle in different low resource settings.

Hence, the intervention will next be implemented in other low-resource settings including BHU's across Pakistan. A large multi-country randomised trial the Active Prevention and Treatment of Maternal Sepsis trial (APT-Sepsis) is also underway in Malawi and Uganda to more robustly ascertain the effectiveness of the FAST-M bundle as part of a wider sepsis prevention and management approach which will add further information on implementation at scale. Lastly, the qualitative evaluation of the study focused only on the perspectives of HCPs who were involved in the implementation of the FAST-M intervention. This focus on the HCPs perspectives might have let us miss the perspectives of patients and their families.

7.3. Conclusions

The systematic review concluded that giving routine antibiotics for uterine procedures may have little or no difference in reducing the risk of getting a uterine infection. However, combined findings from the three high quality studies demonstrated that giving preventive antibiotics reduces the risk of infection in the uterus after procedures for early pregnancy loss and possible reduction in hospitalisation for treatment of infection.

The adapted FAST-M intervention was feasible to implement in a tertiary care hospital of Pakistan and provided promising improvements in the identification and treatment of maternal sepsis cases. Based on this formative research, the long-term vision is that the FAST-M tools and implementation approach in their adapted format will be trialled in other settings across Pakistan, based on the outcomes of this feasibility study, which will help to reduce the high rate of maternal deaths caused by sepsis in the country.

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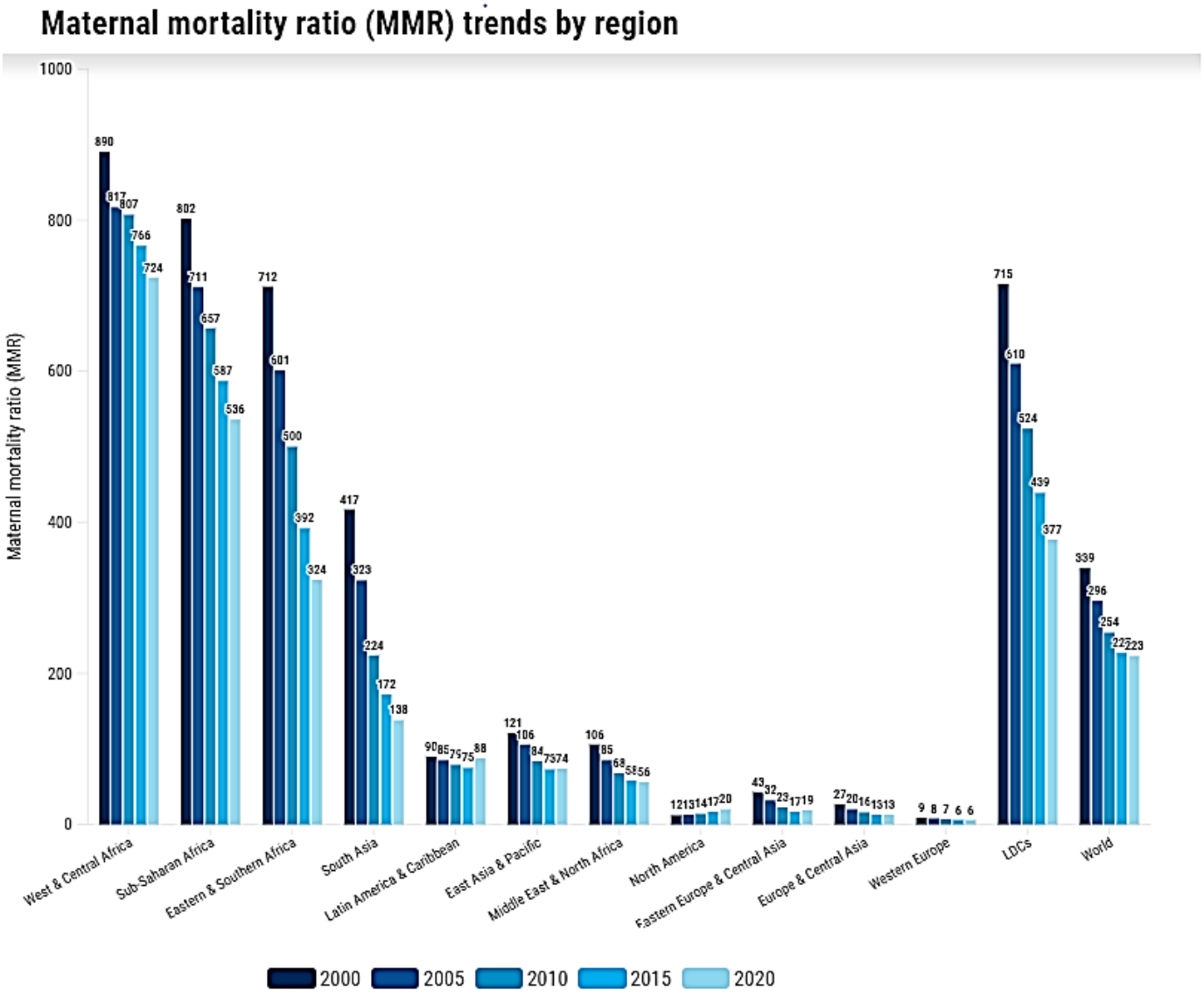
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Appendix 1.1.


Maternal mortality ratio (MMR) trends by region
Maternal mortality ratio (MMR)
1000
800
600
400
200
0
West & Central Africa
Sub-Saharan Africa
Eastern & Southern Africa
South Asia
Latin America & Caribbean
East Asia & Pacific
Middle East & North Africa
North America
Eastern Europe & Central Asia
Europe & Central Asia
Western Europe
LDCs
World
2000
2005
2010
2015
2020

Appendix 2.1: Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL; CRSWeb)
Date searched: Inception to 9 May 2022
1. (Abortion, Spontaneous OR Abortion, Incomplete OR Abortion, Missed OR Abortion, Septic OR Embryo Loss):MH AND CENTRAL:TARGET (643)
2. (("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR post-abortal OR (retained AND concept*) OR (product* AND concept*)):TI OR ("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR post-abortal OR (retained AND concept*) OR (product* AND concept*)):AB) AND CENTRAL:TARGET (6432)
3. #1 OR #2 (6577)
4. (Anti-Bacterial Agents OR Antibiotic Prophylaxis OR Doxycycline OR exp Tetracyclines OR Lactams OR Macrolides OR Metronidazole OR Nitroimidazoles OR Tinidazole OR Quinolones OR Oxolinic Acid OR Penicillins OR Sulfanilamide OR Infection OR Bacterial Infections):MH AND CENTRAL:TARGET (25855)
5. ((anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):TI OR (anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):AB) AND CENTRAL:TARGET (174803)
6. #4 OR #5 (180046)
7. #3 AND #6 (1042)

MEDLINE ALL (Ovid) 1946 to May 6, 2022
Date searched: 9 May 2022
1 Abortion, Spontaneous/ or Abortion, Incomplete/ or Abortion, Missed/ or Abortion, Septic/ or Embryo Loss/ (23945)
2 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*)) or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab,kf,kw. (58781)

3 or/1-2 (70708)
4 exp Anti-Bacterial Agents/ or Antibiotic Prophylaxis/ or Doxycycline/ or exp Tetracyclines/ or exp Lactams/ or exp Macrolides/ or Metronidazole/ or exp Nitroimidazoles/ or Tinidazole/ or exp Quinolones/ or Oxolinic Acid/ or exp Penicillins/ or Sulfanilamide/ or exp Infections/ or exp Bacterial Infections/ (3134258)
5 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab,kf,kw,nm,rn. (904822)
6 or/4-5 (3433577)
7 (controlled clinical trial or randomized controlled trial).pt. or (groups or placebo or random* or trial).ab. or dt.fs. (5135905)
8 (exp animals/ not humans/) or (animal or animals or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or feline or goat or goats or helminths or horse or livestock or mice or mouse or ovine or pig or pigs or porcine or rabbit or rabbits or rat or rats or rattus or sheep or sow or sows or swine).ti. (5189177)
9 7 not 8 (4394990)
10 and/3,6,9 (1820)

Embase.com
Date searched: Inception to 9 May 2022
#1 'incomplete abortion'/de OR 'blighted ovum'/de OR 'fetus wastage'/de OR 'missed abortion'/de OR 'septic abortion'/de OR 'spontaneous abortion'/de (52,575)
#2 'blastocyst disintegration':ti,kw OR (((febrile OR incomplete OR infect* OR missed OR septic OR spontaneous OR tubal) NEAR/3 abortion*):ti,kw) OR ((pregnancy NEAR/3 loss):ti,kw) OR (((embryo* OR fetal OR foetal OR fetus* OR foetus*) NEAR/3 (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)):ti,kw) OR miscarriage*:ti,kw OR postabort*:ti,kw OR 'post abort*':ti,kw OR ((retained NEAR/3 (concept* OR tissue*)):ti,kw) OR ((product* NEAR/3 concept*):ti,kw) (23,406)
#3 #1 OR #2 (62,668)
#4 'antiinfective agent'/exp OR 'antibiotic prophylaxis'/de OR 'doxycycline'/de OR 'lactam'/exp OR 'macrolide'/de OR 'metronidazole'/de OR 'tinidazole'/de OR 'oxolinic acid'/de OR 'penicillin derivative'/exp OR 'sulfanilamide'/exp OR 'tetracycline derivative'/exp OR 'nitroimidazole derivative'/exp OR 'quinolone derivative'/exp OR 'infection'/mj OR 'bacterial infection'/mj OR 'intrauterine infection'/exp (4,015,881)
#5 'anti bacterial*':ti,ab,kw OR antibacterial*:ti,ab,kw OR 'anti biotic*':ti,ab,kw OR antibiotic*:ti,ab,kw OR 'anti mycobacterial*':ti,ab,kw OR antimycobacterial*:ti,ab,kw OR bacteriocid*:ti,ab,kw OR cefoxitin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR doxycycline:ti,ab,kw OR fluroquinolone*:ti,ab,kw OR lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR metronidazole:ti,ab,kw OR nitroimidazole*:ti,ab,kw OR 'oxolinic acid':ti,ab,kw OR penicillin*:ti,ab,kw OR prophyl*:ti,ab,kw OR quinolone*:ti,ab,kw OR ((screen* NEAR/3 treat*):ti,ab,kw) OR tetracycline*:ti,ab,kw OR tinidazole:ti,ab,kw (965,387)
#6 #4 OR #5 (4,327,174)
#7 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de

OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti (2,688,881)
#8 ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim) NOT [humans]/lim OR animal:ti OR animals:ti OR bovine:ti OR canine:ti OR capra:ti OR cat:ti OR cats:ti OR cattle:ti OR cow:ti OR cows:ti OR dog:ti OR dogs:ti OR equine:ti OR feline:ti OR goat:ti OR goats:ti OR helminths:ti OR horse:ti OR livestock:ti OR mice:ti OR mouse:ti OR ovine:ti OR pig:ti OR pigs:ti OR porcine:ti OR rabbit:ti OR rabbits:ti OR rat:ti OR rats:ti OR rattus:ti OR sheep:ti OR sow:ti OR sows:ti OR swine:ti (4,543,611)
#9 #7 NOT #8 (2,461,690)
#10 #3 AND #6 AND #9 (954)

Global Health (Ovid) 1973 to 2022 Week 18
Date searched: 9 May 2022
1 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*)) or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab. (8686)
2 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab. (217234)
3 and/1-2 (380)

Scopus
Date searched: Inception to 9 May 2022
TITLE-ABS-KEY ("blastocyst disintegration" OR ((febrile OR incomplete OR infect* OR missed OR septic OR spontaneous OR tubal) PRE/3 abortion*) OR (pregnancy PRE/3 loss) OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) PRE/3 (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabort* OR post-abort* OR (retained PRE/3 (concept* OR tissue*)) OR (product* PRE/3 concept*)) AND TITLE-ABS-KEY (anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* PRE/3 treat*) OR tetracycline* OR tinidazole) AND TITLE-ABS-KEY (groups OR placebo OR random* OR trial) AND (LIMIT-TO (DOCTYPE , "cp")) (51)

Appendix 2.2. Characteristics of excluded studies

Study	Reason for exclusion
Abudu 1986	Wrong patient population
Achilles 2011	Wrong patient population
Adelusi 1985	Wrong patient population
Al Maani 2014	Wrong intervention
Amarin 1981	Not miscarriage
Anderson 2009	Wrong intervention
Anonymous 1981	Wrong patient population
Barinov 2019	Wrong intervention
Barrett Connor 1969	Not RCT
Baxi 1971	Wrong patient population
Berget 1972	Not miscarriage
Bibileishvili 1988	Wrong patient population
Bigrigg 1990	Wrong patient population
BowesWAJr 2003	Not RCT
Bravo Scandoval 1976	Wrong study design
Brewer 1980	Wrong patient population
Brewer 1980	Wrong patient population
Brown 2003	
Brown 2003a	Not RCT
Caruso 2008	Wrong comparator
Cavanagh 1972	Wrong patient population
Chen 2007	Not RCT
Chimura 2001	Wrong patient population
Chow 1977	

Chow 1977	Wrong patient population
Chow 1977a	Wrong patient population
Colombo 1990	Not miscarriage
Connolly 1972	Not RCT
Cormier 1988	Not miscarriage surgery
Crowley 2001	
Crowley 2001a	Not miscarriage
Dahm 1973	Wrong patient population
Damianov 2004	Wrong patient population
Darj 1987	
Eschenbach 2015	Not RCT
Ezeta 1972	Wrong patient population
Fang 2009	Wrong intervention
Fawcus 1997	Not RCT
Fawcus 1997a	Not RCT
Fjerstad 2011	Not miscarriage
Fouks 2020	Wrong study design
Fox 2002	Not RCT
Foy 2004	
French 1985	Wrong patient population
Fu 2020	Not RCT
Gallos 2017	Wrong intervention
Gebreselassie 2005	
Goisis 1966	Wrong patient population
Gomez 2004	Wrong intervention
Goranitis 2019	Not RCT

Greenland 2003	Wrong intervention
Grimes 1984	Not RCT
Grnlund 2002	Wrong intervention
Gupta 2007	Not RCT
Haas 2008	Wrong patient population
Hechtermans 1969	Wrong patient population
Heisterberg 1986	
Heisterberg 1982	Not miscarriage
Heisterberg 1985	Not miscarriage
Heisterberg 1985b	Wrong patient population
Heisterberg 1985c	Not miscarriage
Heisterberg 1985d	Not miscarriage
Heisterberg 1986	Wrong patient population
Heisterberg 1987	Not miscarriage surgery
Heisterberg 1987	Not miscarriage surgery
Heisterberg 1987a	Not miscarriage surgery
Heisterberg 1988	Wrong patient population
Heisterberg 1992	Wrong patient population
Henriques 1994	
Henriques 1994	Wrong patient population
Hodgson 1975	
Horta 1971	Wrong patient population
Houang 1991	Not RCT
Islam 2020	Not RCT
Islam 2021	Not RCT
ISRCTN11046192 2020	Wrong intervention
ISRCTN14476388 2004	Wrong intervention
ISRCTN66418282 2004	Wrong intervention

ISRCTN97143849 2013	Study Protocol
Jaffe 2006	Wrong intervention
Jin 2005	Not miscarriage surgery
Jones 1967	Wrong patient population
Josey 1970	Wrong patient population
Kapp 2013	Wrong study design
Karlsen 2001	Wrong intervention
Karschnia 1974	Not RCT
Katsulov 1990	Wrong indication
Keith 1971	Wrong patient population
Krohn 1986	Not miscarriage
Lamy 2012	Not RCT
Lapinsky 2013	Not RCT
Larsson 2000	Not miscarriage
Larsson 2006	Not RCT
LedezmaHerrera 1967	Not RCT
Ledger 1977	Wrong patient population
Ledger 1983	Wrong patient population
Ledger 1985	Not RCT
Lehmann 1975	Wrong patient population
Levallois 1988	
Levallois 1988	Wrong patient population
Lichtenberg 2003	
Lichtenberg 2003a	Not miscarriage
Lissauer 2018	Study Protocol
Lissauer 2019a	Duplication
Little 1974	Not RCT

LopezOrtiz 1978	Wrong patient population
LopezOrtiz 1978a	Wrong patient population
Lorincz 1971	Wrong patient population
Low 2012	Not RCT
Marshall 1982	Wrong indication
Martinez 1966	Not RCT
May 2000	Not RCT
May 2007	Not RCT
McNamee 2014	Not RCT
Miller 2004	
Miller 2004a	Wrong patient population
Miller 2005	Not miscarriage
Minasova 1973	Wrong patient population
Minasova 1977	Wrong patient population
Moller 1982	Not miscarriage surgery
Morgan 2006	Wrong patient population
Mphahlele 1979	Not RCT
Nalbanski 2003	No differentiation of the outcomes between the treatment groups
NCT00353743 2006	Wrong patient population
NCT00376493 2006	Wrong patient population
NCT01842100 2013	Not miscarriage surgery
Nielsen 1993	Wrong patient population
Obata 1987	Wrong patient population
ONeill 1972	Not RCT
Osser 1989	Not miscarriage
Ostergard 1970	Wrong intervention

Packard 1982	Not RCT
Pauleta 2009	Wrong intervention
Penney 1997	Wrong patient population
Penney 1997a	Wrong patient population
Penney 1998	
Penney 1998a	Not miscarriage
Petersen 1989	Not RCT
Petrou 2006	Wrong intervention
Plotko 2014	Wrong patient population
Prieto 1995	
Qvigstad 1983	Not miscarriage
Rahangdale 2009	Not RCT
Reeves 2005	Cost-effective analysis - not RCT
Ridgway 1983	Wrong patient population
Rossi 1984	Not miscarriage surgery
Sahin 2001	Wrong intervention
Santamarina 1970	Wrong patient population
Santamarina 1970a	Not RCT
Savaris 2011	Wrong patient population
Savaris 2018	Wrong patient population
Sawaya 1996	Not miscarriage
Schwarz 1976	Not RCT
Shelley 2005	Wrong intervention
Shirkey 1972	Not miscarriage
Shukunami 2005	Wrong intervention
Sivasamboo 1968	Wrong patient population
SLCTR2008011 2008	Wrong intervention

SLCTR2014029 2014	Wrong intervention
SLCTR2017014 2017	Wrong intervention
SLCTR2017023 2017	Wrong intervention
Smith 1970	Wrong patient population
Sonalkar 2019	Not RCT
Sonne Holm 1981	Wrong patient population
Sonne-Holm 1981	
Sorensen 1992	Not miscarriage
Sorensen 1994	Not miscarriage
Soto 1970	Wrong patient population
Soto 1970a	Wrong patient population
Soto 1974	Wrong patient population
Spence 1982	
Trinder 2006	Wrong intervention
Tropea 1970	Not RCT
Udoh 2016	Not RCT
Udoh 2016a	Not RCT
Ugwumadu 2003	Wrong patient population
VanEyk 2012	Wrong patient population
VanEyk 2012a	Wrong patient population
VanEyk 2018	Wrong patient population
vanSchalkwyk 2010	Not RCT
Weeks 2005	Wrong intervention
White 1979	Duplication
Wilkinson 1995	Wrong patient population
Wilkinson 1995a	Not miscarriage

Zahran 2016	Not miscarriage surgery
Zak 1967	Wrong patient population
Zambrano 1991	Wrong study design
ZhangDiKai 2012	Wrong patient population
ZhangZhiMin 2019	Not RCT

Appendix 2.3. Characteristics of included studies

Lissauer 2019

Study characteristics	
Methods	2 arm placebo randomised controlled trial
Participants	3412 women were randomised across 13 centres in Malawi, Tanzania, Uganda and Pakistan between June 2014 to April 2017. Population comprised of women with incomplete or missed miscarriage at less than 22 weeks gestation and were scheduled to undergo uterine evacuation to treat miscarriage by sharp curettage, manual vacuum or suction curettage. Exclusion criteria comprised of women who had evidence of induced abortion or current pelvic infection, a need for immediate surgery, women who were currently or had recently taken antibiotics (within 7 days), and women with an age younger than 16 years, or with any other contraindication to doxycycline or metronidazole.
Interventions	Doxycycline 400 mg (Tetracycline) and metronidazole 400 mg (nitroimidazoles) administered orally approximately two hours before surgery versus placebo administered orally approximately 2 hours before surgery. No other interventions were reported.
Outcomes	The study reported the following outcomes: Uterine infection, adverse effects, antibiotic treatment to treat infection after uterine evacuation procedure to treat miscarriage, hospitalisation for treatment of infection. Uterine infection was defined as two or more of four clinical features — purulent yellow, green, or foul-smelling vaginal discharge; pyrexia (>38.0°C according to ear thermometry); uterine, parametrial, or adnexal tenderness on examination; and a white-cell count of more than 12×109 per litre and was assessed 14 days after miscarriage surgery.
Notes	Gestation at time of procedure: <12weeks, ≥12weeks, and unclear Inclusions (or evidence of) unsafe or surgical abortion: Not commented on Additional interventions: None reported

PrasangaDPGGM 2017

Study characteristics	
Methods	2 arm placebo randomised controlled trial
Participants	394 women were randomised from 1 centre in Sri Lanka from May 2014 - end date not reported. Population comprised of women with incomplete or missed miscarriage at less than 20 weeks gestation and were scheduled to undergo uterine evacuation to treat miscarriage (type of surgery is not reported). Exclusion criteria comprised of women who had evidence of current pelvic infection or with an allergy to doxycycline.
Interventions	Doxycycline 400 mg (Tetracycline) administered orally approximately one hour before surgery versus placebo administered orally approximately 1 hour before surgery.
Outcomes	The study reported the following outcomes: Uterine infection, antibiotic treatment to treat infection after uterine evacuation procedure to treat miscarriage. Uterine infection was defined as three or more of the following: a history of fever, lower abdominal pain, smelly vaginal discharge, pyrexia >37°C, lower abdominal tenderness, positive cervical motion test with or without adnexal tenderness, presence of smelly vaginal discharge and was assessed 14 days after miscarriage surgery.
Notes	Gestation at time of procedure: <=20 weeks Inclusions (or evidence of) unsafe or surgical abortion: Not reported Additional interventions: None reported

Prieto 1995

Study characteristics	
Methods	2 arm randomised controlled trial
Participants	345 women were randomised from one centre in the USA between July 1991 and April 1994. Population comprised of women with incomplete miscarriage less than 14 weeks gestation and were scheduled to undergo uterine evacuation to treat miscarriage by suction curettage. Exclusion criteria comprised of women who had evidence of current pelvic infection, with an allergy to doxycycline or haemodynamically unstable.
Interventions	Doxycycline 100 mg (Tetracycline) administered intravenously at the time of surgery versus placebo intravenously at the time of surgery
Outcomes	The study reported the following outcomes: Uterine infection, hospitalisation for treatment of infection. Uterine infection was defined as two or more of the: low abdominal pain, uterine, adnexal, or cervical motion tenderness, purulent vaginal discharge, white cell count of more than 15,000/mm3, pyrexia >38.0°C.and was assessed 2-3 weeks after miscarriage surgery.
Notes	Gestation at time of procedure: <=14 weeks Inclusions (or evidence of) unsafe or surgical abortion: Not reported Additional interventions: None reported

Ramin 1995

Study characteristics	
Methods	2 arm placebo randomised controlled trial
Participants	300 women were randomised from one centre in the USA between November 1992 and June 1993. Population comprised of women with incomplete miscarriage less than 14 weeks gestation and were scheduled to undergo uterine evacuation to treat miscarriage by suction curettage. Exclusion criteria comprised of women who had evidence of current pelvic infection, with an allergy to tetracycline or doxycycline or antibiotic use within the previous 2 weeks, or any medical illness such as diabetes mellitus or cardiac or pulmonary disease or unstable vital signs.
Interventions	Doxycycline 200 mg (Tetracycline) administered orally approximately 30-60 mins before surgery versus placebo administered orally approximately 30-60 mins before surgery.
Outcomes	The study reported the following outcomes: Uterine infection, hospitalisation for treatment of infection. Uterine infection was defined as pyrexia >38.0C, abdominal pain, tenderness on one or both sides of the abdomen, uterine tenderness, parametrial tenderness elicited upon bimanual examination, and foul-smelling lochia and was assessed two weeks after miscarriage surgery.
Notes	Gestation at the time of procedure: <14 weeks Inclusions (or evidence of) unsafe or surgical abortion: Not commented on Additional interventions: None reported

Seeras 1989

Study characteristics	
Methods	2 arm randomised controlled trial
Participants	140 women were randomised from one centre in the Zimbabwe between February and May 1985. Population comprised of women with incomplete miscarriage (gestational age range was not reported) and were scheduled to undergo uterine evacuation to treat miscarriage (surgery type was not reported). Exclusion criteria comprised of women who had evidence of current pelvic infection.
Interventions	Tetracycline 500mg administered orally four times a day for seven days versus no treatment.
Outcomes	The study reported the following outcomes: Uterine infection, antibiotic treatment to treat infection after uterine evacuation procedure to treat miscarriage. Uterine infection was defined as three of more the following: history of fever, headache or lower abdominal pain, pyrexia >37 degrees Celsius, abdominal tenderness, positive cervical excitation test, foul smelling vaginal discharge and was assessed one week after miscarriage surgery.
Notes	Gestation at time of procedure: Not reported Inclusions (or evidence of) unsafe or surgical abortion: None reported Additional intervention: None reported

Titapant 2012

Study characteristics	
Methods	2 arm placebo randomised controlled trial
Participants	84 women were randomised from one centre in the Thailand between November 2008 and October 2010. Population comprised of women with incomplete miscarriage equal to or below 12 weeks gestation and were scheduled to undergo uterine evacuation to treat miscarriage by uterine curettage (no other details reported). Exclusion criteria comprised of women who had cephalosporin or penicillin allergy, diabetes mellitus, acquired immunodeficiency syndrome, anaemia or hypovolaemic shock.
Interventions	Cefoxitin 1g (cephalosporin) administered intravenously approximately 20 minutes before surgery versus placebo administered intravenously approximately 20 minutes before surgery.
Outcomes	The study reported the following outcomes: Uterine infection, antibiotic treatment to treat infection after uterine evacuation procedure to treat miscarriage. Uterine infection was defined as three or more of the following: history of fever, headache or pelvic pain, pyrexia >38 degrees Celsius, tenderness on one or both sides of the abdomen, positive cervical excitation test, or presence of a foul smelling vaginal discharge and was assessed up to 7 days after miscarriage surgery.
Notes	Gestation at time of procedure: <=12 weeks Inclusions (or evidence of) unsafe or surgical abortion: Not reported Additional interventions: None reported.

