Interventions to Reduce Maternal Mortality in Developing Countries: A Systematic Synthesis of Evidence.

Systematic Reviews of Evidence, Meta-Analysis and Meta-Synthesis

A thesis submitted to the University of Birmingham
for the Degree of
Doctor of Philosophy
by

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ABSTRACT

Background: Every year 287,000 women die from pregnancy related complications.

Methods: Systematic reviews of interventions to reduce maternal mortality in developing countries with meta-analysis or meta-synthesis where appropriate.

Results: Participatory learning and actions cycles with women's groups significantly reduce maternal and neonatal mortality, training and supporting TBAs also reduces perinatal mortality. Clinical officers performing caesareans section do not seem to cause any more maternal or perinatal mortalities than doctors. Prophylactic antibiotics reduce infectious morbidity in surgical abortion, yet the effect on miscarriage surgery is unclear. Cell salvage in ectopic pregnancy and caesarean section appear to be a safe and effective alternative in the absence of homologous transfusion. Motivational interviews may have potential to improve contraceptive use short term. Symphysiotomy may be a safe alternative to caesarean section. The anti-shock garment may improve outcomes when used in addition to standard obstetric haemorrhage management. Potential solutions to emergency transport for pregnant women include motorcycle ambulance programmes, collaboration with local minibus taxis services, and community education and insurance schemes.

Conclusion: Several interventions reviewed in this thesis can be utilised to aid reduction in maternal mortality, however the level of evidence available within each review varies, some allowing firm inferences with others more tentative.

DEDICATION

For every mother who has suffered whilst giving life to their child

ACKNOWLEDGEMENTS

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Finally, I would like to thank all the members at Ammalife for their dedication to making improvements to maternal health care for the world's poorest women.

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List of Abbreviations

AIDS: Acquired Immune Deficiency Syndrome

CHW: Community Health Worker

CI: Confidence Interval

CPD: Cephalopelvic Disproportion

C/S: Caesarean Section

DIC: Disseminated Intravascular Coagulation

HB: Haemoglobin

HIV: Human Immunodeficiency Virus

LHW: Lady Health Worker

MDG: Millennium Development Goal

NR: Not Reported

OR: Odds Ratio

PPH: Post partum Haemorrhage

RCT: Randomised Controlled Trial

RR: Relative Risk / Risk Ratio

SBA: Skilled Birth Attendant

SD: Standard Deviation

TBA: Traditional Birth Attendant

WHO: World Health Organisation

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List of Definitions

Autologous blood transfusion: The transfusion of one's own blood that has been salvaged or donated previously and re-infused.

Adult lifetime risk of maternal death: The probability that a 15-year-old women will die eventually from a maternal cause.

Clinical officers: Mid-level health care provider, who is not a medical doctors, and has a separate training programme to doctors, but their roles include many similar medical and surgical tasks, such as anaesthesia, diagnosis and treatment of medical conditions, and prescribing

Homologous blood transfusion (allogeneic): The transfusion of blood donated by another person.

Maternal mortality (MM): The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes

Maternal mortality ratio (MMR): Number of maternal deaths during a given time period per 100 000 live births during the same time period.

Maternal mortality rate (MMRate): Number of maternal deaths in a given period per 100 000 women of reproductive age during the same time period.

Neonatal mortality (NMR): Number of deaths of live born infants within the first 28 days of life. (Early neonatal mortality refers to a death of a live-born infant within the first seven days of life and late neonatal mortality includes deaths after 7 days of life until before 28 days.

Perinatal mortality (PMR): Number of stillbirths and deaths in the first week of life per 1,000 live births

Skilled birth attendant (SBA): an accredited health professional—such as a midwife, doctor, or nurse—who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth, and the immediate postnatal period, and in the identification, management, and referral of complications in women and newborns.

Symphysiotomy: The artificial separation of the symphysis pubis with a scalpel to enlarge the pelvic diameter to facilitate the process of birth

The proportion of maternal deaths among deaths of women of reproductive age (PM): The number of maternal deaths in a given time period divided by the total deaths among women aged 15–49 years.

Traditional Birth Attendant (TBA): a person who assists the mother during childbirth and who often acquires her skills by delivering babies herself or through an apprenticeship with other TBAs. Roles of a TBA vary and often depend on local customs, interests, and expertise. Tasks can range from provision of intrapartum and postnatal care to domestic chores. TBAs are often known and respected for their knowledge and experience. They are not usually salaried, and are often paid in kind.

Unmet need of family planning: The number of women of reproductive age who are married or in a union, who are fecund and sexually active but are not using any method of contraception, and report not wanting any more children or wanting to delay the birth of their next child.