Appendix 2.4. Risk of bias for analysis

Study	Bias											
	Randomisation process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported results		Overall	
	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement
Lissauer 2019	Low risk of bias	Computerized randomization was performed centrally through a secure Internet facility, with the use of minimization to balance trial-group assignments. Patients, clinicians, and research staff were unaware of the trial-group assignments throughout the trial	Low risk of bias	Patients, clinicians, and research staff were unaware of the trial-group assignments throughout. All analyses were performed according to the intention-to-treat principle.	Low risk of bias	Total missing outcome data <10% (Treatment 24 out of 1700, 1.4%. Placebo 20 out of 1704, 1.2%)	Low risk of bias	Diagnosis criteria was based on the presence of clinical features (two or more of four features). Later the following was added: the presence of one of the clinical features in addition to the clinician's judgment that antibiotics were needed for the treatment of pelvic infection (needed for patient safety) but all caregivers and assessors were blinded. The same definition was used and assessors were blinded	Low risk of bias	ITT – as per SAP pre-specified Sensitivity analyses for the primary outcome include an unadjusted analysis, a per protocol analysis, and assessment of missing primary outcome data, under the assumption that all missing outcomes were pelvic infections and by means of a multiple-imputation approach. Pre-specified SAP in protocol and reported outcomes match protocol	Low risk of bias	Low risk of bias in all domains
PrasangaDPGGM 2017	Low risk of bias	Participants were randomised using computer generated random numbers.	Low risk of bias	blinded – placebo trial, Clinicians were also blinded to the treatment received. Not reported	Low risk of bias	10 women were lost to follow up (4 %). three patients	Low risk of bias	Independent blinded outcome assessor used. Clinical signs of infection were	Some concerns	Not reported if statistical analysis plan present or finalised ahead of analysis. Analysis population	Low risk of bias	Most domains assessed as low risk of bias, with some concerns in reported result but unlikely to impact the

		Sequentially numbered, opaque envelopes used (allocation concealment). Baseline characteristics generally well balanced.		if analysed by intention to treat (but assume this was the case from numbers in CONSORT and numbers analysed). Adherence figures not reported.		in the doxycycline group (2.3 %) and seven patients in the placebo group (5.5 %). Therefore, the presence of pelvic infection was not known to them.		measured before discharge from the unit, and two weeks later by a third person at gynaecology clinic, who also blinded		not formally reported but assumed intention to treat utilised from number of women randomised in CONSORT and number of women analysed in each arm. Same clinical definition was used for primary outcome – reported outcome matches those reported in protocol that was published prospectively. primary outcome matches outcome reported in protocol that was published prospectively		result and overall bias of study.
Prieto 1995	Low risk of bias	Computer software program (TrueEpistat, Richardson, TX) was used to generate a random block allocation sequence to assign patients to either group. sequentially numbered, opaque, sealed packets that were prepared independently of the physicians managing the patient. The randomization was known only after the patient had been enrolled in the study. Baseline characteristics	High risk of bias	Described as an open-label study women were not blinded. Caregivers not blinded. Follow-up physical examinations and cervical cultures were obtained on 240 (69.5%) patients. Fifty-one patients from the doxycycline group and 54 patients from the placebo group (LOS total [30.5%]) were lost to follow-up. Of	High risk of bias	105 (30%) were lost to follow up (balanced between groups, 51 intervention vs. 54 control). No sensitivity analyses reported to account for missing data. It is poss ble that the missingness in	Low risk of bias	No blinding but outcome assessor didn't have knowledge of allocations. Outcome assessor didn't have knowledge of allocations.	Some concerns	Not reported if SAP present or finalised ahead of analysis. Analysis population(s) not reported. The study protocol was unavailable for verification, however no multiple outcome measures were reported and no multiple eligible analyses were reported.	High risk of bias	Not reported if an intention to treat analyss was conducted. High amount of missing data and no sensitivitiy analysis to account for this. Highly likely to impact the overall result.

		relatively well balanced.		those 105 patients, 75 were contacted by phone but did not show up for their examination, 18 had no phone and were sent a certified letter without a response, and 12 patients left the state. Of the 240 patients with follow-up, there were 120 in both the doxycycline and control groups. Random block allocation and a differential between follow-up in each group explains the identical numbers of patients remaining for analysis. Not reported if analysis was by ITT. >5% 105(30%) women out of 345 women were lost to follow up and removed from analyses. Adherence figures not reported.		the outcome depend on its true value although unlikely as the paper states that “this hospital is the only resource for health care. Further more, the patients most likely to appear for follow-up are the ones who are sympto matic. Thus, it is unlikely that many cases of infectiou s morbidit y were missed because the patients would have returned to this institutio n for their care”. The majority of those that did not return for follow up were similar contacte d by phone or letter – not						

						reported if women reported infective symptoms (12 women moved state). Missing outcome data were similar across both arms.						
Ramin 1995	Some concerns	No details on random allocation sequence. Sealed envelopes. Baseline characteristics relatively well balanced.	Some concerns	Double blind but not clear who was blinded (assume women and caregivers). Not reported if analysis was by ITT. After randomization, 11 women were excluded from analysis (arms not reported): 3 women in whom the curettage was not performed, 6 who had had recent antibiotic use, 1 who underwent an emergent hysterectomy for uterine perforation and haemorrhage (criteria making the participants ineligible for study participation), and 1 who did not receive the assigned study drug.	Some concerns	41 with missing outcome data (30 lost to follow up, 11 excluded post-randomisation; 15 from each arm). No sensitivity analyses reported to account for missing data. However, the missing data was similar across arms. Unlikely as the medical records on the 30 women lost to follow up were reviewed, and these women were found to have had either gynaeco	Low risk of bias	Same definition and follow up period for both arms used for all participants – definition commonly used across pelvic/uterine infection trials. Study was double blind but not clear who was blinded, presumed assessors were blinded	Some concerns	Not reported if SAP present or finalised ahead of analysis. Analysis population(s) not reported. Although the study protocol was unavailable for verification the study does not report using multiple eligible outcome measurements or multiple eligible analyses of the data.	Some concerns	Study has limitations in a number of areas but steps taken to acocunt for this - high number of women lost to follow up but medical records were checked. Although not stated who was blinded, study states double blinded. Overall, may bias the result.

						logy or family planning visits within a year after the abortion. None of these women reported complic ations surroun ding the suction curettag e.						
Seeras 1989	Low risk of bias	Patients were randomised into two groups using sealed envelopes containing the treatment modality. Table 1 and 2 show that age and parity distr bution in both treatment and non-treatment groups are similar	High risk of bias	Not mentioned in the text if participants, care givers or assessors aware of their assigned intervention during the trial. no mention of placebo use, and other group did not receive any treatment . The majority (82.6%) had in fact either not taken part of the course or the whole course. The few who did, failed to follow instructions properly. This study demonstrate d that poor compliance to the drug regimen was a major contributory factor relating to the outcome. Authors state high level of non-compliance with intervention in the treatment	Low risk of bias	Treatme nt 2 out of 60 = 3.33% Non-treatme nt 3 out of 75 = 4% (follow-up via post)	Low risk of bias	Review of the patients was undertaken after 1 week. There are five parameters for sepsis, of which three needed to be present to give the sepsis diagnosis. Patients who did not show up for review were contacted via post (27 in total, 19.3%). Those who were well and did not receive treatment elsewhere were considered non septic. Blinded assessor conducted the examination. Examiner did not know study allocation so unl kely – it sounds l ke examiner was the same for all women so unl kely to be differences between	Some concern s	No mention of pre-specified analysis plan. No study protocol available for verification of reported outcomes. The same 'reviewer' that was unaware of the allocation and used a single definition. Protocol was unavailable for verification. No multiple eligible analysis or eligible outcome measureme nts reported.	High risk of bias	The high rate of non-compliance is likely to bias the result.

				arm, therefore it is likely that an ITT was performed, otherwise a substantially smaller data set would have reported outcome data in the intervention arm. No analysis reported				examinations (although reporting is not explicit). States that reviewer was unaware of the intervention allocations.				
Titapant 2012	Low risk of bias	All the patients were randomly allocated into two groups. Randomisation was done via a computer-generated random number list. Allocation concealment was maintained using a sealed opaque envelope. Baseline characteristics relatively well balanced.	Low risk of bias	The patients were not informed about type of medication used. Blinded. The carers and people delivering the interventions were blinded to the treatment received. Did not say whether analysis was ITT. Also did not report adherence. >5% (5 women) excluded from analyses. Adherence figures not reported.	Low risk of bias	During experiment, out of 84 enrolled women five patients were excluded post randomisation (one patient was allergic to cefoxitin, two patients had abnormal pathological reports, and two patients did not show up at the scheduled appointments). Thus, 79 patients left in the experiment. The study group had 40 patients and the control group had 39 patients (<10%).	Low risk of bias	Outcome collectors blinded to the treatment received.	Some concerns	Not reported if SAP present or finalised ahead of analysis. Analysis population(s) not reported. Study protocol was unavailable for verification, however no multiple outcome measurements or multiple analyses were reported in paper.	Low risk of bias	Most domains low risk of bias, no multiple analyses reported. Publication of protocol was common practice after this study was conducted. Unlikely to impact result.

Appendix 2.5. Published protocol

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[Intervention Protocol]

Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage

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Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage

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A B S T R A C T

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:
The objective of this review is to evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage.

B A C K G R O U N D

Description of the condition

Over 208 million women around the world become pregnant each year (Singh 2010), but an estimated 10% to 20% of pregnancies end as a miscarriage (Adolfsson 2006; Linnakaari 2019; Maconochie 2007; Magnus 2019; Patki 2016; Rossen 2018). One in four women experience miscarriage in their lifetime (Alberman 1992). Miscarriage is defined as the unintended loss of pregnancy in the first 24 weeks (Giakoumelou 2016), although this is defined differently around the world with some countries reporting miscarriage up to 28 weeks of pregnancy (WHO 2021). Miscarriage, induced abortion and ectopic pregnancy collectively were estimated to be responsible for around 193,000 maternal deaths between 2003 and 2009 (Say 2014).

The language used around miscarriage is important to women and their families (WHO 2021)._The term 'miscarriage' is preferred to '(spontaneous) abortion'. The change in terminology has been supported by patient organisations and clinicians for several decades (Beard 1985; Cameron 2005; Chalmers 1992; Gardner 1972; Harison_ 1986; Hutchon 1998; Moscrop 2013; Pridjian 1989; Silver 2011). The use of the term miscarriage is also supported by researchers and early pregnancy special interest groups, for consistency (Kolte 2015).
The common clinical signs and symptoms associated with miscarriage can vary with the type of miscarriage that a woman is experiencing and the gestational age or size of the pregnancy (NICE 2019b). A complete miscarriage is when all of the pregnancy tissue is expelled from the uterus. This is associated with heavy vaginal bleeding, severe abdominal pain and the passage of all the pregnancy tissue. Complete miscarriage does not require any interventions for treatment. Incomplete miscarriage is likely to be associated with vaginal bleeding and abdominal pain, as the pregnancy tissue has been partly expelled from the uterus (NICE 2019a). Missed miscarriage (sometimes known as delayed or silent) is when a non-viable pregnancy is identified via ultrasonography. All the pregnancy tissue is retained in the uterus, so women may have no symptoms or a small amount of vaginal bleeding (NICE 2019a).

Incomplete and missed miscarriage can be treated conservatively, medically or surgically. Expectant management involves waiting for the pregnancy tissue to pass naturally. Medical management involves medications (mifepristone plus misoprostol or misoprostol alone) to make the womb expel the pregnancy tissue. Surgical management involves the removal of the pregnancy tissue during surgery. A recent Cochrane Review (Ghosh 2021), found that medical and surgical methods of uterine evacuation to treat miscarriage were more effective than when

compared with expectant management. Expectant management was found to have the lowest chance of successful uterine evacuation and the highest chance of serious complications, including the need for unplanned or emergency surgery. The evidence however, did suggest that surgical methods of uterine evacuation carried higher risks of pelvic infection when compared to medical methods of uterine evacuation or expectant management.

Uterine evacuation procedures to treat miscarriage are a common reason for hospital admission, with some hospitals in low-income settings reporting up to 70% of gynaecological hospital admissions for miscarriage surgery (Lema 1994). A survey of health facilities in Malawi in 2015 estimated that the number of cases treated for post-abortion care was over 67,000 (including both miscarriage and induced abortion), with over 15,000 of these cases being late miscarriages (Polis 2017).

Pregnancy-related infection was estimated to be responsible for 261,000 maternal deaths between 2003 and 2009, with over 99% of these deaths being in low- and middle-income countries (Say 2014).Infection after uterine evacuation procedures to treat miscarriage is reported to occur in 6% of women in high-income countries (Prieto 1995; Ramin 1995), and up to 30% of women in low-income countries (Seeras 1989). Pelvic infection is a serious complication of uterine evacuation procedures to treat miscarriage and can result in serious illness and death (Me lese 2017).It can also have long-term consequences, which can increase rates of ectopic pregnancy and infertility (Cates 1985). As well as physical effects, miscarriage can also have considerable emotional and societal implications for women and their families, with the consequences of miscarriage lasting far beyond the length of the pregnancy (Conway 2000; Farren 2020; Geller 2001; Murphy 2012; Neugebauer 1997).

Description of the intervention

Antibiotic prophylaxis can be defined as the administration of "antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications" (National Centre for Biotechnology Information 2021). Prophylactic antibiotics are given for certain surgical procedures to reduce infection after surgery, including vacuum aspiration for abortion care (Low 2012; WHO 2015). For uterine evacuation procedures to treat miscarriage, the administration of prophylactic antibiotics would mean that women are given antibiotics around the time of uterine evacuation even if they are not known to have genital tract infections.

Studies have demonstrated that almost 50% of women in some regions are prescribed prophylactic antibiotics for uterine evacuation procedures to treat miscarriage (Fawcus 1997), and that prophylactic antibiotics may improve outcomes (Melese 2017). In this review, prophylaxis will be defined by the administration of antibiotics to prevent infection.

A Cochrane Review, May 2007, examined the evidence on antibiotics for incomplete abortion, and, with the inclusion of a single study, (Seeras 1989), concluded there was "not enough evidence to evaluate a policy of routine antibiotic prophylaxis to women with incomplete abortion". This review stated the “real and urgent need to find out whether antibiotics should routinely be used in cases of incomplete miscarriages”. The World Health Organisation (WHO) recommends electric or manual vacuum aspiration as uterine evacuation procedures to treat miscarriage before 12 to 14 weeks (WHO 2015). Vacuum aspiration is also called suction curettage or dilatation and suction and uses a vacuum source to remove pregnancy tissue. Vacuum aspiration does not require electricity and can be used with a handheld vacuum syringe (manual vacuum aspiration) or electric pump. Sharp metal curettage to remove pregnancy tissue after dilatation of the cervix (if required) used to be common practice for uterine evacuation to treat miscarriage (WHO 1995). A sharp metal curettage (also known as dilatation and curettage) was used to remove the pregnancy tissues from the uterus, however, sharp curettage is associated with a higher incidence of pelvic infection when compared to vacuum aspiration (Tuncalp 2010), and is no longer recommended due to the increased incidence of such complications and associations with Asherman’s syndrome (intrauterine adhesions;_FIGO 2011). Many clinicians in low-income settings use sharp metal curettage because they are not trained in vacuum aspiration or do not have the necessary equipment to perform vacuum aspiration.

Uterine evacuation procedures to treat miscarriage beyond 12 weeks usually involve pre-procedure cervical dilatation with medications or osmotic dilators, or both (WHO 2016), and evacuation with a combination of vacuum aspiration and specialised forceps (also known as dilatation and evacuation or D&E). Uterine evacuation procedures to treat miscarriage of more advanced pregnancies can be more complex and associated with greater risk of complications (Tuncalp 2010). Uterine evacuation procedures to treat miscarriage have been reviewed previously (Tuncalp 2010), indicating that vacuum aspiration is safe, quick to perform, and less painful than sharp curettage, and is recommended for use in the management of incomplete miscarriage, but the findings were based on data from a single study.

Perhaps because of the lack of evidence of effectiveness of prophylactic antibiotics for uterine evacuation procedures to treat miscarriage, there is inconsistency in clinical practice and international guidelines (ACOG 2015; Fawcus 1997; NICE 2019a,WHO 2017). Some guidelines do not recommend prophylaxis, reflecting the lack of evidence (NICE 2019a, WHO 2017),whereas other guidelines support their use, based on extrapolation of findings from other indications (ACOG 2015).

This review will not address prophylactic antibiotics for medical management of miscarriage.

How the intervention might work

Uterine evacuation procedures to treat miscarriage can introduce pathogens that cause infection when a surgical instrument is inserted through the cervical canal into the uterine cavity to remove the pregnancy tissue (ACOG 2018). The most common micro-organisms that cause infection in the reproductive tract are enterococci, streptococci, staphylococci, Gram-negative bacilli and anaerobes (Kok 2000). When chlamydia and gonococcus exist in the vagina, they can move up into the uterus during uterine evacuation and cause infection (Workowski 2021). Antibiotics work by killing existing bacteria (bactericidal) or inhibiting the replication of bacteria (bacteriostatic). The types of antibiotics used prophylactically should be e_ective against these common micro-organisms and include the following: ampicillin, cephazolin, clindamycin, vancomycin, azithromycin, and the aminoglycosides (ACOG 2018). Antibiotic prophylaxis before certain operations has been shown to reduce the risk of infections.

There is some evidence to support the use of antibiotic prophylaxis for surgical abortion procedures (Low 2012; Sawaya 1996). Current WHO guidance advocates the use of appropriate prophylactic antibiotics for all women, before or during the procedure (WHO 2017). This recommendation is based on a Cochrane Review of 19 randomised studies showing that prophylactic antibiotics reduce pelvic infection when given for surgical abortion (Low 2012). As the procedures to conduct uterine evacuation for abortion and to treat miscarriage are the same, it can be hypothesised that prophylactic antibiotics could reduce pelvic infection among women undergoing uterine evacuation procedures to treat miscarriage. Identifying populations experiencing miscarriage who have not sought an intervention to end their pregnancy can be complicated, particularly in settings where abortion access is limited by legal restrictions.

Women presenting for medical care to treat miscarriage could be experiencing complications from an incomplete abortion obtained in a safe or unsafe setting. The cause of miscarriage can be unclear, especially in countries where abortion is illegal or access to abortion is heavily restricted. This review aims to estimate the effectiveness of antibiotic prophylaxis among women obtaining a surgical abortion procedure when presenting with a miscarriage, regardless of its cause.

Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage may be effective in reducing maternal death and serious illness caused by infection. Prophylactic antibiotics may play a role in reducing the long-term consequences of pelvic scarring caused by infection, such as ectopic pregnancy and infertility, and may be economically beneficial to the health system as a cost-effective intervention (Goranitis 2019).

Why it is important to do this review

Infection is a serious consequence of uterine evacuation procedures to treat miscarriage and can result in serious illness and death (Melese 2017). Clinical evidence and guidance are clear that antibiotic treatment is needed for women experiencing miscarriage with signs and symptoms of infection (Udoh 2016), because of this we will not include studies that evaluate the

use of antibiotics in women with confirmed or suspected septic miscarriage. However, it is less clear whether antibiotic prophylaxis is effective or necessary at the time of uterine evacuation procedures to treat miscarriage.

This Cochrane Review is an update of the Cochrane Review 'Antibiotics for incomplete abortion' by,May 2007, but this protocol uses the term miscarriage rather than incomplete abortion. Since the Cochrane Review by_ May 2007 there have been further randomised studies (Lissauer 2019; Titapant 2012), including a large, multi-centre, randomised, placebo-controlled study conducted on the use of prophylactic antibiotics before miscarriage treatment with surgical abortion (Lissauer 2019).

Given that miscarriage surgery is common and infective complications are frequent and serious, contributing to the high numbers of preventable maternal deaths around the world, prophylactic antibiotics, may offer a simple and affordable intervention to reduce maternal death and disability. If antibioticprophylaxis proves to be ineffective or causes serious adverse events, unnecessary use of antibiotics could be minimised, which is essential given the growing problem of antibiotic resistance. Therefore, the policy, practice and cost implications arising from this review will be important.

O B J E C T I V E S

The objective of this review is to evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) that directly compare antibiotics with placebo or no treatment, including those of parallel design, factorial studies and multi-arm RCTs. We will include studies that randomise at the individual or cluster level.

We will include full-text studies, conference abstracts (if sufficient data are provided) and unpublished data. We will include studies irrespective of their publication status and language of publication. We will exclude non-randomised studies.

Types of participants

This review will include all types of miscarriage, of any gestational age, treated with ‘surgical’ uterine evacuation. We will include studies that enrol women attending healthcare facilities, who present with miscarriage. There will be no gestational age limit.

We appreciate that studies may include participants who present for miscarriage treatment following an unreported safe or unsafe abortion but do not present with physical or clinical evidence indicating prior interventions; they would receive standard clinical treatment for

miscarriage and we will therefore include this population in this review. We will report if studies state any evidence of prior interventions found in women after randomisation. We will exclude studies that explicitly include both women having uterine evacuation procedures to treat miscarriage and women having surgical abortion, unless the groups are reported separately throughout the study, as there is clear guidance that women having surgical abortion should be given antibiotic prophylaxis (WHO 2017). We will include studies that include women with prior medical management, but who require further management with uterine evacuation. We will report prior interventions (such as medical management) in the table of characteristics. We will exclude studies that include only women with miscarriage who are experiencing signs and symptoms of infection, as there is clear guidance stating that antibiotics should be given (WHO 2017), or studies that include only women undergoing surgical abortion or unsafe abortion, as there is clear guidance stating that antibiotics prophylaxis should be given (WHO 2017).