List of Publications

Wilson A, Gallos ID, Plana N, Lissauer D, Khan KS, Zamora J, et al. Effectiveness of strategies incorporating training and support of traditional birth attendants on perinatal and maternal mortality: meta-analysis. BMJ. 2011;343:d7102.

Audrey Prost, Tim Colbourn, Nadine Seward, Kishwar Azad, Arri Coomarasamy, Andrew Copas, Tanja A Houweling, Edward Fottrell, Abdul Kuddus, Sonia Lewycka, Christine MacArthur, Dharma S Manandhar, Joanna Morrison, Charles Mwansambo, Nirmala Nair, Bejoy Nambiar, David Osrin, Christina Pagel, Tambosi Phiri, Anni-Maria Pulkki-Brannstrom , Mikey Rosato, Jolene Skordis-Worrall, Naomi Saville, Neena S More, Bhim Shrestha, Prasanta Tripathy, **Amie Wilson,** Anthony Costello, Women's groups practising participatory learning and action to improve maternal and newborn health in low-resource settings: a systematic review and meta-analysis. Lancet. 2013 May 18;381(9879):1736-46.

Wilson A, Lissauer D, Thangaratinam S, Khan KS, MacArthur C, Coomarasamy A. A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world: meta-analysis of controlled studies. BMJ. 2011;342:d2600.

Wilson A, Hillman S, Rosato M, Skelton J, Costello A, Hussein J, et al. A systematic review and thematic synthesis of qualitative studies on maternal emergency transport in low- and middle-income countries. Int J Gynaecol Obstet. 2013 Sep;122(3):192-201.

CHAPTER 1: INTRODUCTION

In 2010 it was estimated that 278 000 women died from pregnancy related complications (1). The enormity of the matter was brought into focus with the launch of the MDGs in September 2000 (2, 3) (table 1) when the maternal mortality rate was 529,000. World leaders committed to reduce poverty, hunger, disease, illiteracy, environmental degradation, and discrimination against women (3). Improving maternal health and reducing maternal mortality rates featured amongst these goals (MDG5). MDG 5 endeavours to improve maternal health by reducing maternal mortality by three quarters and achieve universal access to reproductive health services by 2015.

Since conscious efforts have been made to reduce maternal mortality, improvements have occurred. However substantial improvements were not seen until 2010. In 1990 the number of maternal deaths was 543,000, in 2000 this toll was 529,000 and in 2005 the total was 536,000, almost double the 2010 figures (278,000). Between 1990 and 2010 global maternal death decreased by 47% and many countries in sub-Saharan Africa experienced reductions of up to half. Despite this progress, the targeted 5.5% annual reduction set by the MDGs in 2000 is not yet being achieved globally. Between 1990 and 2010 the global annual reduction was just 3.1%. Ten countries however including Estonia, Romania, and the Islamic Republic of Iran have already achieved the targeted 5.5% annual reduction in maternal mortality rates, and a further nine more countries are on track to achieve this goal by 2015 (1). Yet twenty five countries have made less progress (classed as insufficient progress or no progress) in reducing maternal mortality and are not on track towards achieving MDG five, with some achieving less than 1% reduction (1).

There is great disparity in maternal mortality across the globe: in 2010 99% of maternal deaths occurred in developing countries. Half of all global maternal deaths occurred in Sub-Saharan Africa and a third in South Asia alone. Comparatively, developed countries attain just 1% of all maternal deaths (1). This is demonstrated in Figure 1 and equates to a ratio of 240 maternal deaths per 100,000 live births for developing countries, and 16 per 100,000 live births for developed countries. The disproportion in maternal deaths globally is not only evident between developing and developed regions; it also exists between urban and rural areas particularly within developing regions.

There are notable variations both historically and geographically with maternal mortality trends. Figure 1 also demonstrate the geographical variation in maternal mortality, it gives a global picture of maternal mortality in 2010, providing the maternal mortality ratios across countries. The map demonstrates the marked differences within continents such as Africa. For example, sub-Saharan countries such as Chad and the Central African Republic (MMR 1100 and 890 per 100, 000 live births respectively) have an MMR ten times that of Northern countries such as Algeria (97 per 100,000 live births). Even in continents where MMR is low, such as Europe, there is still some variation, for example the MMR in Belarus is 4 per 100,000 live births, and in the Republic of Moldova this statistic is 41 per 100,000 live births. There is however much greater variation between continents, which is demonstrated clearly in Figure 2. Figure 3 illustrates the annual rate of decline in maternal mortality per country between 1990 and 2008, thus showing the variable geographical progression towards achieving millennium development goal 5. The variability in maternal mortality rate within urban and rural regions is shown in Figure 4; this shows the difference in maternal mortality rates between rural and urban areas of countries in sub-Saharan Africa. This is suggested to be due to issues relating to obstetric care access or the poor quality of emergency obstetric care in hospitals or clinics (4).