Types of interventions

We will include studies that compare any prophylactic antibiotic regimen with no antibiotics (placebo or no treatment). This may include antibiotics administered by any route; orally, intravenously or intramuscularly; antibiotics of different classes, nitroimidazoles (e.g. metronidazole), tetracyclines (e.g. doxycycline) or beta lactams (e.g. amoxicillin); and antibiotics of differing regimes or doses (e.g. doxycycline 400 mg plus metronidazole 400 mg single dose or doxycycline 100 mg twice a day for three days). All antibiotic classes, routes, doses and regimes will be included with no limits as long as the antibiotics are given as a means of infection prevention for women undergoing uterine evacuation procedures to treat miscarriage.

We will define prophylaxis by the intention of administering antibiotics before, during or shortly after surgery as a means of infection prevention. We will include studies that assess multiple interventions such as blood transfusion, medications for pain relief, or comparisons of different types of surgical miscarriage management in addition to antibiotic treatment, as long as the study groups compare an antibiotic with placebo or no treatment.

Types of outcome measures

We will not exclude studies if they report the secondary outcomes only, nor will we exclude studies in the absence of reporting outcome data. We will present outcomes in the 'Characteristics of studies' tables.

We will focus on clinical, infection-related outcomes for this review, to evaluate the effectiveness and safety of antibiotic prophylaxis. The time frame for outcome assessment will be within six weeks, in line with Centers for Disease Control (CDC) procedure-associated infections (Berríos-Torres 2017),_and the peripartum period (WHO 2016). The outcomes are based on the core outcome set developed by Whitehouse and colleagues (Whitehouse 2021), and the CDC (CDC 2021). The primary outcome of uterine infection in accordance with the CDC definition may include infections anatomically localised to other parts of the reproductive tract,

therefore we will present the location of the infection in the 'Characteristics of studies' tables, as presented in the primary studies.

Primary outcomes

1. Uterine infection (Whitehouse 2021), as defined by the following criteria (CDC 2021). The woman has at least two of the following signs or symptoms:
a. fever (> 38.0 °C);
b. pain or tenderness (uterine or abdominal, with no other recognised cause); or
c. purulent drainage from uterus.
2. Adverse effects of treatment

Secondary outcomes

1. Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage
2. Pelvic inflammatory disease (PID)
3. Hospitalisation for treatment of infection

Search methods for identification of studies

The Fertility Regulation Group Information Specialist will conduct a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. The search strategies for each database will be modelled on the search strategy designed for MEDLINE ALL (Ovid).

Electronic searches

We will search the following databases from their inception:
1. Cochrane Central Register of Controlled Trials (CENTRAL; current year, latest issue) in the Cochrane Library
2. MEDLINE ALL (Ovid)
3. Embase.com
4. Global Health (Ovid)
5. Scopus (conference abstracts only)

1. Guttmacher_ Institute_ www.guttmacher.org/united-states/abortion
2. International Planned Parenthood Federation_www.ippf.org/
3. Ibis_Reproductive Health_ibisreproductivehealth.org/
4. Women on Waves_www.womenonwaves.org/
5. Marie Stopes_International_www.mariestopes.org/
6. Population_Council_www.popcouncil.org/
7. Population Services International_www.psi.org/
8. Ipas_www.ipas.org/

Searching other resources
We will check the bibliographies of included studies and any relevant systematic reviews that we identify for further references to relevant studies. We will contact experts and organisations in the field to obtain additional information on relevant studies. If necessary, we will contact authors of included studies for data clarification and further information.

Data collection and analysis
The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth (Cochrane PCG).

At least two review authors will independently assess the studies for inclusion in the review, assess study quality, extract the data and grade the body of evidence.

Selection of studies
We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two review authors (SI, AA) will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports or publications and two review authors (SI, AA) will independently screen the full texts and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (AW). We will list studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021).

Data extraction and management
We will use a standard data collection form for study characteristics and outcome data; we will pilot the form on at least one study in the review. Two review authors (SI, AA) will independently extract the study characteristics from the included studies, this may include:
1. methods: study design, number of study centres, type of study centre, study setting and location, date of study, follow-up;
2. participants: number, inclusion criteria, exclusion criteria, other relevant characteristics;
3. interventions: intervention components; dose, route, regime, co-interventions, comparison, compliance;
4. outcomes: outcomes specified and collected, time points reported;
5. notes: funding for study, notable conflicts of interest of study authors, ethical approval.

Two review authors (SI, AA) will independently extract outcome data from included studies. If any of the review authors have been involved in a study that is included in the review, they will not participate in the risk of bias assessment or data extraction (additional support will be provided by the central Cochrane team if required). We will note in the 'Characteristics of

included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author (AW).

Assessment of risk of bias in included studies

Two review authors (SI, AA) will independently assess the risk of bias for key outcomes for results of randomised studies using the Cochrane RoB 2 tool (Sterne 2019), and criteria outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). We will resolve any disagreement by discussion or by involving a third review author (AW). We will assess the key outcomes defined in this protocol for risk of bias. We will assess the following domains using answers to signalling questions, with overall judgments derived from the tool.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

An additional domain is included for cluster-randomised studies as outlined in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021): 1b. bias arising from identification or recruitment of individual participants within clusters.

We will use the variants of RoB 2 for cluster-RCTs if we include any studies of this design in our review. This variant will address the following issues with bias specific to cluster-RCTs in addition to those above.

1. Bias arising from the randomisation process
2. Bias arising from the timing of identification and recruitment of participants
3. Bias due to deviations from intended interventions
4. Bias due to missing outcome data
5. Bias in measurement of the outcome

We will judge each potential source of bias as high, low, or 'some concerns' and provide a quote from the study report together with a justification for our judgment in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very di_erent than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the risk of bias table. We will not exclude studies on the grounds of their risk of bias but will clearly report the risk of bias when

presenting the results of the studies. When considering treatment effects, we will consider the risk of bias for the studies that contribute to that outcome. We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment e9ect

For dichotomous data, we will use the numbers of events in each arm of each study to estimate the effect of the intervention using risk ratio together with the appropriate associated 95% confidence interval.

Unit of analysis issues

Cluster-randomised studies

We will include cluster-randomised studies in the analyses along with individually randomised studies. Where necessary, we will adjust their standard errors using the methods described in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation co-efficient (ICC) derived from the study (if possible), from a similar study or from a study of a similar population (Higgins 2021b). If we identify both cluster-randomised studies and individually-randomised studies, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Multi-arm studies

We will include multi-arm studies that use different antibiotics, as long as the comparison is antibiotic versus placebo or no treatment. In this situation we will combine the antibiotic arms into one, and the primary comparison will remain antibiotic versus placebo or no treatment.

Factorial studies

We will include factorial studies where one or more arms contain an antibiotic (+/- other interventions) and one or more arms contain no antibiotic (i.e. placebo or no treatment, +/- other interventions).

We will combine any study arms that include antibiotic and combine any study arms that do not. The primary comparison will remain antibiotic versus placebo or no treatment.

Dealing with missing data

We will contact study authors in order to verify key study characteristics and obtain missing outcome data where possible (e.g. when a study is identified as abstract only).

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will perform analyses, as far as possible, on an intention-to-treat basis. That is, we will attempt to include all participants randomised to each group in the analyses, and we will analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each study will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

To evaluate the presence of clinical heterogeneity, we will generate descriptive statistics for study characteristics and study population characteristics across all eligible studies.
If we find a sufficient number of studies, we will conduct a meta-analysis. We will assess statistical heterogeneity in each meta-analysis using TauW, the IW statistic (Higgins 2003), and Chi^2 statistic (Deeks 2011).We will describe the clinical diversity and methodological variability of the evidence in the review text and with study tables describing study characteristics including design features, population characteristics, and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between confidence intervals. We will also consider the statistics generated in forest plots that measure statistical heterogeneity.

We will use the I^2 statistic to quantify inconsistency among the studies in each analysis. We will also consider the P value from the Chi^2 test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity we will report the finding and explore possible explanatory factors using prespecified subgroup analysis.

We will use a rough guideline to interpret the I^2 statistic value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I^2 statistic and Tau^2) will be estimated with high uncertainty when the number of studies is small (Deeks 2021).
1. 0% to 40%: heterogeneity might not be important
2. 30% to 60%: may represent moderate heterogeneity*
3. 50% to 90%: may represent substantial heterogeneity*
4. 75% to 100%: considerable heterogeneity*
*The importance of the observed value of the I^2 statistic depends on

1. magnitude and direction of effects, and 2. strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for the IW statistic: uncertainty in the value of the IW statistic is substantial when the number of studies is small).

Assessment of reporting biases

We will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results. If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible publication biases, interpreting the results with caution (Sterne 2011).

Data synthesis

We will undertake meta-analyses only where this is meaningful because the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. If it is reasonable to assume that each study contributing to the meta-analysis for that outcome is estimating the same underlying treatment effect (i.e. similar interventions, study populations and settings, and similar methods used) we will conduct a fixed effect meta-analysis. If there is clear clinical diversity between studies, which is sufficient to expect that the underlying treatment effects differ between studies, or if we detect substantial statistical heterogeneity (as described above), we will use a random effects meta-analysis. A random effects meta-analysis assumes that the different studies are estimating an average pooled effect from a distribution of related intervention effects.

Subgroup analysis and investigation of heterogeneity

The effectiveness of antibiotic prophylaxis for uterine evacuation procedures to treat miscarriage could be influenced by several factors. These factors include gestational age at the time of the procedure (pregnancies of a greater gestation may have a higher incidence of pelvic infection due to the complexities involved with the surgical procedure), the type of surgery used (manual vacuum aspiration, suction curettage or sharp curettage; the type of miscarriage (missed or incomplete; incomplete miscarriage may be associated with a higher incidence of pelvic infection when compared to missed miscarriage), and the legal status of abortion for the study setting (legal, heavily restricted or illegal; studies conducted in settings where abortion is legal may be less likely to include cases of unsafe interventions).

We plan to carry out the following subgroup analyses to compare the effects estimated in studies that differ according to the following characteristics.

1. Gestational weeks at time of procedure (< 12 weeks, $\geq$ 12 weeks, unclear)
2. Type of surgery (manual vacuum aspiration, suction curettage, sharp curettage, dilation and evacuation)
3. Type of miscarriage (missed miscarriage, incomplete miscarriage)
4. Evidence of unsafe or surgical abortion (no evidence, some evidence)
5. Antibiotic class (tetracyclines, others)
6. Antibiotic regime (short course; < 3 days, longer course > 3 days; NICE 2019b)
7. Antibiotic route (oral, intravenous)

In studies of individuals that span the categories described above (e.g. different types of surgery or type of miscarriage types included in the same study), we will stratify the analyses into categories that reflect the majority of participants or will include a subgroup category of mixed populations. We will conduct interaction tests for subgroup differences and will only describe the estimates of effect for different strata if there is evidence of an interaction effect.

Sensitivity analysis

For the primary outcomes we will perform sensitivity analyses defined a priori to assess the robustness of our conclusions and explore its impact on effect sizes for the following.

1. Restricting the analyses to studies with antibiotics as a single intervention
2. Risk of bias (restricted to low risk of bias studies only): we will rank studies as 'low risk of bias' if they are double-blinded and have allocation concealment and outcome data available for nearly all participants randomised (less than 10% missing). We will consider protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses because protocol publication only became widespread in recent years.
3. Use of fixed-effect versus random-effects model. We will assess differences by evaluating the relative effects and assessment of model fit.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for the intervention comparison of any prophylactic antibiotic versus no treatment or placebo. The table will describe the results for each of the key outcomes defined in this protocol in accordance with the GRADE approach. These outcomes include pelvic infection and adverse effects of treatment. We will also present the findings from subgroup comparisons testing the effect of different treatment groups (such as antibiotic class and regime) on pelvic infection and adverse effects (e.g. short course of doxycycline versus short course of all other antibiotics).

If, during the review process, we become aware of important outcomes that we failed to list in our planned summary of findings table, we will include the relevant outcomes and explain the reasons for this is the section 'Differences between protocol and review'. Two review authors will independently assess the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias;_Guyatt 2008). We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of interventions* (Schünemann 2021), and the EPOC worksheets (EPOC 2013), and use GRADEpro GDT soOware (GRADEpro GDT). We will resolve disagreements on certainty ratings by discussion and provide justification for decisions to down- or upgrade the ratings using footnotes in the table and make comments to aid readers' understanding of the review where necessary. We will use plain language statements to report these findings in the review (EPOC 2013). We will consider whether there is any additional outcome information that we were not able to incorporate into metaanalyses and note this in the comments, and state if it supports or contradicts the information from the meta-analyses. If it is not possible to meta-analyse the data, we will summarise the results in

the text.

A C K N O W L E D G E M E N T S

Robin Paynter, Fertility Regulation Review Group Information Specialist. This protocol is based on standard text and guidance provided by Cochrane Fertility Regulation group and the Cochrane Pregnancy and Childbirth group.

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References to other published versions of this review

May 2007
May_W, _Gülmezoglu_AM, _Ba-Thike_K. Antibiotics for incomplete abortion. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No: CD001779. [DOI: 10.1002/14651858.CD001779] [PMID: 17943756]

A P P E N D I C E S

Appendix 1. Model Search Strategy

Cochrane Central Register of Controlled Trials (CENTRAL; CRSWeb)

Date searched: 29 January 2021

1. (Abortion, Spontaneous OR Abortion, Incomplete OR Abortion, Missed OR Abortion, Septic OR Embryo Loss):MH AND CENTRAL:TARGET (643)
2. (("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR post-abortal OR (retained AND concept*) OR (product* AND concept*)):TI OR ("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR postabortal OR (retained AND concept*) OR (product* AND concept*)):AB) AND CENTRAL:TARGET (6432)
3. #1 OR #2 (6577)
4. (Anti-Bacterial Agents OR Antibiotic Prophylaxis OR Doxycycline OR exp Tetracyclines OR Lactams OR Macrolides OR Metronidazole OR Nitroimidazoles OR Tinidazole OR Quinolones OR Oxolinic Acid OR Penicillins OR Sulfanilamide OR Infection OR Bacterial Infections):MH AND CENTRAL:TARGET (25855)
5. ((anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):TI OR (antibacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR

ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):AB) AND CENTRAL:TARGET (174803)
6. #4 OR #5 (180046)
7. #3 AND #6 (1042)

MEDLINE_ALL (Ovid) 1946 to January 28, 2021
Date searched: 29 January 2021
1 Abortion, Spontaneous/ or Abortion, Incomplete/ or Abortion, Missed/ or Abortion, Septic/ or Embryo Loss/ (23945)
2 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*)) or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab,kf,kw. (58781)
3 or/1-2 (70708)
4 exp Anti-Bacterial Agents/ or Antibiotic Prophylaxis/ or Doxycycline/ or exp Tetracyclines/ or exp Lactams/ or exp Macrolides/ or Metronidazole/ or exp Nitroimidazoles/ or Tinidazole/ or exp Quinolones/ or Oxolinic Acid/ or exp Penicillins/ or Sulfanilamide/ or exp Infections/ or exp Bacterial Infections/ (3134258)
5 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab,kf,kw,nm,rn. (904822)
6 or/4-5 (3433577)
7 (controlled clinical trial or randomized controlled trial).pt. or (groups or placebo or random* or trial).ab. or dt.fs. (5135905)
8 (exp animals/ not humans/) or (animal or animals or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or feline or goat or goats or helminths or horse or livestock or mice or mouse or ovine or pig or pigs or porcine or rabbit or rabbits or rat or rats or rattus or sheep or sow or sows or swine).ti. (5189177)
9 7 not 8 (4394990)
10 and/3,6,9 (1820)

Embase.com
Date searched: 29 January 2021
#1 'incomplete abortion'/de OR 'blighted ovum'/de OR 'fetus wastage'/de OR 'missed abortion'/de OR 'septic abortion'/de OR 'spontaneous abortion'/de (52,575)
#2 'blastocyst disintegration':ti,kw OR (((febrile OR incomplete OR infect* OR missed OR septic OR spontaneous OR tubal) NEAR/3

abortion*):ti,kw) OR ((pregnancy NEAR/3 loss):ti,kw) OR (((embryo* OR fetal OR foetal OR fetus* OR foetus*) NEAR/3 (death OR deaths
OR demise OR disintegrat* OR loss OR losses OR resorption*)):ti,kw) OR miscarriage*:ti,kw OR postabort*:ti,kw OR 'post abort*':ti,kw OR
((retained NEAR/3 (concept* OR tissue*)):ti,kw) OR ((product* NEAR/3 concept*):ti,kw) (23,406)
#3 #1 OR #2 (62,668)
#4 'antiinfective agent'/exp OR 'antibiotic prophylaxis'/de OR 'doxycycline'/de OR 'lactam'/exp OR 'macrolide'/de OR 'metronidazole'/
de OR 'tinidazole'/de OR 'oxolinic acid'/de OR 'penicillin derivative'/exp OR 'sulfanilamide'/exp OR 'tetracycline derivative'/exp OR
'nitroimidazole derivative'/exp OR 'quinolone derivative'/exp OR 'infection'/mj OR 'bacterial infection'/mj OR 'intrauterine infection'/exp
(4,015,881)
#5 'anti bacterial*':ti,ab,kw OR antibacterial*:ti,ab,kw OR 'anti biotic*':ti,ab,kw OR antibiotic*:ti,ab,kw OR 'anti mycobacterial*':ti,ab,kw
OR antimycobacterial*:ti,ab,kw OR bacteriocid*:ti,ab,kw OR cefoxitin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR doxycycline:ti,ab,kw OR
fluroquinolone*:ti,ab,kw OR lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR metronidazole:ti,ab,kw OR nitroimidazole*:ti,ab,kw OR
'oxolinic acid':ti,ab,kw OR penicillin*:ti,ab,kw OR prophyl*:ti,ab,kw OR quinolone*:ti,ab,kw OR ((screen* NEAR/3 treat*):ti,ab,kw) OR
tetracycline*:ti,ab,kw OR tinidazole:ti,ab,kw (965,387)
#6 #4 OR #5 (4,327,174)
#7 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR
random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1
blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti (2,688,881)
#8 ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim) NOT [humans]/lim OR animal:ti OR
animals:ti OR bovine:ti OR canine:ti OR capra:ti OR cat:ti OR cats:ti OR cattle:ti OR cow:ti OR cows:ti OR dog:ti OR dogs:ti OR equine:ti
OR feline:ti OR goat:ti OR goats:ti OR helminths:ti OR horse:ti OR livestock:ti OR mice:ti OR mouse:ti OR ovine:ti OR pig:ti OR pigs:ti OR
porcine:ti OR rabbit:ti OR rabbits:ti OR rat:ti OR rats:ti OR rattus:ti OR sheep:ti OR sow:ti OR sows:ti OR swine:ti (4,543,611)
#9 #7 NOT #8 (2,461,690)
#10 #3 AND #6 AND #9 (954)

Global Health (Ovid)_1973 to 2021 Week 04

Date searched: 29 January 2021
1 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy
adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*))
or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab. (8686)
2 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin
or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or
penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab. (217234)
3 and/1-2 (380)

Scopus

Date searched: 29 January 2021;
TITLE-ABS-KEY ("blastocyst disintegration" OR ((febrile OR incomplete _OR _infect* _OR _missed _OR _septic _OR _spontaneous _OR _tubal)
_PRE/3 _abortion*) _OR _(pregnancy _PRE/3 _loss) _OR _((embryo* _OR _fetal _OR _foetal _OR _fetus* _OR _foetus*) _PRE/3 _(death _OR _deaths
_OR _demise _OR _disintegrat* _OR _loss _OR _losses _OR _resorption*)) _OR _miscarriage* _OR _postabort* _OR _post-abort* _OR _(retained
_PRE/3 _(concept* _OR _tissue*)) _OR _(product* _PRE/3 _concept*)) _AND _TITLE-ABS-KEY (anti-bacterial* _OR _antibacterial* _OR _anti-biotic*
_OR _antibiotic* _OR _anti-mycobacterial* _OR _antimycobacterial* _OR _bacteriocid* _OR _cefoxitin _OR _ciprofloxacin _OR _doxycycline _OR
_fluroquinolone* _OR _lactam* _OR _macrolide* _OR _metronidazole _OR _nitroimidazole* _OR _"oxolinic acid" _OR _penicillin* _OR _prophyl*
_OR _quinolone* _OR _(screen* _PRE/3 _treat*) _OR _tetracycline* _OR _tinidazole) _AND _TITLE-ABS-KEY (groups _OR _placebo _OR _random*
_OR _trial) _AND _(LIMIT-TO (DOCTYPE, _"cp")) (51)

C O N T R I B U T I O N S _ O F _ A U T H O R S

Conceiving the protocol: AW, SI, AA, CM, DL
Designing the protocol: AW, SI, AA, CM, DL
Co-ordinating the protocol: MM, AW
Designing search strategies: RP (FRG information specialist)
Writing the protocol: AW, SI
Providing general advice on the protocol: AC, AMG, DL, CM, JC
Securing funding for the protocol: N/A
Performing previous work that was the foundation of the current study: AMG, KB, WM

D E C L A R A T I O N S _ O F _ I N T E R E S T

Sheikh Irfan: none known
Anne Ammerdor_er: none known
Catherine Moakes: CM was the Medical Statistician for the AIMS trial (ISRCTN 97143849).
James Cheshire: none known
Ahmet Metin Gülmezoglu: none known
Arri Coomarasamy: AC was the Chief Investigator for the AIMS trial (ISRCTN 97143849).
David Lissauer: DL was the Trial Manager for the AIMS trial (ISRCTN 97143849).
Amie Wilson: AW was the Trial Co-ordinator for the AIMS trial (ISRCTN 97143849).