The high rates of maternal mortality in developing regions often reflect the inequality in healthcare services and access to healthcare provisions. As most maternal deaths are preventable with good quality obstetric care, it is comprehensible that most maternal deaths occur in regions where women are less likely to receive this care. For example in developed countries where maternal mortality rates are low almost all births are attended by skilled birth attendants, and almost all women receive at least the four antenatal visits advised by the WHO. For example in Ireland (2010) 99.8% of births are attended by skilled birth attendants, with the same amount receiving the recommended antenatal care, the maternal mortality ratio was 4 per 100,000 live births. Comparatively in developing countries where maternal mortality rates are high, less than half of women receive skilled birth attendance, and one third receive the advised minimum of four antenatal visits. For example in Afghanistan the MMR is 460 per 100,000 live births, 36.3% of births are attended by skilled birth attendants, and 14.6% receive the recommended antenatal care.

The historical variation in maternal mortality is demonstrated in Figure 2, this shows the trends in maternal mortality over the twenty years from 1990 to 2010 by WHO region. Globally there was a 47% decline during these two decades, with Europe and the Americas even though low still showing some decline, but Africa and South East Asia showing the greatest reductions in maternal mortality between that period. Maternal mortality rates have not always been low developed countries: in 1800s and 1900s in England and Wales for example maternal mortality rates were much higher. It was not until the 1930s that maternal mortality rates began to fall, however a substantial reduction in rates was not seen until the 1950s (Figure 6). The reduction in maternal deaths from 1930s, with a steeper reduction in the 1950s may be due to the introduction, followed by the wider use, of antibiotics and blood transfusion. It is also suggested that some of the substantial reduction may be due to the change in the measurement of maternal mortality, for example measuring maternal death in the

population at risk, only those of childbearing age, usually defined as women aged 15–44, rather than the whole female population, or the classification of ‘true’ maternal deaths and how this changed in 1933 to include only ‘diseases of pregnancy, childbirth and the puerperal state’ (4). Furthermore after 1927, with the registration of stillbirths, the denominator that was used was total births (live and stillbirths), rather than just live births, and the gestational age in the classification of stillbirths was increased from 20 weeks to 28 weeks gestation in 1930.

Not only is there variation in maternal mortality rates historically and geographically, the leading causes of maternal mortality also fluctuate between time periods and geographical locations. Figure 5 demonstrates the geographical variation in distribution of causes of maternal deaths in Africa, Asia, Latin American and Developed countries. A systematic review conducted by the World Health Organisation (5) found that Haemorrhage was the leading cause of death in Africa and in Asia, representing 30% of all maternal deaths**.** Hypertensive disorders caused most deaths in Latin America and the Caribbean. Abortion related deaths were the highest in Latin America and the Caribbean**.** Deaths due to sepsis were lower in developed countries than in Africa, Asia, Latin America and the Caribbean. Ectopic pregnancy was reported as the cause of death in 1% of deaths in developing countries but nearly 5% in developed countries.

The varying rates of maternal mortality, and the main causes of maternal death in specific regions, are often a reflection on the quality of healthcare services available, as well as access and to healthcare provisions (6, 7) although, the social status of women is often connected. Although Figure 5 provides information of the clinical causes of death, it does not account for the underlying causes that may lead to maternal mortality. Gender inequality, lack of education or lack of autonomy in decision making are key factors reported in the literature (8, 9). Poverty is another factor that is suggested to be closely linked to maternal death (9, 10). A models that examines the

societal causes of maternal death is the three delays model (7). This model focuses on access to care and how it is impeded. These three steps are not independent and are linked closely to one another; a delay in one stage of the woman's journey can often result in subsequent delays.

The three delays model describes the three different types of delay in care access (Figure 7)(7);

Delay 1: A delay in making the decision to seek care (e.g. in the case of an obstetric emergency); this may due to a lack of awareness of the need to seek care, often due to lack of education or low social status of women.

Delay 2: A delay in reaching care (e.g. an appropriate obstetric facility that can perform caesarean section); this may be due to poverty, not being able to afford the transport required to reach the facility, or the cost of the treatment; or a lack of autonomy, the woman not being allowed to seek care or make the decisions to seek care.

Delay 3: A delay in receiving care (e.g. receiving the caesarean section that is needed); this may be due to poverty and gender inequality, with maternity care being poorly supported with staff and resources. It may also be due to a lack of education and empowerment, with the women not asserting a right to safe, effective care.

This model (7) emphasis the need for comprehensive consideration of the problem of maternal mortality, and can be used to guide our understanding of the way in which the problem should be addressed.