S O U R C E S _ O F _ S U P P O R T

Internal sources

• University of Birmingham, UK
• Aga Khan University Hospital, Pakistan
• Concept Foundation, Switzerland
• Malawi-Liverpool-Wellcome Trust Research Institute, Blantyre, Malawi
• University of Liverpool, Liverpool, UK
• Tommy's National Centre for Miscarriage Research, University of Birmingham, Birmingham, UK

External sources

• No sources of support provided

2.6. Antibiotic versus Placebo No Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Uterine infection	6	4371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.28]
1.2 AE - Vomiting	1	3404	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.61, 2.38]
1.3 AE - Diarrhoea	1	3404	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.51, 1.65]
1.4 AE - Allergy	1	3404	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.12, 73.76]
1.5 AE - Anaphylaxis	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.6 Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage.	3	3574	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.54, 1.64]
1.7 Hospitalisation for treatment of infection	3	3859	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.40, 1.46]
1.8 Pelvic inflammatory disease	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9 Sensitivity Analysis: Uterine infection by studies with low risk of bias	3	3737	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.86]
1.10 Subgroup: Uterine infection by gestation	2	3481	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.24, 1.14]
1.10.1 Gestation <12 weeks	2	1744	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.73]
1.10.2 Gestation >=12 weeks	1	1737	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.46, 1.51]
1.11 Subgroup: Uterine infection by antibiotic class	6	4371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.28]
1.11.1 Uterine infection (tetracyclines)	5	4292	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.48, 1.34]

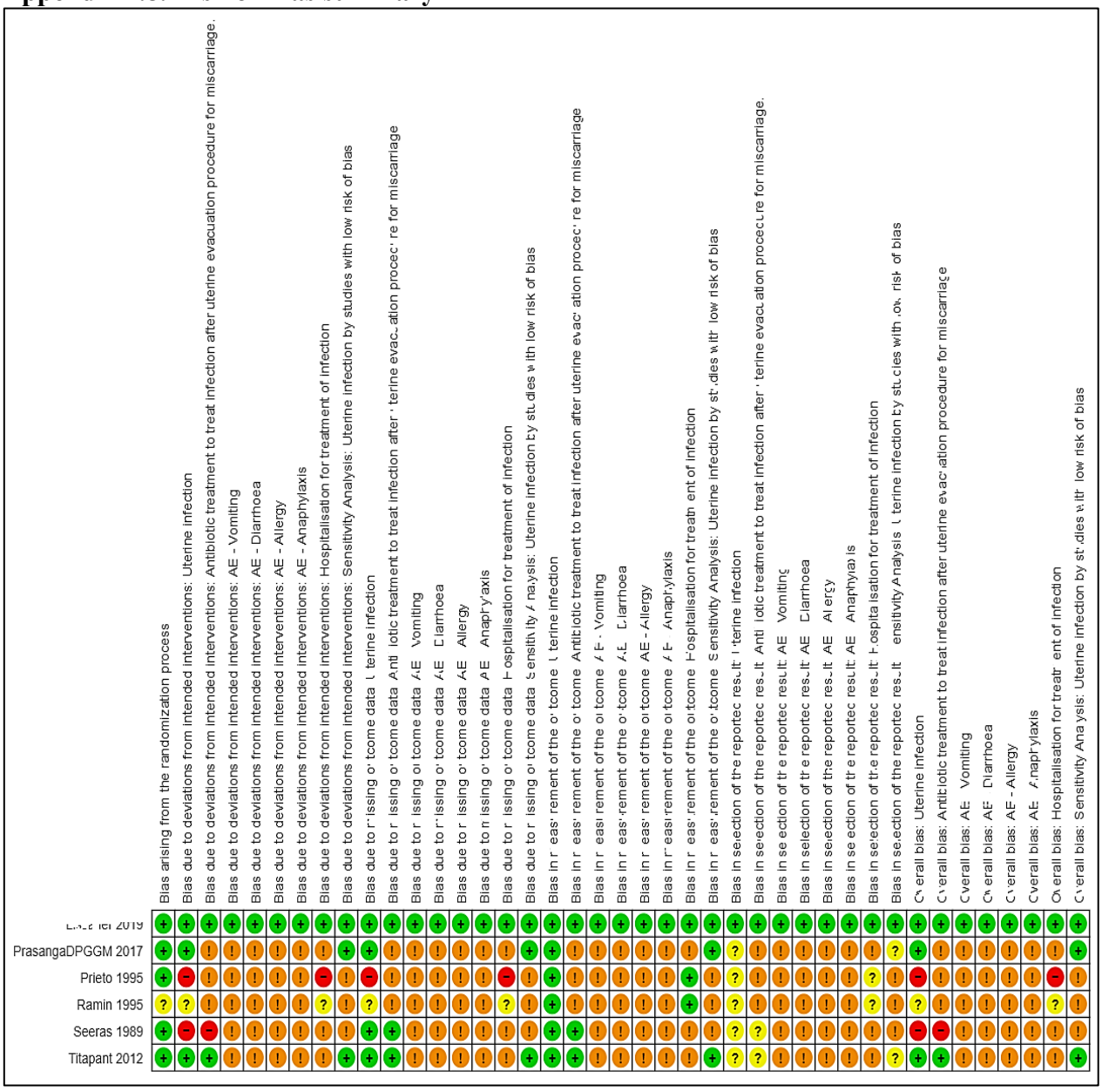
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.2 Uterine infection (other antibiotic classes)	1	79	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.94]
1.12 Subgroup: Uterine infection by treatment course length	6	4371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.28]
1.12.2 Uterine infection (short treatment course)	5	4236	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.42, 0.90]
1.12.3 Uterine infection (long treatment course)	1	135	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.86, 2.14]
1.13 Subgroup: Uterine infection by administration route	6	4371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.28]
1.13.1 Uterine infection (oral route)	4	4052	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.37]
1.13.2 Uterine infection (intravenous administration route)	2	319	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.23, 3.16]

Appendix 2.7. Characteristics of ongoing studies

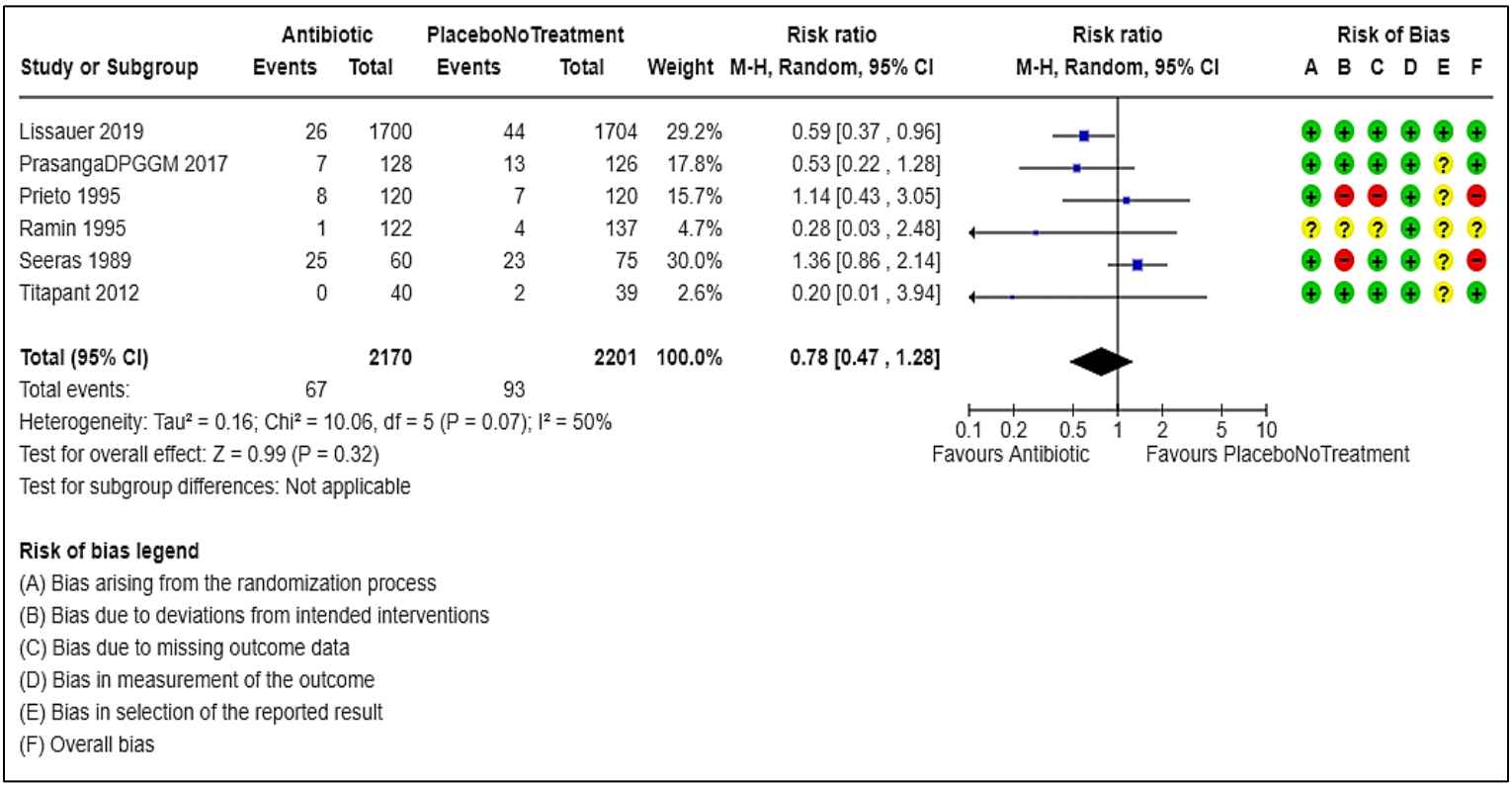
Eid 2021

Study name	Role of Prophylactic Antibiotics in Preventing Pelvic Infection After Surgical Evacuation
Methods	Randomised trial
Participants	Inclusion criteria: Maternal age :18-35 years Gestational age: up to 12 6/7 weeks of gestation (confirmed by a reliable date for the last menstrual period or /and 1st trimester ultrasound scan). Singleton miscarriage Type of miscarriage: Incomplete or Missed miscarriage Surgical evacuation will be done within 2 weeks of diagnosis of miscarriage .
Interventions	Patients will be randomized to receive either prophylactic antibiotic [a single dose of oral doxycycline (200 mg) and metronidazole (500 mg)] or placebo using identical sealed envelopes.Included cases are those with early miscarriage (within the first trimester 12 6/7 weeks of gestation) , missed or incomplete miscarriage, undergoing surgical management will be included in the study.
Outcomes	Change of pelvic infection after surgical evacuation of miscarriage with use of antibiotic prophylaxis. [Time Frame: 2 weeks from surgery] White cell count >12 *10^9 cells / L by CBC,. Change in the risk of severe puerperal sepsis following the surgical procedure [Time Frame: 2 weeks from surgery] Signs of puerperal sepsis in form of puerperal pyrexia >38 C and/or purulent vaginal discharge.
Starting date	01/01/2021
Contact information	
Notes	

Appendix 2.8. Risk of Bias summary



Appendix 2.9. Forest plot (Uterine infections)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

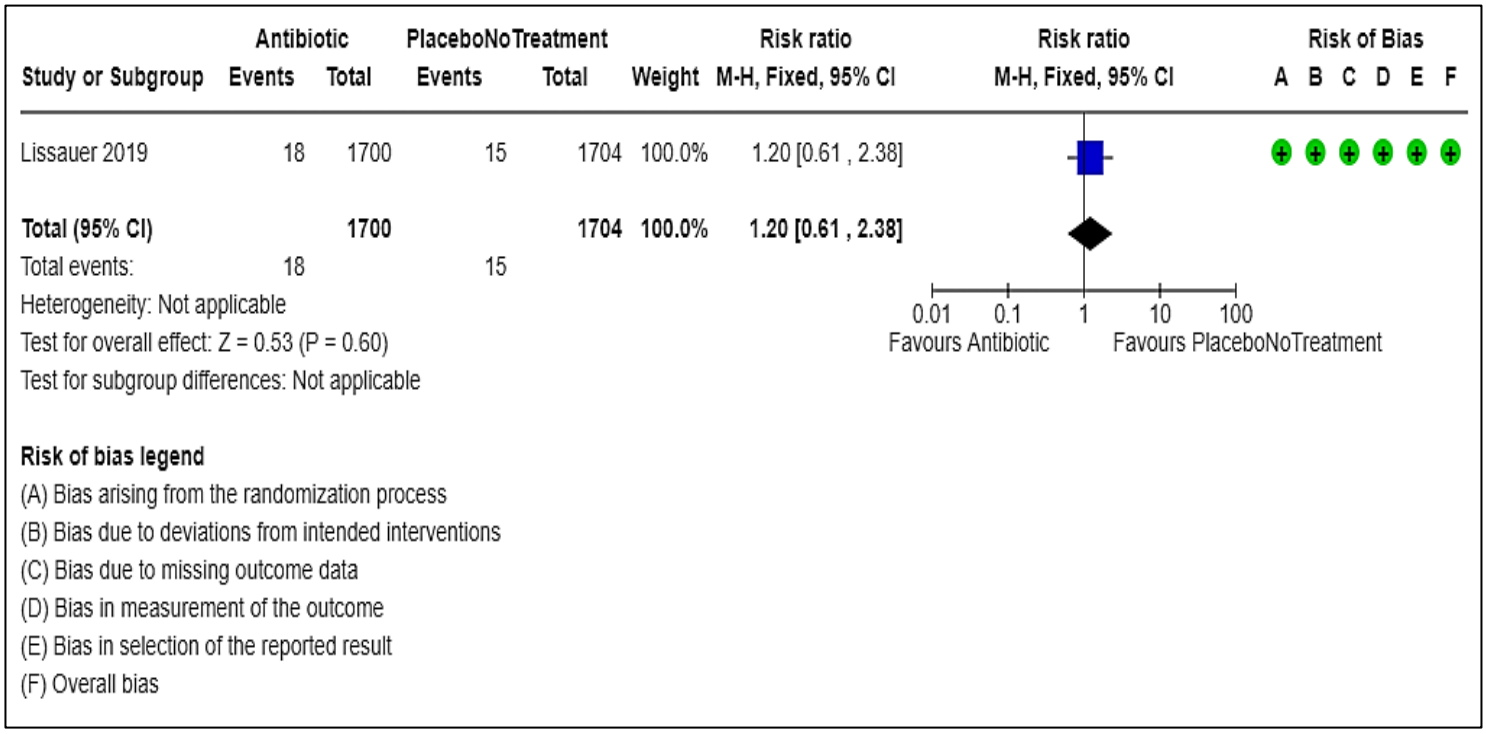
(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

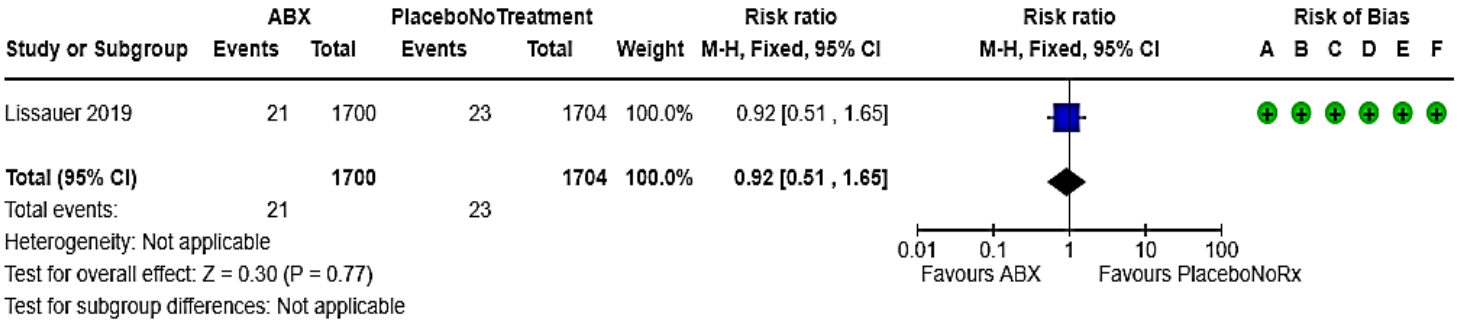
(E) Bias in selection of the reported result

(F) Overall bias

Appendix 2.10. Forest plot (Vomiting)



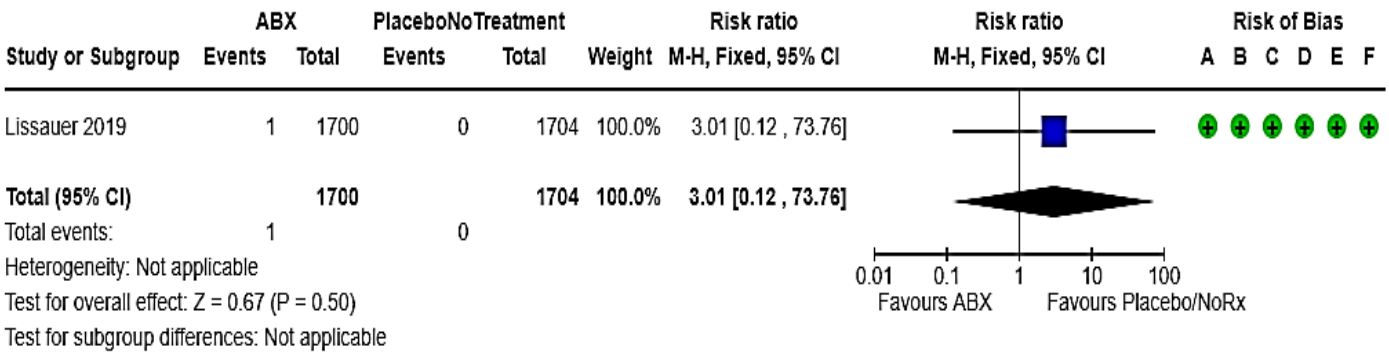
Appendix 2.11. Forest plot (Diarrhea)



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Appendix 2.12. Forest plot (Allergy)



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

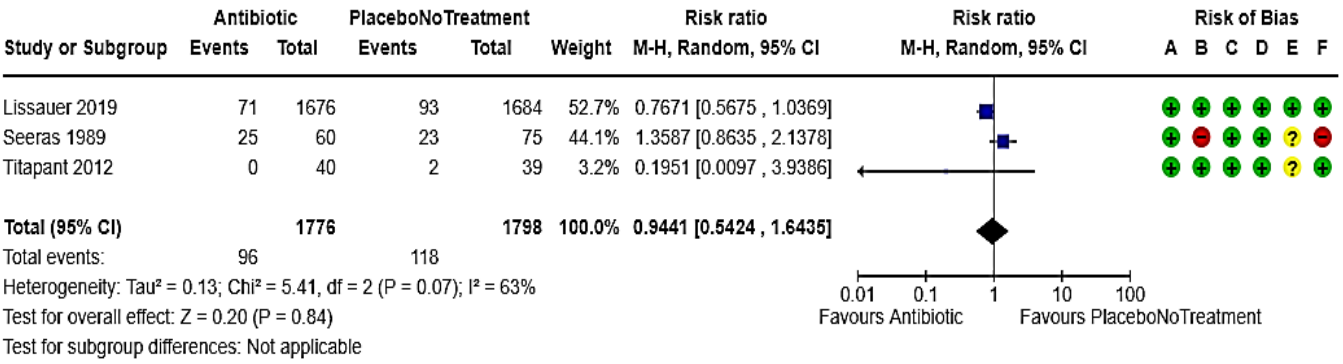
(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

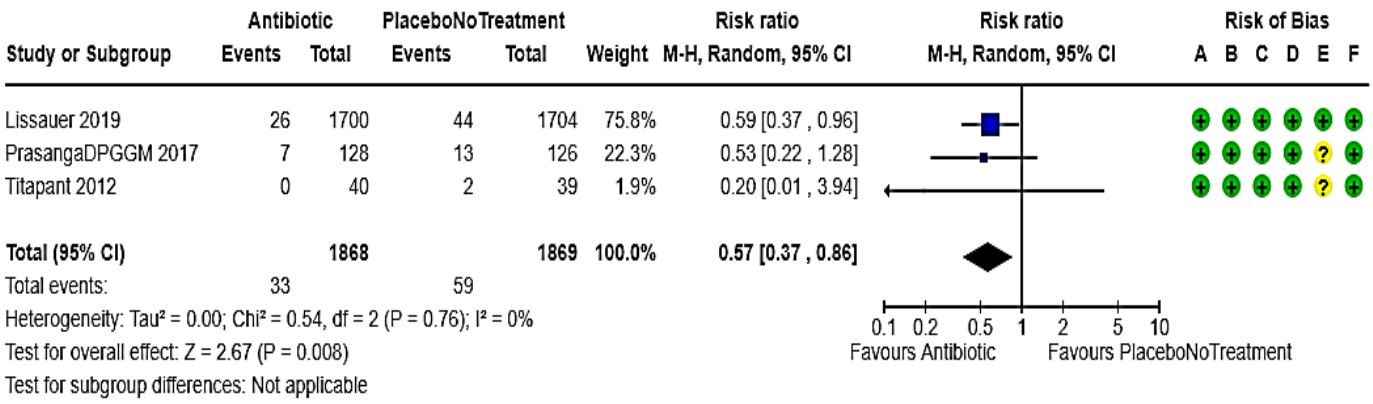
Appendix 2.13. Antibiotic treatment to treat infection



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Appendix 2.14. Hospitalisation



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

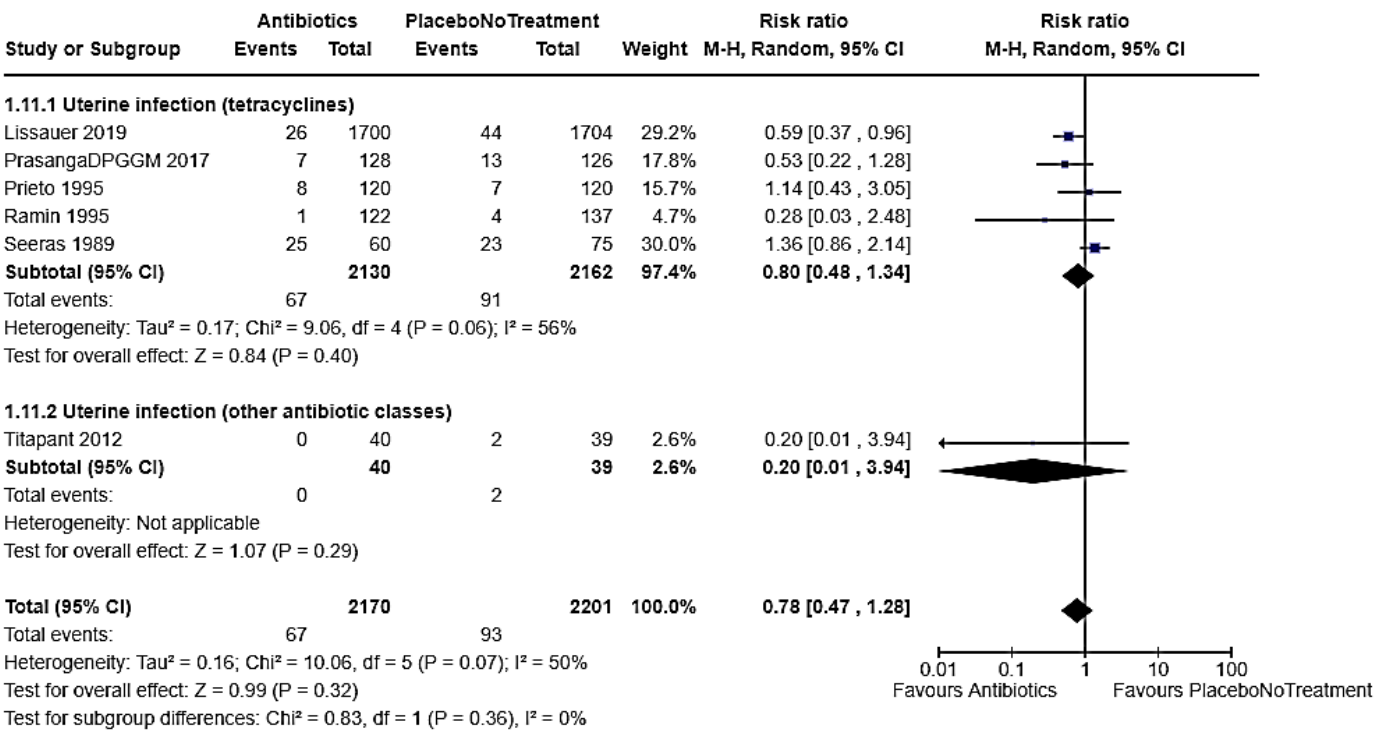
(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

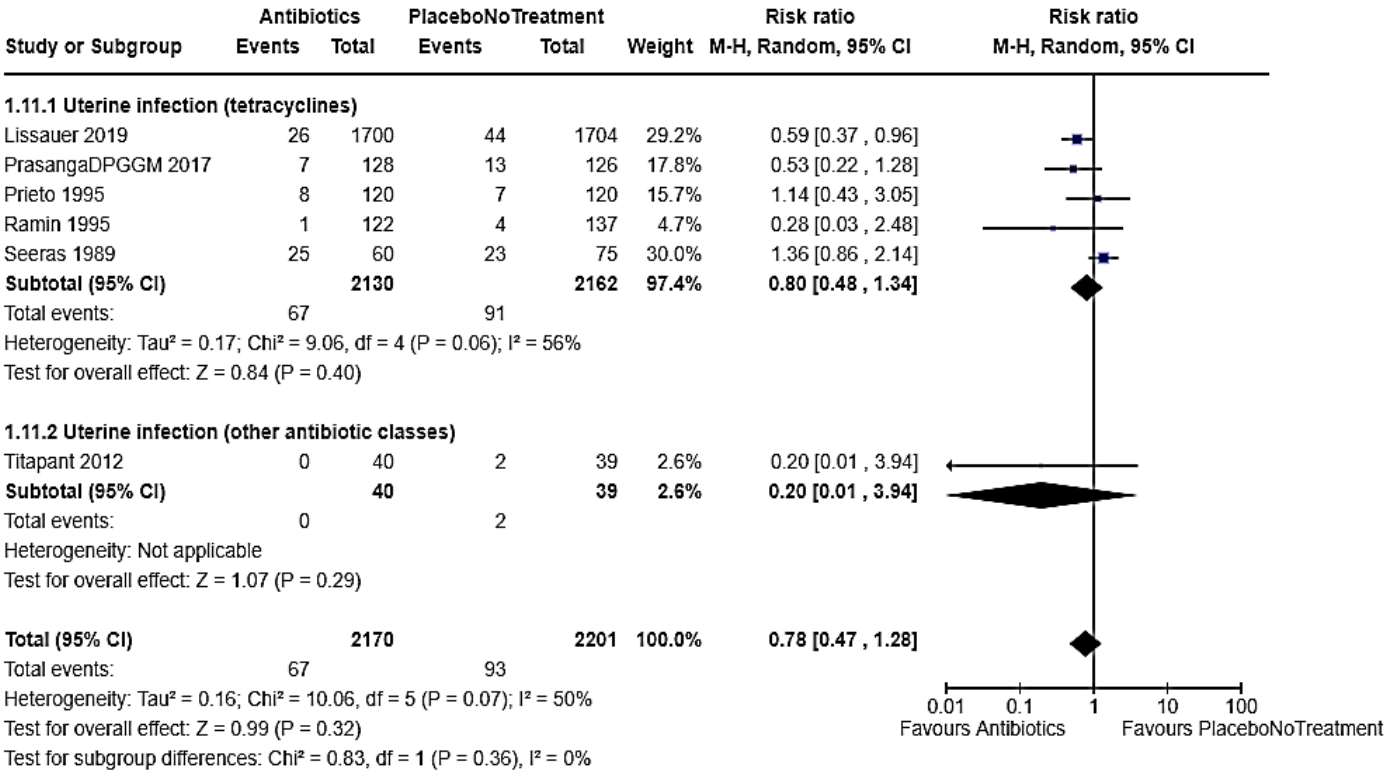
(E) Bias in selection of the reported result

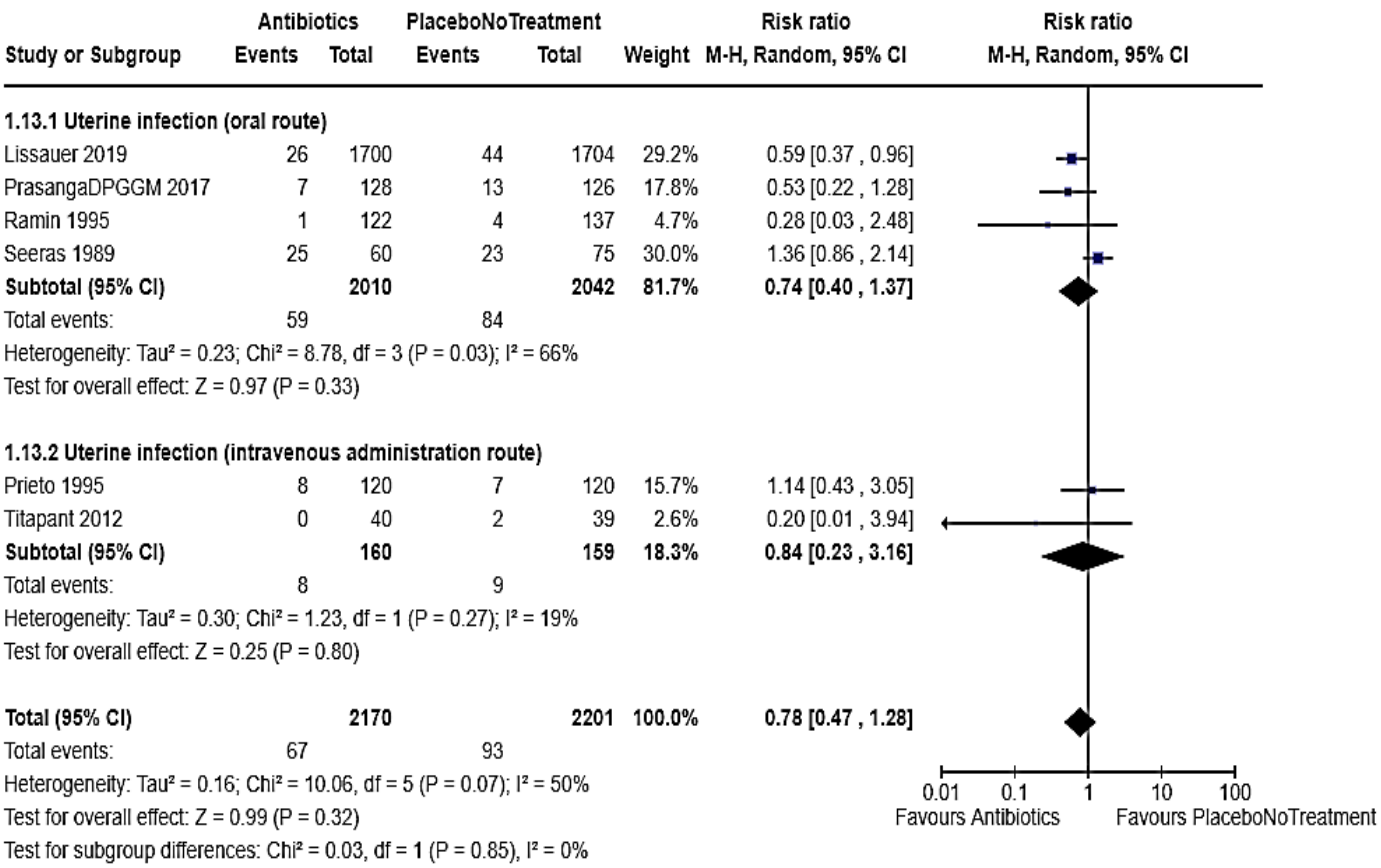
(F) Overall bias

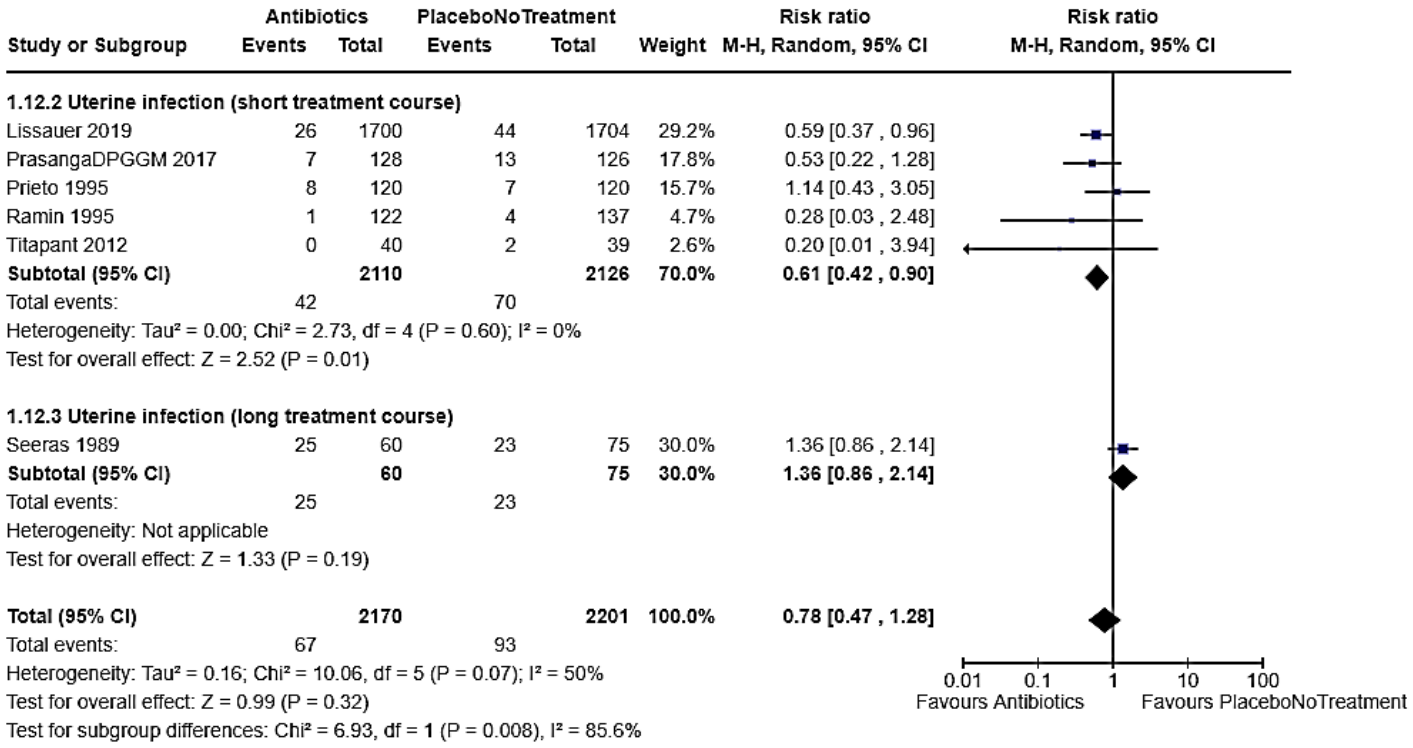
Appendix 2.15. Antibiotic prophylaxis when compared to placebo

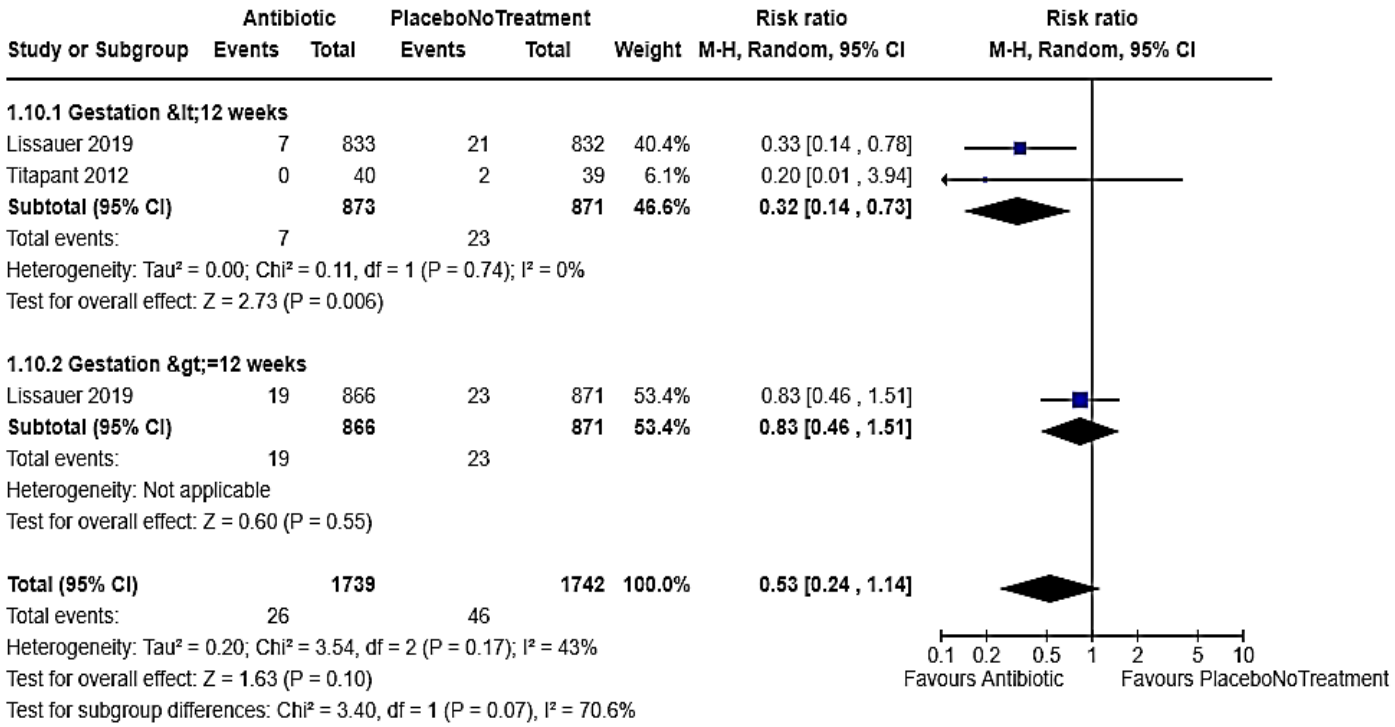


Appendix 2.16. Antibiotic versus Placebo No Treatment, Outcome: Subgroup: Uterine infection by gestation

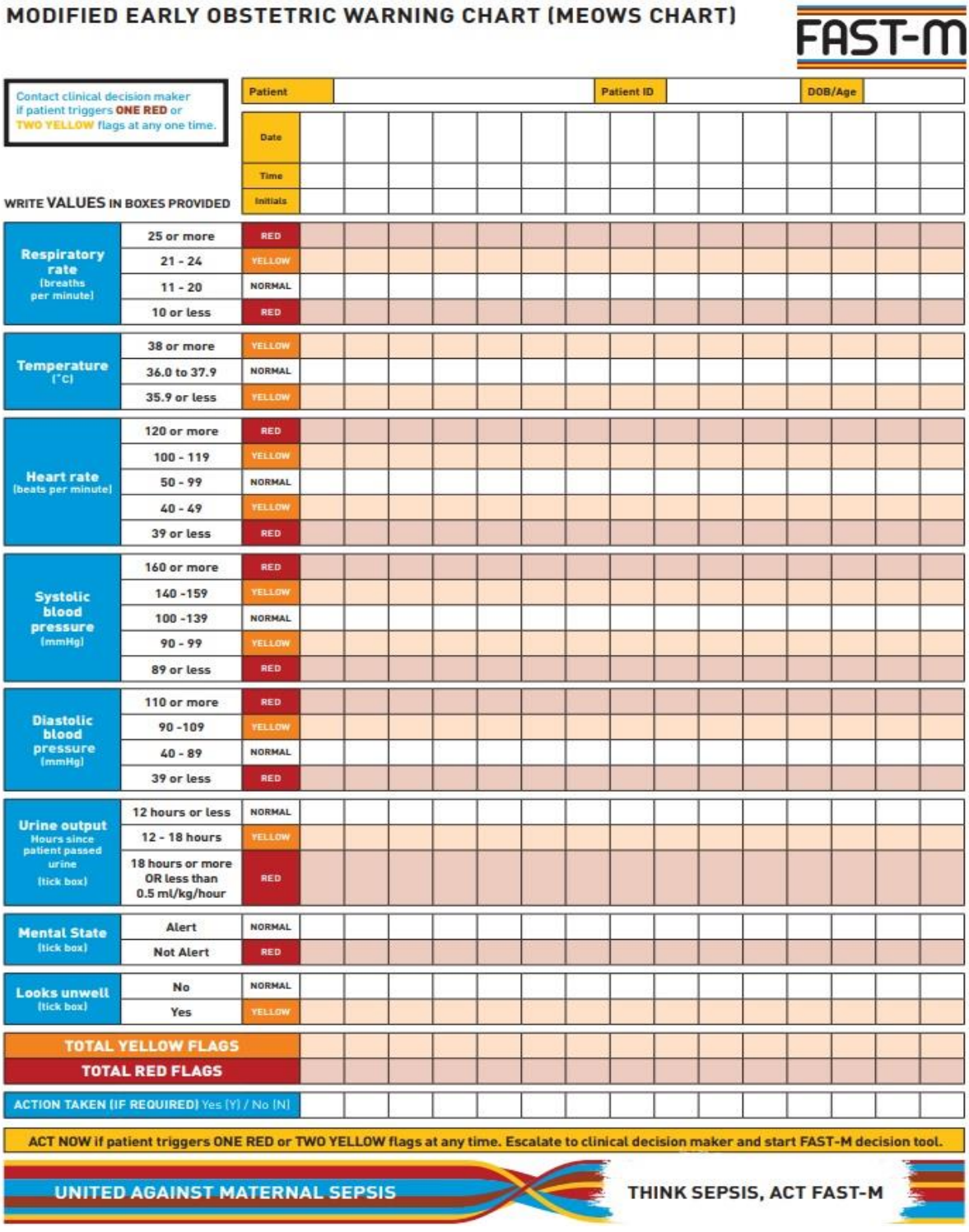



Antibiotics
PlaceboNoTreatment
Risk ratio
Risk ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.13.1 Uterine infection (oral route)
Lissauer 2019 26 1700 44 1704 29.2% 0.59 [0.37 , 0.96]
PrasangaDPGGM 2017 7 128 13 126 17.8% 0.53 [0.22 , 1.28]
Ramin 1995 1 122 4 137 4.7% 0.28 [0.03 , 2.48]
Seeras 1989 25 60 23 75 30.0% 1.36 [0.86 , 2.14]
Subtotal (95% CI) 2010 2042 81.7% 0.74 [0.40 , 1.37]
Total events: 59 84
Heterogeneity: Tau² = 0.23; Chi² = 8.78, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 0.97 (P = 0.33)
1.13.2 Uterine infection (intravenous administration route)
Prieto 1995 8 120 7 120 15.7% 1.14 [0.43 , 3.05]
Titapant 2012 0 40 2 39 2.6% 0.20 [0.01 , 3.94]
Subtotal (95% CI) 160 159 18.3% 0.84 [0.23 , 3.16]
Total events: 8 9
Heterogeneity: Tau² = 0.30; Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.25 (P = 0.80)
Total (95% CI) 2170 2201 100.0% 0.78 [0.47 , 1.28]
Total events: 67 93
Heterogeneity: Tau² = 0.16; Chi² = 10.06, df = 5 (P = 0.07); I² = 50%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%
0.01 0.1 1 10 100
Favours Antibiotics
Favours PlaceboNoTreatment


Antibiotics
PlaceboNoTreatment
Risk ratio
Risk ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.12.2 Uterine infection (short treatment course)
Lissauer 2019 26 1700 44 1704 29.2% 0.59 [0.37 , 0.96]
PrasangaDPGGM 2017 7 128 13 126 17.8% 0.53 [0.22 , 1.28]
Prieto 1995 8 120 7 120 15.7% 1.14 [0.43 , 3.05]
Ramin 1995 1 122 4 137 4.7% 0.28 [0.03 , 2.48]
Titapant 2012 0 40 2 39 2.6% 0.20 [0.01 , 3.94]
Subtotal (95% CI) 2110 2126 70.0% 0.61 [0.42 , 0.90]
Total events: 42 70
Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)
1.12.3 Uterine infection (long treatment course)
Seeras 1989 25 60 23 75 30.0% 1.36 [0.86 , 2.14]
Subtotal (95% CI) 60 75 30.0% 1.36 [0.86 , 2.14]
Total events: 25 23
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.19)
Total (95% CI) 2170 2201 100.0% 0.78 [0.47 , 1.28]
Total events: 67 93
Heterogeneity: Tau² = 0.16; Chi² = 10.06, df = 5 (P = 0.07); I² = 50%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Chi² = 6.93, df = 1 (P = 0.008), I² = 85.6%
0.01 0.1 1 10 100
Favours Antibiotics
Favours PlaceboNoTreatment


Antibiotic
PlaceboNoTreatment
Risk ratio
Risk ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.10.1 Gestation <12 weeks
Lissauer 2019 7 833 21 832 40.4% 0.33 [0.14 , 0.78]
Titapant 2012 0 40 2 39 6.1% 0.20 [0.01 , 3.94]
Subtotal (95% CI) 873 871 46.6% 0.32 [0.14 , 0.73]
Total events: 7 23
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)
1.10.2 Gestation >=12 weeks
Lissauer 2019 19 866 23 871 53.4% 0.83 [0.46 , 1.51]
Subtotal (95% CI) 866 871 53.4% 0.83 [0.46 , 1.51]
Total events: 19 23
Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Total (95% CI) 1739 1742 100.0% 0.53 [0.24 , 1.14]
Total events: 26 46
Heterogeneity: Tau² = 0.20; Chi² = 3.54, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%
0.1 0.2 0.5 1 2 5 10
Favours Antibiotic
Favours PlaceboNoTreatment

Appendix 3.1. FAST-M tools



MODIFIED EARLY OBSTETRIC WARNING CHART (MEOWS CHART)

FAST-M

Contact clinical decision maker if patient triggers ONE RED or TWO YELLOW flags at any one time.

Patient | Patient ID | DOB/Age

Date | Time | Initials

WRITE VALUES IN BOXES PROVIDED

Respiratory rate (breaths per minute)	25 or more	RED
	21 - 24	YELLOW
	11 - 20	NORMAL
	10 or less	RED
Temperature (°C)	38 or more	YELLOW
	36.0 to 37.9	NORMAL
	35.9 or less	YELLOW
Heart rate (beats per minute)	120 or more	RED
	100 - 119	YELLOW
	50 - 99	NORMAL
	40 - 49	YELLOW
	39 or less	RED
Systolic blood pressure (mmHg)	160 or more	RED
	140 -159	YELLOW
	100 -139	NORMAL
	90 - 99	YELLOW
	89 or less	RED
Diastolic blood pressure (mmHg)	110 or more	RED
	90 -109	YELLOW
	40 - 89	NORMAL
	39 or less	RED
Urine output Hours since patient passed urine (tick box)	12 hours or less	NORMAL
	12 - 18 hours	YELLOW
	18 hours or more OR less than 0.5 ml/kg/hour	RED
Mental State (tick box)	Alert	NORMAL
	Not Alert	RED
Looks unwell (tick box)	No	NORMAL
	Yes	YELLOW

TOTAL YELLOW FLAGS

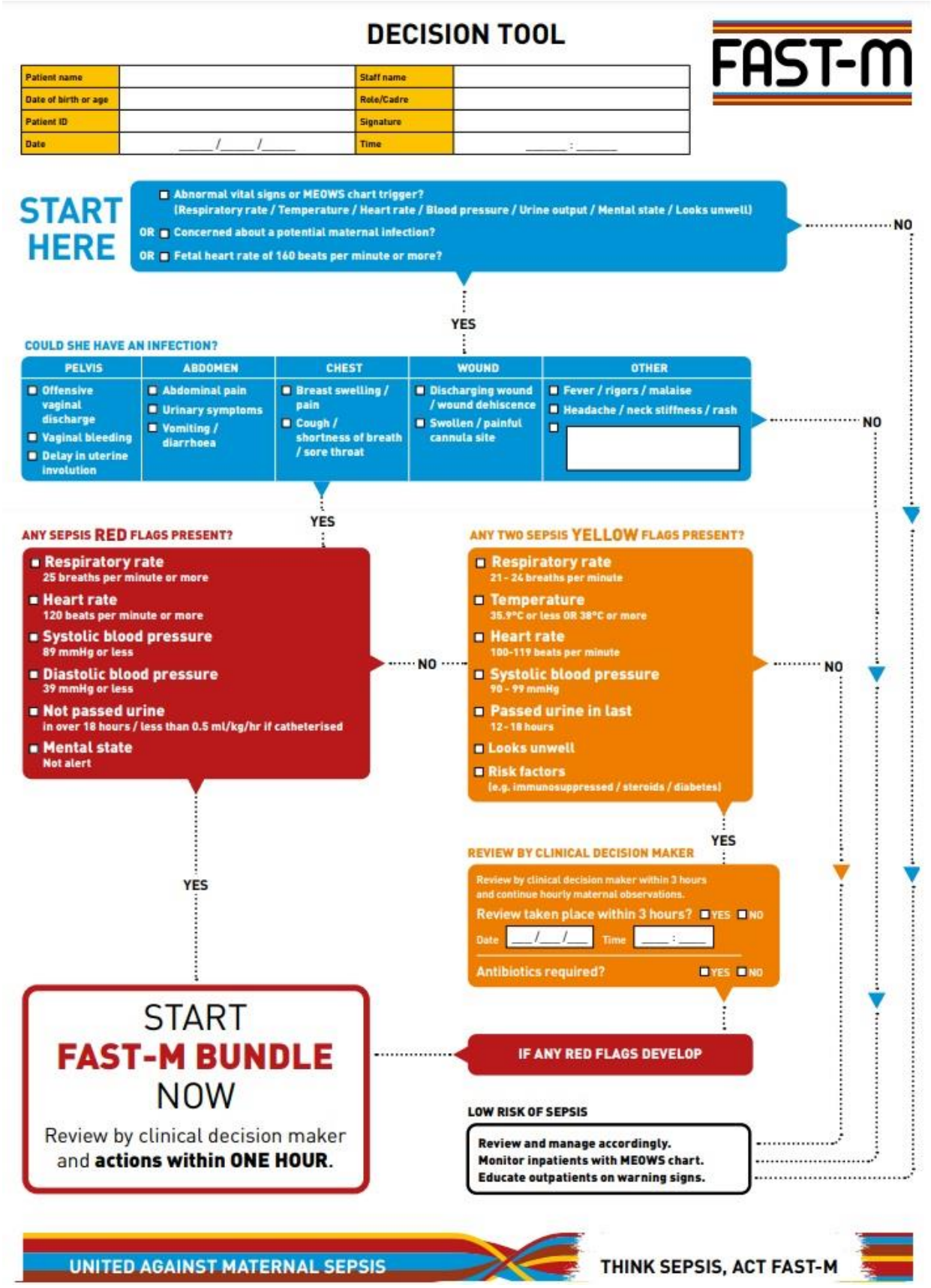
TOTAL RED FLAGS

ACTION TAKEN (IF REQUIRED) Yes (Y) / No (N)

ACT NOW if patient triggers ONE RED or TWO YELLOW flags at any time. Escalate to clinical decision maker and start FAST-M decision tool.

UNITED AGAINST MATERNAL SEPSIS

THINK SEPSIS, ACT FAST-M


DECISION TOOL
FAST-M
Patient name
Staff name
Date of birth or age
Role/Cadre
Patient ID
Signature
Date
Time
START HERE
Abnormal vital signs or MEOWS chart trigger?
(Respiratory rate / Temperature / Heart rate / Blood pressure / Urine output / Mental state / Looks unwell)
OR Concerned about a potential maternal infection?
OR Fetal heart rate of 160 beats per minute or more?
NO
YES
COULD SHE HAVE AN INFECTION?
PELVIS
Offensive vaginal discharge
Vaginal bleeding
Delay in uterine involution
ABDOMEN
Abdominal pain
Urinary symptoms
Vomiting / diarrhoea
CHEST
Breast swelling / pain
Cough / shortness of breath / sore throat
WOUND
Discharging wound / wound dehiscence
Swollen / painful cannula site
OTHER
Fever / rigors / malaise
Headache / neck stiffness / rash
NO
YES
ANY SEPSIS RED FLAGS PRESENT?
Respiratory rate
25 breaths per minute or more
Heart rate
120 beats per minute or more
Systolic blood pressure
89 mmHg or less
Diastolic blood pressure
39 mmHg or less
Not passed urine
in over 18 hours / less than 0.5 ml/kg/hr if catheterised
Mental state
Not alert
NO
ANY TWO SEPSIS YELLOW FLAGS PRESENT?
Respiratory rate
21 - 24 breaths per minute
Temperature
35.9°C or less OR 38°C or more
Heart rate
100-119 beats per minute
Systolic blood pressure
90 - 99 mmHg
Passed urine in last
12 - 18 hours
Looks unwell
Risk factors
(e.g. immunosuppressed / steroids / diabetes)
NO
YES
REVIEW BY CLINICAL DECISION MAKER
Review by clinical decision maker within 3 hours and continue hourly maternal observations.
Review taken place within 3 hours? YES NO
Date ___/___/___ Time ___:___
Antibiotics required? YES NO
YES
START
FAST-M BUNDLE
NOW
Review by clinical decision maker and actions within ONE HOUR.
IF ANY RED FLAGS DEVELOP
LOW RISK OF SEPSIS
Review and manage accordingly.
Monitor inpatients with MEOWS chart.
Educate outpatients on warning signs.
UNITED AGAINST MATERNAL SEPSIS
THINK SEPSIS, ACT FAST-M

TREATMENT BUNDLE

FAST-M

REMEMBER TO COMPLETE THESE ACTIONS WITHIN ONE HOUR

Patient name		Staff name	
D.O.B or age		Role/Cadre	
Patient ID		Signature	
Date & time of red flag observation	___/___/___ ___:___	Date & time bundle started	___/___/___ ___:___
Date & time of review by clinical decision maker	___/___/___ ___:___		

F

FLUIDS (caution in pre-eclampsia, severe anaemia and pulmonary oedema)

Date	___/___/___	Time fluids initiated	____:____	Initials	
Details / reason not completed					

Give 500 ml crystalloid immediately. Repeat 500 ml boluses to a maximum of 30 ml/kg if hypotension persists.

A

ANTIBIOTICS

Date	___/___/___	Time started	____:____	Initials	
Details / reason not completed					

See antibiotic guidelines below

S

SOURCE – identify and treat the source of infection

Date	___/___/___	Time considered	____:____	Initials	
Details / reason not completed					

See source identification and treatment boxes below

T

TRANSPORT (to higher level hospital or location within hospital, if required)

Date & time transport considered	___/___/___ ___:___	Initials		Transport Required	☐ YES ☐ NO
Date & time transport requested	___/___/___ ___:___	Initials		☐ N/A	
Date & time patient left facility	___/___/___ ___:___	Initials			
Destination					
Reason for any delay					

M

MONITORING (start MEOWS chart if not already started. Repeat observations every 30 minutes until otherwise decided by clinical decision maker)

Date & time monitoring commenced	___/___/___ ____:____	Details / reason not completed
Maternal / fetal monitoring should include	• Respiratory rate • Temperature • Heart rate • Blood pressure • Urine output • Mental state • Fetal heart rate	
Neonatal monitoring and review commenced	☐ YES ☐ NO ☐ N/A	

ANTIBIOTIC GUIDELINES

Insert local guidance here

Immediate treatment for Maternal Sepsis:

- Ceftriaxone 2 g IV once daily (if no IV access this can be given as 2 IM injections of 1 g in different sites).
- If possible intra-abdominal source add Metronidazole 500 mg IV three times daily or 400 mg PO three times daily.

If above antibiotic regime is not available then give:

- Chloramphenicol 1 g IV/IM four times daily plus Gentamycin 240 mg IV/IM once daily.

If maternal infection source is known, or as soon as it is identified:

- Use specific treatment based on Malawi Standard Treatment Guidelines.

IDENTIFY THE SOURCE

Consider

• Clinical history	• Blood cultures	• Sputum sample
• Clinical examination	• HIV and Malaria testing	• Imaging (abdominal, chest)
• Blood tests (if available) (FBC, U&Es, LFTs, CRP, clotting)	• Urine sample	• Lumbar puncture
	• Swabs (wound, vagina, throat)	• Other _____

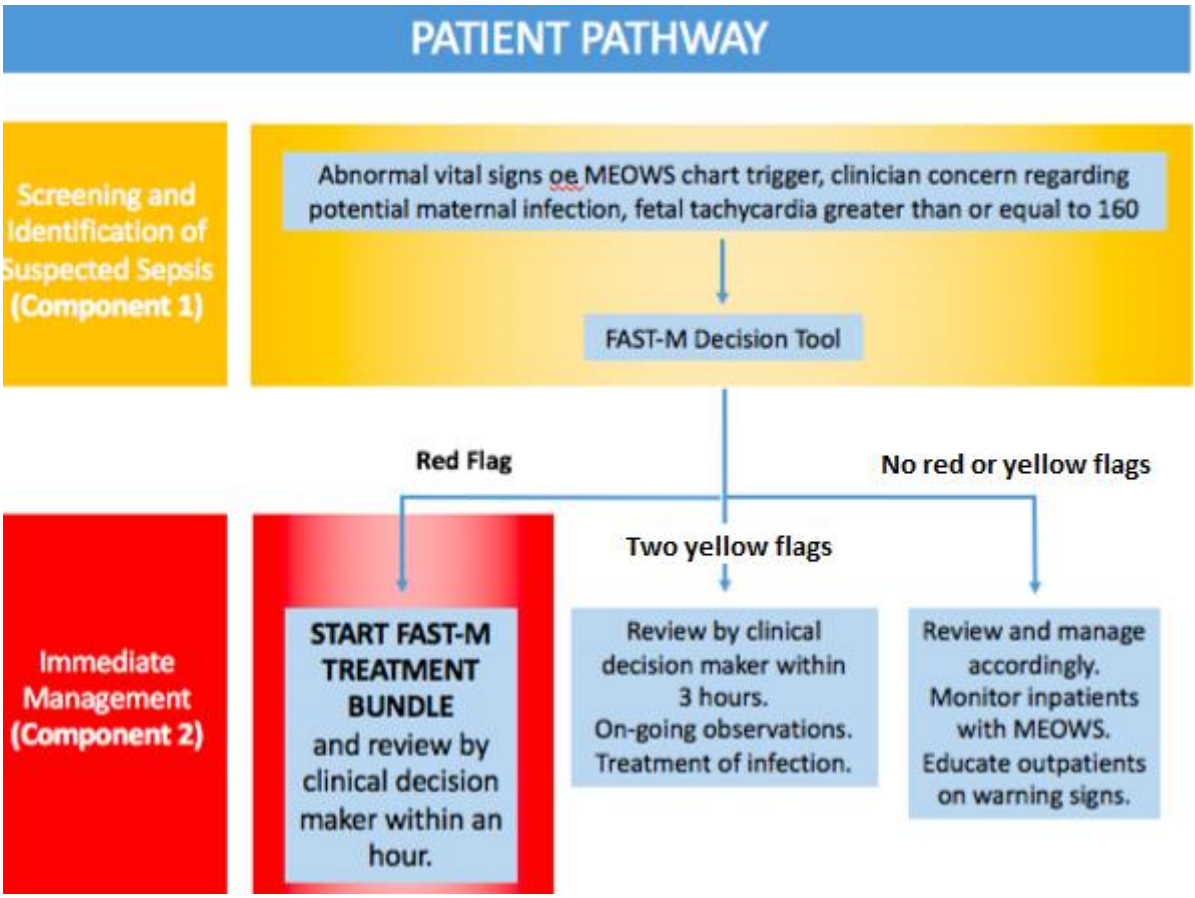
REMOVE / TREAT THE SOURCE

Consider

• Malaria treatment	• Removal of infected cannula / line
• Consider delivery of baby	• Hysterectomy
• Removal of retained products of conception	• Targeted antibiotics once source known
• Debridement of wound / drainage of collection	

UNITED AGAINST MATERNAL SEPSIS

THINK SEPSIS, ACT FAST-M


PATIENT PATHWAY
Screening and Identification of Suspected Sepsis (Component 1)
Abnormal vital signs oe MEOWS chart trigger, clinician concern regarding potential maternal infection, fetal tachycardia greater than or equal to 160
FAST-M Decision Tool
Red Flag
No red or yellow flags
Two yellow flags
Immediate Management (Component 2)
START FAST-M TREATMENT BUNDLE and review by clinical decision maker within an hour.
Review by clinical decision maker within 3 hours. On-going observations. Treatment of infection.
Review and manage accordingly. Monitor inpatients with MEOWS. Educate outpatients on warning signs.

Appendix 3.2: Interview guide

Interview Guide

Intervention Characteristics

1. What do you know about the intervention or its implementation?

2. How different is this intervention from your existing practices?

3. What kind of information or evidence are you aware of that shows whether or not the intervention will work in your setting?

4. What kinds of changes or alterations do you think you will need to make to the intervention so it will work effectively in your setting?
   - Do you think you will be able to make these changes? Why or why not?

5. What is your perception of the bundling of the intervention for implementation and quality of the supporting materials? Prompts: format, design, user-friendly. Duration, scope, intricacy and number of steps

Outer Setting

6. How do you think the individuals served by your organisation will respond to the intervention?

7. What barriers will the individuals served by your organisation face to participating in the intervention?

8. What kind of local, state, or national performance measures, policies, regulations, or guidelines might be important in influencing how this intervention can be implemented?

Inner Setting

9. Can you describe how the intervention will be integrated into current processes?

10. What are your current guidelines to assess and manage patients with maternal sepsis? Probes: tool, framework or guidelines for maternal sepsis, lactate test

11. What is your knowledge about importance of lactate test and what is your current practice about lactate testing? Probes: implications for lactate test, guidelines for lactate test

12. What is your current patient to doctor and patient to nurse's ratio in your setting?

13. Explain the role of doctors and nurses in management of maternal sepsis in your organisation. Which cadre is responsible for care and at what level of care? Probes: nurses, doctors, technicians and other health care cadres

14. Other than human resources, what resources are utilised in management of maternal sepsis in your hospital?

15. Do you expect to have sufficient resources to implement and administer the intervention?

- [If no] What resources will not be available? Probes: human resource, equipments, critical units etc

16. Do you feel the training planned for you will prepare you to carry out the roles and responsibilities expected of you?

- What are the positive aspects of planned training? What is missing?

Characteristics of Individuals

17. How do you feel about the intervention being used in your setting?

18. Do you think the intervention will be effective in your setting? Why or why not?

Process

19. Who will lead implementation of the intervention?

20. Are there people in your organisation who are likely to champion (go above and beyond what might be expected) the intervention?

Prompts: Position of these champions have in your organisation?

21. How do you think they will help with implementation?

Appendix 3.3. FGD guide

Thank you so much for reading the participant information sheet and consenting to participate in our research project.

Questions:

Let's start the discussion by talking about the FAST-M intervention and its implementation in your study setting?

How different was this intervention from your existing practices and how was this integrated into your process?
Probes: charts, communication, systematised plan for monitoring, patient documentation, records

What kind of information or evidence showed whether or not the intervention worked in your setting?
Probes: statistics, transfer of patients, sepsis rates, maternal morbidity, and mortality, administration of bundle components

Did you have sufficient resources to implement and administer the intervention?
Probes: Fluids, antibiotics, laboratory, ambulances, stretchers, FAST-M tools, monitoring equipment, human resource

Who were the key individuals who implemented the intervention?
Probes: doctors, interns, Hos, nurses, residents, admin, HODs

Do you feel the champions selected, helped in the implementation of the FAST-M intervention?
Probes: in communication, in arranging supplies and equipment, in coordination with stakeholders, in implementation of FAST-M intervention

Do you think the intervention was effective in your setting? Why or why not?
Probes: Patient improvement, length of stay of patients, patient transfer

What are your views about the sustainability of this intervention in your setting?
Probes: sepsis policies, protocols, integration of FAST-M intervention

Do you think this intervention helped to improve maternal and newborn health outcomes?

Probes: length of stay, fetal and neonatal wellbeing, transfer of newborn to pediatric critical units, condition of mothers and newborns at discharge, follow-up status of patients

What are your views about using this intervention to improve patient outcomes?
Probes: early detection of infection, deterioration of health, transfer of patients, timely monitoring

What strategies and activities helped you in implementation?
Probes: the display of posters, clinical champions, refreshers, training, monitoring visits, coordination with HODs

What were the barriers to the implementation of intervention? And what actions were taken to remove those barriers?
Probes: resources, the rigidity of HCPs to change the existing policies, compliance, administrative and clinical support

What are your views about using the MEOWs chart for early detection of maternal sepsis cases?
Probes: red triggers, yellow triggers, pre-eclamptic cases, patients condition, frequent monitoring

How effective was the decision tool in making decisions about sepsis patients?
Probes: clinical review, timely administration of treatment bundle

What are your views about the applicability of the overall elements of the FAST-M bundle that is Fluids, Antibiotics, Source control, Transport, and monitoring for management of maternal sepsis cases?
Probes: timely administration, need for administration, reasons for not administring, availability of resources

That concludes our focus group. Thank you so much for coming and sharing your thoughts and opinions with us. We have a short evaluation form that we would like you to fill out if you have time. If you have additional information that you did not get to say in the focus group, please feel free to write it on this evaluation form.

Appendix 4.1. Informed consent

Title of study:	FAST-M maternal sepsis bundle in Pakistan, a feasibility study
Chief Investigator:	Professor David Lissauer
Site:	Liaquat University of Health Sciences Pakistan
Site Principal Investigator:	Dr Sheikh Irfan Ahmed
Site CO-PI's	Dr Lumaan Sheikh, Dr Raheel Sikandar and Dr. Rubina Barolia
Ethics approval:	AKU ERC-2019-2061-7102, LUMHS/ REC/-886, 4-87/NBC-515/20/
Affiliated organisations:	University of Birmingham, University of Liverpool & Aga Khan University Hospital Pakistan & Liaquat University of Medical & Health Science, Jamshoro.

We would like to invite you to take part in this research study. Before you decide, we would like you to understand the study, why the research is being done and what this part of the study involves for you. One of the team will explain the study to you and answer any questions you may have.

Part 1: Purpose of the study

What is the purpose of the overall study?

We are developing an intervention that we hope will improve the care of patients with maternal sepsis around the world. Sepsis is when an infection has become severe enough to lead to organ dysfunction and become life threatening.

The intervention is composed of three things:

1. The MEOWS (Maternal Early Warning Scores) chart tool to help you monitor patient's observations and help detect maternal sepsis

2. The FAST-M sepsis "bundle", to help ensure fast, consistent and effective treatment of maternal sepsis

3. A training day to learn to use the tools to help recognise and treat maternal sepsis

We hope that this intervention will make caring for patients with maternal sepsis easier. This study aims to discover whether it is possible to introduce this intervention into Pakistan healthcare facilities.

We hope to try and understand the good and bad aspects of the bundle to try and make it more user friendly and effective. We hope that using this bundle will make caring for patients with maternal sepsis easier.

In order to achieve this we hope to:

1. Understand your current experiences in managing maternal sepsis at your hospital

2. Understand what you thought was good and bad about the intervention.

3. Understand ways to improve the intervention.

4. Evaluate the intervention to see if it improves care in your hospital.

We hope you will be willing to participate in all of the activities for the study mentioned above.

Why have I been invited to participate?

You have been invited to participate because you work in maternity care and we would like to understand your experiences of maternal sepsis and the proposed intervention.

What will I have to do if I take part?

You will be interviewed several times over a period of six to eight months. Sometimes these will be one on one interviews and sometimes in groups. The interviews will be in English and take up to an hour. The interview will take place at or close-by to your place of work, at a time that is convenient to you. The interview will be audio-recorded to allow us to analyse the information you give us. Some or all of the information will be transcribed word for word. This information will be used in several ways – all of which will be anonymous so that your identity is not disclosed. The table describes how your information will be used.

At the start of the study the information that you give us will be used to understand current practice at your hospital for the management of maternal sepsis. During the study the information that you give us will be used to discover the good and bad aspects of the intervention and how it could be improved to make it easier for you to manage patients with maternal sepsis. This will help us decide whether the intervention is a success or not. Some of the information you give us, including word for word extracts, will be used in the final project report, which may also be published in a journal.

Do I have to take part?

It is completely up to you to volunteer to be interviewed and it will have no effect upon your work. We will describe the study and go through this information sheet with you. If you decide to take part, we will then ask you to sign a consent form.

What are the possible disadvantages and risks of taking part?

Before participating you should consider that we will be asking you about your experiences, opinions, beliefs and feelings in relation to the intervention. We are interested in finding out about the positive things that help you do your work and anything that hinders your work. Although unlikely, there is a possibility that you might feel upset when answering these questions during the interview. If this was to occur, you would be able to take a break or continue another day.

There will be an opportunity at the end of the interview for you to consider whether there is anything that you have discussed that you would prefer not to be included in the transcript. The transcript will also be made available to you to review by email if you would like. As a participant you are free to withdraw during the interview and up to a month afterwards, without giving a reason.

What are the possible benefits of taking part?

We hope that you will find the experience interesting and enjoyable. The information we collect from this study will be used to help us make the intervention the best it can be. Your interview will also be very important in evaluating the interventions effects at your hospital and its potential usefulness in the management of maternal sepsis.

What are the financial considerations of taking part in this study?

We would like to provide you a token of thanks at the end of the interview for providing your time and information with us.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible difficulty you might suffer will be addressed. Information on this is given in Part 2.

Will my taking part in the study be kept confidential?

We will follow ethical practice and all information about you will be handled in confidence. Further details are included in Part 2.

This completes part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2: Conduct of the study

What will happen if I don't want to carry on with the study?

You may withdraw from the study without giving a reason. If you chose to withdraw from the study during or up to one month after your interview, we might ask you whether we can use the information you have given us, such as your interview answers. If you don't want to carry on with the study but you give us permission to use the information already collected, we will proceed to keep it securely. If you wish to withdraw and don't want your data to be used for the study, we will delete any recordings and destroy transcript files.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to the researchers, who will do their best to answer your questions. Their contact details are on the last page.

Will my taking part in this study be kept confidential?

The study will take place at your workplace, and for this reason it is possible that other work colleagues will be aware of your participation. However, we will follow these procedures for collecting, storing, processing and destroying information about you to ensure your confidentiality and safeguard your data:

- The recording of any information you give us during your interview will be stored in a password protected file and only authorised people will have access to it. This will help prevent people identifying your voice.
- The data transcribed from recordings will be stored securely on a computer with access restricted by a password. Transcripts will not include names or locations. Consent forms and printed transcripts will be kept in a locked cabinet, only accessible to authorised researchers.
- Data collected will be used for this study but, with your permission, might also be retained to include it anonymously in future studies.
- The identifiable data will be retained for the duration of the study and will be disposed of securely (i.e. shredding documents).

As a participant, you would have the right to check the accuracy of data held about you and correct any errors.

What will happen to the results of the research study?

The researchers will write a report outlining the results of this study. You will not be identified in any report, presentation or publication, however extracts from your interviews may be reproduced. The results will be used to inform local practice and a future possible larger scale trial of the intervention. If you are interested in the outcome of the research, then a summary of the findings can be sent to you via email and if you wish you will be invited to attend a feedback day at the end of the project.

Who is organising the research

This study is being carried out by the University of Birmingham, UK. University of Liverpool, UK and Aga Khan University Hospital(AKUH), Pakistan The research team is being led by Dr David Lissauer, Dr Lumaan Sheikh and Dr Sheikh Irfan is the researcher conducting this part of the study.

Who has reviewed the study?

This study has been reviewed by the National Bioethics Committee Pakistan and College Research Ethics Committee in AKUH.

Contact details:

Dr Sheikh Irfan Ahmed, Senior Instructor, AKUH National stadium road, Karachi Email: [redacted] Telephone number: [redacted]

Dr David Lissauer Lecturer in Maternal and Fetal Medicine, University of Birmingham, UK Email: [redacted]

Dr Lumaan Sheikh Associate Professor, AKUH National stadium road, Karachi Email: [redacted] Telephone number: [redacted]

Dr Raheel Sikandar Professor, Liaquat University of Medical & Health Sciences, Jamshoro Email: [redacted] Telephone number: [redacted]

Please keep this information sheet for your own records.

Dr Rubina Barolia, Associate Professor and Assistant Dean, School of Nursing, AKU, Email: [redacted] Telephone number: [redacted]

Bakhtawar Khowaja, Research Coordinator, AKUH National stadium road, Karachi Email: [redacted] Telephone number: [redacted]

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I have read the information sheet version 2.5 for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw up to one month after my participation without giving any reason. ☐

3. I agree to be interviewed for research in this study. I agree to my interview being audio-recorded and I understand that transcripts will be anonymised. I understand that participating in the interview for this research is voluntary and that I am free to withdraw my approval for use of the audio recordings and transcripts up to one month after my participation. ☐

4. I understand that anonymised sections of data collected during the study, may be ☐

looked at by individuals from regulatory authorities in the UK or Pakistan. I give permission for these individuals to have access to my anonymised transcript.

5. I understand that the researchers might publish an article in a journal with the results of this study. I give permission for my transcripts to be used for this purpose. I understand that these transcripts will be anonymised. ☐
6. I know how to contact the research team if I need to. ☐
7. I understand that I may terminate the interview at any time ☐
8. I am happy for information about me related to the study being stored on a password protected computer system, which will be backed-up in a separate location to keep this information safe. Data collected will be used for this study but, might also be retained to include it anonymously in future studies ☐
9. I agree to participate in this study. ☐

SIGNATURES:

Participant Name and Surname _____ Date_____

Signature _____

Researcher Name and Surname _____ Date _____

Signature_____

Appendix 4.2. Interview guide

1. What do you know about the intervention or its implementation?
2. How different is this intervention from your existing practices?
3. What kind of information or evidence are you aware of that shows whether or not the intervention will work in your setting?
4. What kinds of changes or alterations do you think you will need to make to the intervention so it will work effectively in your setting?
    - Do you think you will be able to make these changes? Why or why not?
5. What is your perception of the bundling of the intervention for implementation and quality of the supporting materials? Prompts: format, design, user-friendly. Duration, scope, intricacy and number of steps
6. How do you think the individuals served by your organisation will respond to the intervention?
7. What barriers will the individuals served by your organisation face to participating in the intervention?
8. What kind of local, state, or national performance measures, policies, regulations, or guidelines might be important in influencing how this intervention can be implemented?
9. Can you describe how the intervention will be integrated into current processes?
10. What are your current guidelines to assess and manage patients with maternal sepsis? Probes: tool, framework or guidelines for maternal sepsis, lactate test
11. What is your knowledge about importance of lactate test and what is your current practice about lactate testing? Probes: implications for lactate test, guidelines for lactate test
12. What is your current patient to doctor and patient to nurse's ratio in your setting?
13. Explain the role of doctors and nurses in management of maternal sepsis in your organisation. Which cadre is responsible for care and at what level of care? Probes: nurses, doctors, technicians and other health care cadres
14. Other than human resources, what resources are utilised in management of maternal sepsis in your hospital?
15. Do you expect to have sufficient resources to implement and administer the intervention?

- [If no] What resources will not be available? Probes: human resource, equipments, critical units etc

16. Do you feel the training planned for you will prepare you to carry out the roles and responsibilities expected of you?
    - What are the positive aspects of planned training? What is missing?
17. How do you feel about the intervention being used in your setting?
18. Do you think the intervention will be effective in your setting? Why or why not?
19. Who will lead implementation of the intervention?
20. Are there people in your organisation who are likely to champion (go above and beyond what might be expected) the intervention?
    Prompts: Position of these champions have in your organisation?
21. How do you think they will help with implementation?

Appendix 4.3. CRF 1

FORM 1: FACILITY AUDIT

FACILITY ☐☐ – ☐☐☐

Facility ID e.g. DH, KH *Visit ID e.g. 001, 002 etc.*

Today's Date: d d – m m – y y y y Time: h h : m m

QA01.Date previous form completed (or if first Visit, date study opened at this site): d d – m m – y y y y

QA02. Are you collecting the data during? **Baseline** ☐ **Intervention** ☐

QA03. How many of the following **MATERNAL OUTCOMES** have you had since the last visit or if first time since last 6 months?

Maternal Outcome	Number
Maternal Sepsis	
Maternal Deaths	
Post-Partum haemorrhage (>1L)	
Ante-Partum haemorrhage (>50ml)	
Severe pre-eclampsia/eclampsia (>160/110 and >2+protein in urine)	
Blood transfusions	
Uterine rupture	
Patient with reduced conscious level	
Injury (e.g. uterine, bladder, bowel)	
Anaphylaxis	
Pulmonary oedema	
Return to theatre	
Admission to ICU/HDU	
Broken down wounds (e.g. c/s, perineal)	
Placenta previa and Abruptio	

QA04. How many of the following **NEONATAL OUTCOMES** have you had since the last visit?

Neonatal Outcome	Number
Live Births	
Neonatal deaths before discharge from hospital	
Babies requiring antibiotics	
Sill births	
Admission to nursery care	
Apgar score of less than 7 at 5 mins after birth	

QA05. How many of the following **RESOURCES** are available today?

Resource	**Amount**			
	BAGS			
Type of IV Fluids:	0	1-5	6-10	>10
0.9% Saline	☐	☐	☐	☐
Ringers Lactate	☐	☐	☐	☐
5% dextrose	☐	☐	☐	☐
50% dextrose	☐	☐	☐	☐

QA06. Type of oral antibiotics	**Type of oral antibiotics**			
	0	1-5	6-10	>10
Amoxicillin	☐	☐	☐	☐
Augmentin	☐	☐	☐	☐
Cephalosporin (e.g. Cefalexin)	☐	☐	☐	☐
Cefixime	☐	☐	☐	☐
Ciprofloxacin	☐	☐	☐	☐
Doxycycline	☐	☐	☐	☐
Clindamycin	☐	☐	☐	☐
Chloramphenical	☐	☐	☐	☐
Erythromycin	☐	☐	☐	☐
Metronidazole	☐	☐	☐	☐
Other (please state):	☐	☐	☐	☐

QA07. Type of IM / IV antibiotics	**VIALS**			
	0	1-5	6-10	>10
Amoxicillin	☐	☐	☐	☐
Ampicillin	☐	☐	☐	☐
Benzyl-penicillin	☐	☐	☐	☐
Penicillin G	☐	☐	☐	☐

Cefazolin	☐	☐	☐	☐
Cephalosporin (e.g. ceftriazone etc.)	☐	☐	☐	☐
Chloramphenical	☐	☐	☐	☐
Ciprofloxacin	☐	☐	☐	☐
Clindamycin	☐	☐	☐	☐
Erythromycin	☐	☐	☐	☐
Gentamycin	☐	☐	☐	☐
Metronidazole	☐	☐	☐	☐
Vancomycin	☐	☐	☐	☐
Other (please state)	☐	☐	☐	☐

QA08. Manual vacuum aspiration (MVA) kits ready for use:	KITS			
	0	1-5	6-10	>10
	☐	☐	☐	☐

* Good availability defined as a supply that is unlikely to run out before the next anticipated delivery

FORM 1: FACILITY AUDIT

FACILITY ☐☐ – ☐☐☐

Facility ID e.g. DH, KH *Visit ID e.g. 001, 002 etc.*

QA09. Resource	Availability			
	Good *	Limited	None	Not Known
Equipment for IV line (cannula, dressings etc)	☐	☐	☐	
Malaria tests	☐	☐	☐	
Syphilis test	☐	☐	☐	
HIV test	☐	☐	☐	
Functioning theatre and staff able to remove source of infection	☐	☐	☐	
Working thermometers	☐	☐	☐	
Working BP machines	☐	☐	☐	
Working O2 saturation machines(Pulse Oximeters)	☐	☐	☐	
Fetoscopes /Pinnards/fetal stethoscopes	☐	☐	☐	
Clocks/watches	☐	☐	☐	
Spare batteries	☐	☐	☐	
Wound swabs	☐	☐	☐	
Corona virus swabs	☐	☐	☐	
Urine dips	☐	☐	☐	
Sputum cultures	☐	☐	☐	
Blood cultures	☐	☐	☐	
Pregnancy tests	☐	☐	☐	
Hematology blood tests	☐	☐	☐	
Biochemistry blood tests	☐	☐	☐	
Corona virus tests	☐	☐	☐	
Blood taking equipment	☐	☐	☐	
Functioning radiology department	☐	☐	☐	
Functioning ultrasound machine and person to scan	☐	☐	☐	

Functioning theatre and staff able to remove source of infection	☐	☐	☐	
Weighing scales	☐	☐	☐	
Urinary catheters	☐	☐	☐	
ZA) Gloves	☐	☐	☐	
ZB) Aprons	☐	☐	☐	

QA010. How many of the following **STAFF** is available TODAY?

Resource	Number
Doctors	
Medical Officers	
Medical Students	
Registered Nurse	
Nursing students	
Hospital and Ward Attendants	

QA011. Are the following **FACILITIES** in working order TODAY?

Resource	Yes	No
Does the ward have electricity?		
Does the ward have running water?		
Does the ward have soap?		
Does the ward have alcohol gel?		
Are the autoclaves working?		
Are the washing facilities for staff available?		
Are the washing facilities for patients available?		
Are flushable toilet facilities for staff available?		
Are flushable toilet facilities for patients available?		

* Good availability defined as a supply that is unlikely to run out before the next anticipated delivery

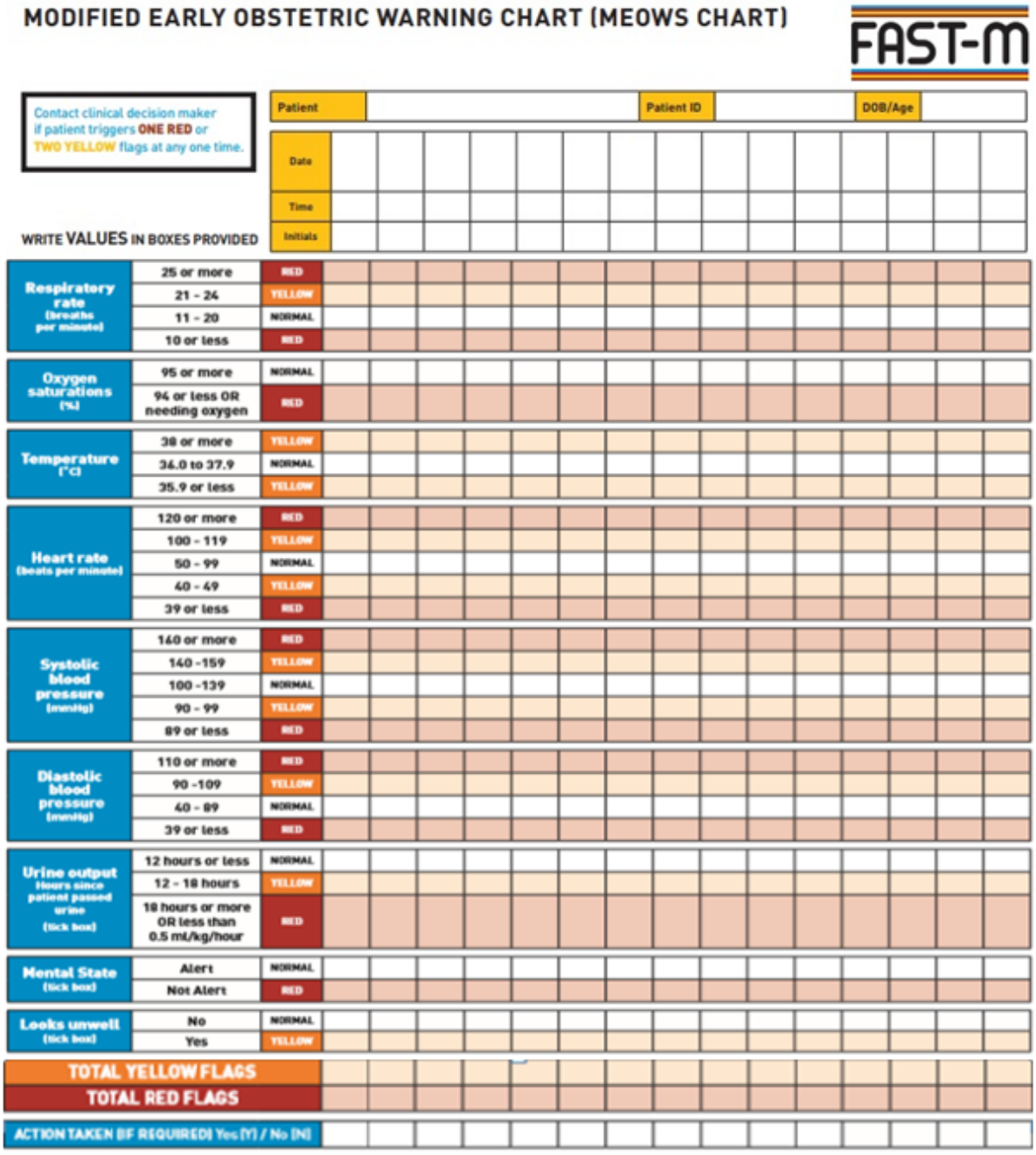
Completed by:

Role:

Signature:

Date: *DD*/*MMM* /*YYYY*

Appendix 4.4. FAST-M tools (adapted)



MODIFIED EARLY OBSTETRIC WARNING CHART (MEOWS CHART)

FAST-M

Contact clinical decision maker if patient triggers ONE RED or TWO YELLOW flags at any one time.

Patient | Patient ID | DOB/Age

WRITE VALUES IN BOXES PROVIDED

			Date	Time	Initials
Respiratory rate (breaths per minute)	25 or more	RED			
	21 - 24	YELLOW			
	11 - 20	NORMAL			
	10 or less	RED			
Oxygen saturations (%)	95 or more	NORMAL			
	94 or less OR needing oxygen	RED			
Temperature (°C)	38 or more	YELLOW			
	34.0 to 37.9	NORMAL			
	35.9 or less	YELLOW			
Heart rate (beats per minute)	120 or more	RED			
	100 - 119	YELLOW			
	50 - 99	NORMAL			
	40 - 49	YELLOW			
	39 or less	RED			
Systolic blood pressure (mmHg)	160 or more	RED			
	140 -159	YELLOW			
	100 -139	NORMAL			
	90 - 99	YELLOW			
	89 or less	RED			
Diastolic blood pressure (mmHg)	110 or more	RED			
	90 -109	YELLOW			
	40 - 89	NORMAL			
	39 or less	RED			
Urine output (hours since patient passed urine) (tick box)	12 hours or less	NORMAL			
	12 - 18 hours	YELLOW			
	18 hours or more OR less than 0.5 ml/kg/hour	RED			
Mental State (tick box)	Alert	NORMAL			
	Not Alert	RED			
Looks unwell (tick box)	No	NORMAL			
	Yes	YELLOW			
TOTAL YELLOW FLAGS					
TOTAL RED FLAGS					
ACTION TAKEN (IF REQUIRED) Yes (Y) / No (N)					

DECISION TOOL



TREATMENT BUNDLE

FAST-M

REMEMBER TO COMPLETE THESE ACTIONS WITHIN ONE HOUR

Patient name		Staff name			
D.O.B or age		Role/Cadre			
Patient ID		Signature			
Date & time of red flag observation	__/__/__ __:__	Date & time bundle started	__/__/__ __:__	Date & time of review by clinical decision maker	__/__/__ __:__

F — FLUIDS (caution in pre-eclampsia, severe anaemia and pulmonary oedema)

Date	___/___/___	Time fluids initiated	___:___	Initials	
Details / reason not completed					

Give 500 ml crystalloid immediately. Repeat 500 ml boluses to a maximum of 30 ml/kg if hypotension persists.

A — ANTIBIOTICS

Date	___/___/___	Time started	___:___	Initials	
Details / reason not completed					

See antibiotic guidelines below

S — SOURCE – identify and treat the source of infection

Date	___/___/___	Time considered	___:___	Initials	
Details / reason not completed					

See source identification and treatment boxes below

T — TRANSPORT (to higher level hospital or location within hospital, if required)

Date & time transport considered	___/___/___ ___:___	Initials		Transport Required	☐ YES ☐ NO
Date & time transport requested	___/___/___ ___:___	Initials		☐ N/A	
Date & time patient left facility	___/___/___ ___:___	Initials			
Destination					
Reason for any delay					

M — MONITORING (start MEOWS chart if not already started. Repeat observations every 30 minutes until otherwise decided by clinical decision maker)

Date & time monitoring commenced	__/__/__ ___:___	Details / reason not completed
Maternal / fetal monitoring should include	• Respiratory rate • Oxygen Saturations • Temperature • Heart rate • Blood pressure • Urine output • Mental state • Fetal heart rate	
Neonatal monitoring and review commenced	☐ YES ☐ NO ☐ N/A	

ANTIBIOTIC GUIDELINES

Insert local guidance here

Immediate treatment for Maternal Sepsis:

- Ceftriaxone 2 g IV once daily (if no IV access this can be given as 2 IM injections of 1 g in different sites).
- If possible intra-abdominal source add Metronidazole 500 mg IV three times daily or 400 mg PO three times daily.

If above antibiotic regime is not available then give:

- Tazobactam 4.5 g IV daily two time a day
- Meropenem 1 g IV daily two times a day

IDENTIFY THE SOURCE

Consider

• Clinical history	• Blood cultures	• Sputum sample
• Clinical examination	• HIV and Malaria testing	• Imaging (abdominal, chest)
• Blood tests (if available) (FBC, U&Es, LFTs, CRP, clotting)	• Urine sample	• Lumbar puncture
	• Swabs (wound, vagina, throat)	• Other _____

REMOVE / TREAT THE SOURCE

Consider

• Malaria treatment	• Removal of infected cannula / line
• Consider delivery of baby	• Hysterectomy
• Removal of retained products of conception	• Targeted antibiotics once source known
• Debridement of wound / drainage of collection	

Appendix 5.1. CRF 2

FORM 2: PATIENT CARE AUDIT FORM

Patient ID Number: ☐☐-☐☐☐

Facility ID e.g. UWK, KAB etc *Unique ID e.g. A001, B002 etc*

Baseline ☐ **or** **Intervention** ☐

Date of audit: d d - m m - y y y y Time of audit: h h : m m

QA01.Clinical status at admission:

Antenatal ☐ Miscarriage ☐

Post-natal ☐ Termination of pregnancy ☐

FORM 2: PATIENT CARE AUDIT FORM PATIENT ID ☐☐☐-☐☐☐☐

QA02. Which of the following observations were recorded when the patient was first assessed?

	Yes	No
A) Respiratory rate	☐☐	☐☐
B) Saturations	☐☐	☐☐
C) Temperature	☐☐	☐☐
D) Heart rate	☐☐	☐☐
E) Systolic BP	☐☐	☐☐

	Yes	No	Not recorded	Not Applicable
F) Diastolic BP	☐☐	☐☐		
G) Urine output	☐☐	☐☐		
H) Mental State	☐☐	☐☐		
I) Fetal heart rate	☐☐	☐☐		

QA03. Were the observations recorded on a chart?

Yes ☐ No ☐ N/A ☐

↳ A) If intervention phase, were they recorded on a MEOWS chart?
Yes ☐ No ☐ Other chart ☐

QA04. Has the patient been admitted for the last 24 hours?

Yes ☐ No ☐

If yes, go to question 5, if No got to Question 6

QA05. During the last 24 hours, please state the number of times each observation has been taken and charted:

	Number of times
A) Respiratory rate	☐
B) Oxygen saturation	☐
C) Temperature	☐
D) Heart rate	
E) Systolic BP	☐

	Number of times
F) Diastolic BP	
G) Urine output	
H) Mental state	
I) Fetal heart rate	

QA06. During their inpatient stay, did the patient have any of the following observations?

	Yellow trigger		Red trigger		No abnormal Observation	Not recorded
A) Respiratory rate	21-24		25 or more	10 or less	11 - 20	
	☐		☐	☐	☐	☐
B) Oxygen Saturations			94 or less Or needing oxygen		95 or more	☐
			☐		☐	☐
C) Temperature	38 or more	35.9 or less			36.0 to 37.9	
	☐	☐			☐	☐
D) Heart rate	100-119	40-49	120 or more	39 or less	50 - 99	
	☐	☐	☐	☐	☐	☐
E) Systolic Blood Pressure	140-159	90-99	160 or more	89 or less	100 -139	
	☐	☐	☐	☐	☐	☐
F) Diastolic Blood Pressure	90-109		110 or more	39 or less	40 - 89	
	☐		☐	☐	☐	☐
G) Urine output	In last 12-18 hours		In over 18 hours or less than 0.5ml/kg/hr		12 hours or less	
	☐		☐		☐	☐
H) Appearance	Looks unwell				Look well	
	☐				☐	☐
I) Mental state			Not alert		Alert	
			☐		☐	☐

Take a photograph of the MEOWS chart **(if intervention phase)**. Ensure the patient and provider names are covered.

FORM 2: PATIENT CARE AUDIT FORM

PATIENT ID NUMBER ☐☐☐-☐☐☐☐

REVIEW EVERY PATIENT'S NOTES WITH AN ABNORMAL OBSERVATION AND CONSIDER COMPLETING FORM 3 IF THERE IS CONCERN ABOUT MATERNAL INFECTION

QA07. Completed by: _____

QA08. Role:

QA09. Signature: _____ QA010. Date: *DD / MMM / YYYY*

You must have signed the Site Signature & Delegation Log

Appendix 5.2. CRF 3

FORM 3: INDIVIDUAL PATIENT FORM

Screen the notes for every patient that had a suspected infection.
Only complete this form for patients that fulfil the criteria in q1-4 below.

Also complete this form for any patient you observe during the patient care audit (Form2) that fulfils the criteria below.

CONSIDER QUESTIONS 1-4 TO DETERMINE IF THIS FORM NEEDS TO BE COMPLETED

QA01. Was there a concern about a potential maternal infection?

Yes ☐ No ☐ → **DO NOT COMPLETE FORM**

A) Date and time suspected: d d m m y y y y h h : m m

QA02. Have observations taken?

Yes ☐ No ☐ → **COMPLETE FORM**

QA03. Was there a fetal tachycardia (heart rate) greater than or equal to 160 bpm?

Yes ☐ No ☐ Not Recorded ☐ Not Applicable ☐

QA04. Did the patient have abnormal vital signs or MEOWS chart trigger - 1 or more red flags or 2 or more yellow flags?

Yes ☐ No ☐ Not Applicable ☐

IF NO TO BOTH QUESTIONS, DO NOT

FORM 3: INDIVIDUAL PATIENT FORM

Patient ID number: ☐☐☐☐ ☐☐☐☐

Time of assessment medical record: ☐☐ ☐☐

Date of assessment medical record: d D m m y y Y y

QA05. Study phase:

Baseline ☐ **Intervention** ☐

QA06. At the time of assessment for maternal infection by the health care staff, were they an inpatient or outpatient?

Inpatient ☐ Outpatient ☐

A) Date of admission: d d m m y y y y

B) Whilst an inpatient, was a chart used for the patient? FAST-M MEOWS chart: ☐ Other chart ☐

C) If no, why not? fr[redacted]

QA07. Were the patient referred from health facility

Yes ☐ No ☐

QA08. What treatment(s) did the patient receive before being referred? (Tick all the boxes that have been collected)

Fluids ☐ Antibiotics ☐ Source control ☐

Monitoring ☐ Not recorded ☐

QA09. What was the patient's pregnancy status when infection was first suspected/diagnosed?

<12 weeks ☐ 28+ weeks ☐ Miscarriage/ Abortion within the last 6 weeks ☐

12-28 ☐ Post-natal (up to 6 weeks) ☐

QA010. What type of infection was suspected? (Tick one or more options)

A)Offensive vaginal discharge

B) Vaginal bleeding

C)Delay in uterine involution

D)Abnormal pain

E) Urinary symptoms

F) Vomiting/diarrhea

G) Breast swelling/pain

H) Cough/shortness of breath/sore throat

I) Discharging wound/wound dehiscence

J) Swollen /painful cannula site

K) Fever /rigors/malaise

L) Headache/Neck stiffness/rash

M) Others, please state_____ _____

QA011. Did the patient have any of the following observations at time infection was first suspected/diagnosed

(see q1)?

	Yellow trigger		Red trigger		No abnormal Observation	Not recorded
A) Respiratory rate	21-24		25 or more	10 or less	11 - 20	
	☐		☐	☐	☐	☐
B) Oxygen Saturations			94 or less Or needing oxygen		95 or more	
			☐		☐	☐
C) Temperature	38 or more	35.9 or less			36.0 to 37.9	
	☐	☐			☐	☐
D) Heart rate	100-119	40-49	120 or more	39 or less	50 – 99	
	☐	☐	☐	☐	☐	☐

E) Systolic Blood Pressure	140-159	90-99	160 or more	89 or less	100 -139	
	☐	☐	☐	☐	☐	☐
F) Diastolic Blood Pressure	90-109		110 or more	39 or less	40 – 89	
	☐		☐	☐	☐	☐
G) Not passed urine	In last 12-18 hours		In over 18 hours or less than 0.5ml/kg/hr.		12 hours or less	
	☐		☐		☐	☐
H) Appearance	Looks unwell				Look well	
	☐				☐	☐
I) Mental state			Not alert		Alert	
			☐		☐	☐

QA012. At the time the decision tool was initiated (if intervention phase) or if not used that the infection was most serious there were:

Yellow flags ___ (enter number)

Red flags ___ (enter number)

A) If 2 or more yellow flags, or 1 or more red flags was the FAST-M bundle initiated (if intervention phase)?

Yes ☐ No ☐ Not recorded ☐ Not Applicable ☐

QA013. If one or more red flags present? Was the FAST-M bundle initiated (within 1 hour) (if intervention phase)?

Yes ☐ No ☐

Not recorded ☐ Not Applicable ☐ Go to question 12

QA014. If 2 or more yellow flags were present, did a review take place within 3 hours?

Yes ☐ No ☐ Not recorded ☐ Not Applicable ☐

QA015. Was the patient an inpatient for 24 hours or more prior to infection being suspected/ diagnosed?

Yes ☐ No ☐

QA016. If yes, During the last 24 hours or more, please state the number of times each observation has been recorded prior to infection being suspected / diagnosed:

	Number of times
A) Respiratory rate	
B) Temperature	
C) Heart rate	
D) Systolic BP	

	Number of times
E) Diastolic BP	
F) Urine output	
G) Mental state	
H) Fetal heart rate	

QA017. At the first time that a yellow or red trigger occurred, was action taken within 3 hours (if two or more yellow flags) or within 1 hour (if red)?

Yes ☐ No ☐ Not Recorded ☐ Not Applicable ☐

QA018.What action was taken (answer yes or no for each option)?

	Yes	**No**
A) Medical Officer informed	☐	☐
B) Nurse in charge informed	☐	☐

H) Others (please state) _____

C) Resident Doctor informed ☐ ☐

D) Treatment started ☐ ☐

E) Consultant Doctor ☐ ☐

Informed ☐ ☐

F) Nurse

G) Decision tool started, ☐ ☐

if intervention phase?

QA019. Who took action (answer yes or no for each option)?

	Yes	No		Yes	No
A) Medical Officer	☐	☐	E) Nurse	☐	☐
B) Resident Doctor	☐	☐			
C) Consultant Doctor	☐	☐	F) Nurse In-charge	☐	☐
D) Medical assistant	☐	☐			

QA020. If the patient was in an outpatient setting was the patient subsequently admitted?

Yes ☐ No ☐ N/A ☐

QA021.Was the patient commenced on an observation chart?

Yes ☐ No ☐

QA022. In the 24 hours or more after suspecting maternal infection, did the patient have their observations repeated WHILST they were awaiting the clinical review?

Yes ☐ No ☐ No, because review happened at the same time ☐

Not Done ☐

	½ Hourly	Hourly	Less Frequent than hourly
Respiratory rate			
Temperature			
Heart rate			
Systolic BP			

	½ Hourly	Hourly	Less Frequent than hourly	Not Recorded	Not Applicable
E)Diastolic BP					
F) Urine output					
G) Mental state					
H) Fetal heart rate					

QA023. Did the patient receive a clinical review within 1 or 3 hours' review of recognition of maternal infection/sepsis?

Yes ☐ No ☐ Not Applicable ☐

A) Date and time of review d d m m y y y y h h : m m

B) Did the patient receive a clinical review within 3 hours? Yes ☐ No ☐
C) Did the patient receive a clinical review within 1 hour? Yes ☐ No ☐

QA024. Following the clinical review was the specified frequency of observations given?
Yes ☐ No ☐

QA025. Did the patient undergo observations at this specified frequency?
Yes ☐ No ☐

QA026. Was the patient treated for maternal infection/sepsis?
Yes ☐ No ☐

QA027. If intervention phase was the FAST-M decision tool was used for the patient?

Yes ☐ No ☐

MANAGEMENT

QA028. Were IV fluids given?

Ye ☐ No ☐ A) Why not? _____

B) Date of started: d d m m y y y y

☐ or tick if not recorded

D) Time of started h h m m

☐ or tick if not recorded

QA029. Were antibiotics administered within one hour?

Yes ☐ No ☐ Not Recorded Why not? _____

B) Date of administered: d d m m y y y y

C)

☐ or tick if not recorded

D) Time of administered: h h m m

☐ or tick if not recorded

SOURCE CONTROL/ IDENTIFICATION

QA030. Was an attempt made to identify the source of infection?

Yes ☐ No ☐ A) Why not? _____

B) Date: d d m m y y y y D) Time h h m m

☐ or tick if not recorded ☐ or tick if not recorded

QA030_F. What attempts were made to identify the source?

	Yes	No		Yes	No		Yes	No
a) Clinical history	☐	☐	e) HIV test	☐	☐	h) Imaging (abdominal, chest)	☐	☐
b) Clinical examination	☐	☐				i) Lumbar puncture	☐	☐
c) Blood test (if available)	☐	☐	f) Malaria test	☐	☐	j) Sputum sample	☐	☐
d) Blood cultures	☐	☐	g) Urine sample	☐	☐	k) Others (please state) _____		

QA031. Was the source identified?

Yes ☐ No ☐

A) Date: d d m m y y y y B) C) h h m m D)

☐ or tick if not recorded ☐ or tick if not recorded

E) What was the source of infection?

	Yes	No
a) Breast	☐	☐
b)Chorioamnionitis	☐	☐
c) Endometritis	☐	☐
d) Infected Cannula/ line	☐	☐
e) Malaria	☐	☐
f) Meningitis/ cerebral infection	☐	☐
g) Other wound/ skin infection	☐	☐
k) Other (please state _____)	☐	☐
h) Peritonitis	☐	☐
i) Respiratory infection	☐	☐
j) Urinary Tract Infection	☐	☐

.

QA032. Was the source treated?

Yes ☐ No ☐ A) Why not? _____

B) Date: d d m m y y y y

☐ or tick if not recorded

D) Time h h m m

☐ [redacted]

F) How was it treated?

	Yes	No
a) Delivery of the baby	☐	☐
b) Removal of retained products of conception	☐	☐
c) Hysterectomy	☐	☐
d) Removal of infected cannula/line	☐	☐
e) Targeted antibiotics	☐	☐
f) Malaria treatment	☐	☐
g) Antivirals	☐	☐
h) Incision and drainage	☐	☐
i) Percutaneous drainage	☐	☐
j) Debridement of wound	☐	☐
k) Laparotomy and washout	☐	☐
l) Others (Please state) _____	☐	☐

[redacted]

TRANSPORT

QA033. Was there a need to transport the patient to a higher level of care considered?

Ye ☐ No ☐ A) Why not? _____ Not recorded ☐

B) Date: d d m m y y y y C) ☐ or tick if not recorded

D) h h m m ☐ or tick if not recorded

QA034. Was the patient transferred?

Ye ☐ No ☐ A) Why not? _____ Not recorded ☐

B) Date requested: d d m m y y y y C) ☐ or tick if not recorded

D) Time requested: h h m m E) ☐ or tick if not recorded

F) Date patient left the facility: d d m m y y y y G) ☐ or tick if not recorded

H) h h m m I) ☐ or tick if not recorded

QA035. Where was the patient transferred to? _____

QA036. Was a transfer letter sent with the patient?

Yes ☐ No ☐ A) Why not? _____

MONITORING

QA037. Did the patient have ongoing monitoring commenced after the recognition of maternal suspected/sepsis?

☐ Yes ☐ No ☐ N/A (24hrs hadn't elapsed)

	1/2 hourly or Less	Hourly or Less	Daily or More	Less than Daily	not done
A)Respiratory rate	☐	☐	☐	☐	☐
B)Temperature	☐	☐	☐	☐	☐
C)Heart rate	☐	☐	☐	☐	☐
D)Systolic BP	☐	☐	☐	☐	☐

	½ hourly or Less	Hourly or Less	Daily or More	Less than Daily	Not done	NR	NA
E) Diastolic BP	☐	☐	☐	☐	☐		
F) Urine output	☐	☐	☐	☐	☐		
G) Mental state	☐	☐	☐	☐	☐		
H) Fetal heartrate	☐	☐	☐	☐	☐		

FORM 3: INDIVIDUAL PATIENT FORM **PATIENT ID NUMBER** ☐☐☐-☐☐☐

PATIENT OUTCOMES

QA038. Did the patient have any of the following complications recorded during their treatment?

	Yes	No
Pulmonary oedema	☐	☐
Blood transfusion	☐	☐
Return to theatre	☐	☐
Allergic reaction	☐	☐

	Yes	No
E) Change in mental state	☐	☐
Reduced urine output (no output for >18 hours or <0.5ml/kg/hr)	☐	☐
Other, please state	☐	☐

QA039. Was the patient admitted to high dependency/ intensive care during their treatment?

Yes ☐ No ☐

A) No. of ☐☐ Days

QA040. Did the patient have any of the following near miss events recorded during their stay?

QA040_A. Cardiovascular dysfunction		
Event	**Yes**	**No**
a) Shock	☐	☐
b) Cardiac arrest	☐	☐
c) Severe hypo perfusion (lactate >5mmol/L)	☐	☐
d) Severe acidosis (pH<7.1)	☐	☐
e) Use of continuous vasoactive drugs	☐	☐
f) Cardio-pulmonary resuscitation	☐	☐
QA040_B. Respiratory dysfunction		
a) Acute cyanosis	☐	☐
b) Gasping	☐	☐
c) Severe tachypnea (respiratory rate >40)	☐	☐

d) Severe bradypnea (respiratory rate <6)	☐	☐
e) Severe hypoxaemia (O2 sats <90% for >60 mins or PAO2/FiO2 <200)	☐	☐
f) Intubation and ventilation not related to anaesthesia	☐	☐

PATIENT OUTCOMES

QA040_C. Renal dysfunction		
a) Oliguria non-responsive to fluids or diuretics	☐	☐
b) Creatinine >300 µmol/ml or >3.5 mg/dL	☐	☐
c) Dialysis for acute renal failure	☐	☐
QA40_D. Coagulation dysfunction		
a) Failure to form clots	☐	☐
b) Severe acute thrombocytopenia (50,000 platelets/ml)	☐	☐
c) Massive transfusion of blood or red cells (≥5 units)	☐	☐
QA40_E. Hepatic dysfunction		
a) Jaundice in the presence of pre-eclampsia	☐	☐
b) Severe acute hyperbilirubinemia (bilirubin>100 µmol/L or >6.0 mg/dL)	☐	☐
QA40_F. Neurological dysfunction		
a) Prolonged unconsciousness or coma (lasting >12 hours)	☐	☐
b) Stroke	☐	☐
c) Uncontrollable fit / status epilepticus	☐	☐
d) Global paralysis	☐	☐

QA40_G. Uterine dysfunction		
a) Hysterectomy due to uterine infection or haemorrhage	☐	☐

PATIENT OUTCOMES

QA041. Date of final discharge from hospital/health centre: d d - m m - y y y y

QA042. Total number of days spent in hospital: ☐ days

QA043. What was the outcome of the patient at discharge?

Alive and well, no follow-up required ☐

Alive and well, follow-up arranged ☐

Death ☐

A) Date of Death: d d - m m - y y y y

B) Time of Death: h h : m m

C) Cause of death: _____

PREGNANCY OUTCOMES (if event occurred during same admission)

Tick if not applicable ☐

QA044. What was the pregnancy outcome?

Miscarriage ☐

Ectopic pregnancy ☐

Induced abortion ☐

Live birth ☐

Still birth (> 28 weeks) ☐

Pregnancy terminated before admission ☐

A) Date occurred or diagnosed: d d - m m - y y y y

QA045. Was monitoring of the new-born commenced?

Yes ☐ No ☐ N/A ☐

A) Date: d d m m y y y y

☐ or tick if not recorded

C) h h m m

☐ or tick if not recorded

QA046. Was fetal monitoring done if the patient was antenatal?

Yes ☐ No ☐ N/A ☐

A) Date: d d m m y y y y

☐ or tick if not recorded

C) h h m m

☐ or tick if not recorded

NEONATAL OUTCOMES AT BIRTH

Tick if not applicable ☐

QA047. Gestation: ☐ Months OR ☐ weeks ☐ days

QA048. Weight: ☐ g Not recorded ☐

QA049. Did the baby have any of the following complications?

	Yes	No	Not recorded
A) Resuscitation	☐	☐	☐
B) Agpars below 7 at 5 mins after birth	☐	☐	☐
C) Admitted to neonatal unit/special care	☐	☐	☐

D) Other (Please state) _____

QA050. Was the baby thought to have sepsis?

Yes ☐ No ☐

A) Did the baby receive antibiotic prophylaxis anyway?

Yes ☐ No ☐

B) Were they treated for sepsis?

Yes ☐ No ☐ Not recorded

QA051.What was the outcome of the baby at discharge?

Alive and well, no follow-up required ☐

Alive and well, follow-up required ☐

Death ☐

Not recorded

A) Date of Death d d m m y y y y

B) Time of Death h h m m

C) Cause of _____

QA052. Completed by: _____

QA053. Role: _____

QA054. Signature: _____ QA055. Date:
DD / MM / YYYY

You must have signed the Site Signature & Delegation Log

Appendix 5.3. Patient consent form

Title of study	Evaluation of the FAST-M maternal sepsis bundle, a feasibility study
Chief Investigator	Prof. David Lissauer
Site Principal Investigator:	Dr Sheikh Irfan Ahmed
Affiliated organisations	University of Birmingham, UK, Aga Khan University Hospital (AKUH) Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi. Liaquat University of Medical & Health Sciences, Jamshoro

Information for you about the study: patient information sheet

What is the purpose of the overall study?

We are developing a way of improving the care of women with pregnancy or birth related infections around the world.

We are introducing three things:
1. a chart to help the nurses record your vital signs and detect infection before it becomes worse
2. A tool to help the medical staff treat infection
3. A training day to teach the medical staff about pregnancy or birth related infections

We hope that this will make caring for patients with pregnancy or birth related infections easier.

Why have I been invited to participate?
We are asking all patients pregnant or recently pregnant patients who are receiving treatment in hospital or who have an infection to participate. Being invited to take part does not necessarily mean you have an infection.

What will I have to do if I take part?
Nothing. If you agree to take part, you will receive the normal care. The information from your medical notes and your treatment will help us decide if our study is working.

Are there any possible risks or discomfort?
There is no drug or substance being administered to the woman. Therefore there are no major risks involved of being in this study.

Are there any extra costs involved?

The study will not incur any cost to you other than the time during sample collection.You will not be charged for the blood test.

Do I have to take part?
No you do not have to take part it is your decision. If you don't want to take part that is fine, it will not affect how you are cared for when you are in hospital.

Will my taking part in the study be kept confidential?
Yes. All the information from your notes will be stored securely and will not contain any identifiable information.
What are the possible benefits of taking part?
By giving us permission to look at your notes and your clinical care we hope that we will be able to find out if the study is working. If the study works then this will hopefully help to improve the care of mothers with infections.

What will happen if I don't want to carry on with the study?
You may withdraw from the study without giving a reason for up to one month after. If you wish to withdraw we will delete all the information we had collected about you.

What if there is a problem?
If you have a concern about any aspect of this study, you can speak to the researchers, who will do their best to answer your questions. Their contact details are on the next page.

Who is organising the research?
This study is being carried out by the University of Birmingham, UK.

Aga Khan University Hospital (AKUH) will be facilitating the day to day running of the study, including looking at your medical notes and collecting the information.

Who has reviewed the study?
This study has been reviewed by the National Bioethics Committee Pakistan and College Research Ethics Committee in AKUH and Liaquat University of Medical Health and Sciences(LUMHS).

Contact details:

Dr Sheikh Irfan Ahmed, Senior Instructor, AKUH National stadium road, Karachi Email: [redacted] Telephone number: [redacted]
Dr David Lissauer Lecturer in Maternal and Fetal Medicine, University of Birmingham, UK Email: [redacted]
Dr Lumaan Sheikh Associate Professor, AKUH National stadium road, Karachi Email: [redacted] Telephone number: [redacted]
Dr Raheel Sikandar Professor, Liaquat University of Medical & Health Sciences, Jamshoro Email: [redacted] Telephone number: [redacted]

Please keep this information sheet for your own records.
Registered study ID number:

Please keep this information sheet for your own record

Thank you for reading the information sheet about our research project. If you would like to take part, please read and sign this form.

Consent for the current study

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION

1. I have read the information sheet for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.
2. I understand that my participation is voluntary and that am free to withdraw up to one month after my participation without giving any reason.
3. I understand that all data collected about me will be anonymised and will not contain any identifiable information. I understand that allowing access to my notes is voluntary and that I am free to withdraw my approval for up to one month after my participation.
4. I understand that anonymised sections of data collected during the study, may be looked at by individuals from regulatory authorities in the UK or Pakistan. I give permission for these individuals to have access to anonymised information from my notes
5. I understand that the researchers might publish the results from this study. I give permission for the anonymised information from my notes to be used for this purpose.
6. I know how to contact the research team if I need to
7. I am happy for the information about me related to the study being stored on a password protected computer system, which will be backed up in a separate location to keep this information safe. Data collected will be used for this study but, might also be retained to include it anonymously in future studies.
8. I agree to participate in this study.

SIGNATURES

_____	_____	_____
Patient name and surname	Date	Signature / Thumbprint

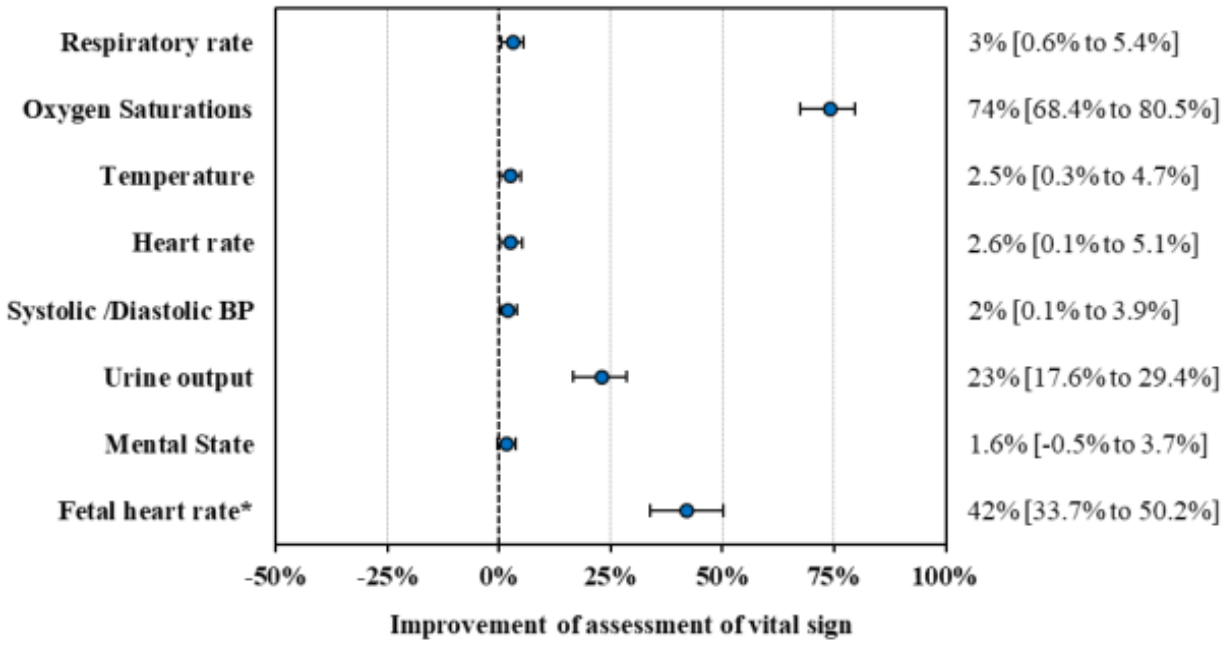
Participant Study ID Number: _____/_____

Witness:

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

_____	_____	_____
Witness name and surname	Date	Signature / Thumbprint
_____	_____	_____
Person obtaining consent Name and surname	Date	

Appendix 5.4. Vital signs assessment (n=439)



Appendix 5.5.

Table: Characteristics of suspected maternal sepsis patients (n=138)

Variables	Baseline n=60	Intervention n=78
Gestational at presentation		
<12 weeks	2(3.3%)	0(0%)
12-28 weeks	2(3.3%)	1(1.3%)
>28 weeks	31(51.7%)	38(48.7%)
Post-natal (up to 6 weeks)	25(41.7%)	39(50%)
Abnormal Trigger		
Respiratory Rate (>25 or <10 per minute)	41(68.3%)	41(52.6%)
Temp (>38 or <35.9 °C)	25(41.7%)	35(44.9%)
Heart Rate (>120 or <39 beats per minute)	32(53.3%)	38(48.7%)
Systolic Blood Pressure (>160 or <89 mmhg)	43(71.7%)	43(55.1%)
Diastolic Blood Pressure (>110 or <39 mmhg)	35(58.3%)	38(48.7%)
Urine Output (In over 18 hours or less than 0.5ml/kg/hr)	4(6.7%)	4(5.1%)
Mental State (Not alert)	9(15%)	28(35.9%)
Appearance (Looks unwell)	7(11.7%)	49(62.8%)
Source of maternal infection/sepsis*		
Breast	1(1.7%)	1(1.3%)
Chorioamnionitis	13(21.7%)	7(9%)
Endometritis	4(6.7%)	2(2.6%)
Infected Cannula/ line	1(1.7%)	0(0%)
Malaria	0(0%)	5(6.4%)
Meningitis/ cerebral infection	1(1.7%)	0(0%)
Other wound/ skin infection	3(5%)	5(6.4%)
Peritonitis	2(3.3%)	7(9%)
Respiratory infection	29(48.3%)	14(17.9%)
Urinary Tract Infection	9(15%)	6(7.7%)
Others	13(21.7%)	31(39.7%)
Unknown	7(11.7%)	14(17.9%)

*Thirty patients had multiple infection

Appendix 5.6

Table: Laboratory investigations of suspected maternal sepsis patients

Laboratory Investigations	Baseline phase (n=60)	Intervention phase (n=78)
Blood test (if available)	55 (92%)	78 (100%)
Blood cultures	27 (45%)	67 (86%)
HIV test	52 (87%)	72 (92%)
Malaria test	1 (2%)	21 (27%)
Urine sample	10 (17%)	63 (81%)
Swabs (wound, vagina, throat)	9 (15%)	2 (3%)
Imaging (abdominal, chest)	8 (13%)	38 (49%)
Lumbar puncture	0 (0%)	2 (3%)
Sputum sample	2 (3%)	2 (3%)

Appendix 5.7.

Table: Assessment of Maternal statistics (from facility audit CRF1)

Total Admissions (N=24,000)	January to June 2021 (n=11205)	July to December 2021 (n=12795)	P-value
Maternal Sepsis	210 (1.8%)	160 (1.2%)	.0005
Maternal Mortality	159 (1.4%)	120 (0.9%)	.001
Post-Partum Hemorrhage	110 (0.9%)	175 (1.36%)	.006
Antepartum Hemorrhage	194 (1.73%)	110 (0.85%)	.0005
Severe Pre-Eclampsia	133 (1.18%)	88 (0.68%)	.0005
Uterine Rupture	36 (0.32%)	28 (0.21%)	.125