Another structure that can guide our understanding is the structure for analysing the determinants of maternal mortality (11). This places the pregnant woman at the crux of the structure and considers the three stages that contribute to maternal death. The first set of components are the immediate determinants of maternal health; these are the complications associated with pregnancy. This includes haemorrhage, infection,

obstructed labour, hypertension, and unsafe abortion (Figure 8), the most common causes accounting for 80% of all maternal deaths (1). Interventions that target the immediate determinants of maternal health focus on improving the outcome for women who develop such complications.

The second set of components in the framework, intermediate determinants of maternal health, are the health status of the woman, access to and the use of health services, and healthcare seeking behaviour. This includes diseases and conditions that affect the health of the woman and her ability to cope with the immediate determinants (complications of pregnancy), for example HIV/AIDS, malaria, malnutrition and anaemia (MDG 6). It also includes the concepts that affect the care received, such as a lack of available, acceptable or accessible care, or the quality of the care received. Interventions that target the intermediate determinants focus on reducing the likelihood of a woman experiencing a serious complication.

The third set of components; the distant determinants are more complex and affect the family and community in addition to the individual woman. This includes, but is not restricted to gender inequalities, female autonomy and advocacy (MDG 3), poverty (MDG 1), and education (MDG 2). Interventions that target these determinants focus on reducing the likelihood of unplanned or unwanted pregnancy.

Despite maternal mortality being halved globally, progress towards achieving MDG 5 is still inadequate, with some regions showing more progress than others. It has been acknowledged that improvements in maternal mortality rates have been seen in some developing countries. Countries such as Bangladesh, Sri Lanka and Nepal (1) share a number of common features; increased contraceptive use, delaying or limiting childbearing, enhanced access to high quality healthcare, and improvements in education and social status of women. Many developing countries however, are yet to

accomplish these standards. Instead poor political will, inadequate governance, and minimal economical input into healthcare are suggested to hinder improvements in maternal health (12-14). Inequality (15), conflict, and famine, as well as poor quality care or a lack of available obstetric care due to various barriers (16) may impede improvement further.

Poor maternal health and maternal mortality greatly influence perinatal, neonatal and infant health and mortality rates, as they are inextricably linked (MDG 4). Infants of mothers that die are between three and ten times more likely to die within two years of their mothers deaths (12). For this reason perinatal and neonatal mortality rates are also examined within this thesis. These rates can be useful when examining interventions to reduce maternal mortality, as greater improvements are often seen in these outcomes first, due to the sample size needed to show an effect in maternal mortality.

High maternal mortality rates profoundly influence the wider community. Poor health among women and children can gravely impede economic growth, with an estimated £9.4 billion being lost in potential productivity annually (13, 17-19). The WHO advocates the global importance of maternal and neonatal health, stating the central roles they encompass in global well-being. The effect of affordable interventions on neonatal health has been demonstrated, even in the poorest countries it is suggested that between 41% and 72% of neonatal deaths could be prevented if simple, evidence-based, cost effective interventions were implemented (20). Has the same effect been shown with interventions to reduce maternal mortality rates?

The effect of interventions on maternal mortality in developing countries is more difficult to measure. It is complicated by a lack of reliable data, incomplete and sporadic reporting of individual deaths, as well as the difficulty with assessing the true causality

of each death (1) (21). Despite this, many interventions have aimed to reduce maternal mortality, and improve maternal health, but some have neglected the economic, geographic and social constraints of developing countries. Without such consideration, interventions can be targeted incorrectly, thus not able to demonstrate the largest possible effect. One example of this is focusing efforts on skilled birth attendants *only*, or providing interventions *only* within health facilities. This does not take into account the global deficit of skilled birth attendants, and that most women in developing countries receive care from a lay-provider at home, or outside of health facilities. Targeting interventions that utilise available resources and comply with the current infrastructure may prove more successful in implementation, size of effect, generalisabilty to population, as well as overall outcome. An example of targeting interventions is training and supporting TBAs or participatory learning and action cycles with women's groups (chapter 3 and 4).

Not only can complexities arise with measuring maternal mortality, and assessing progress toward achieving MDG5, it is often difficult to assess the impact of interventions within a specific setting, or single interventions within complex packages. The design and implementation of interventions and projects to reduce maternal mortality can be poorly documented or reported, often lacking sufficient detail for direct inferences to be made. Therefore assessing the impact of interventions too can also be problematic, particularly if they have been evaluated in a non-systematic and non-rigorous manner (13). Good quality data from well designed and well executed systematic reviews and meta-analyses, are the ideal source of evidence to guide clinical practice and projects. In the absence of these, well designed and well executed RCTs are the next best form of evidence. RCTs however are not always feasible or ethical, thus the next best available evidence should be assessed as per the hierarchy of evidence. It is however important to consider the strength of the evidence from which inferences are made.

This thesis aims to systematically synthesise, review and assess the evidence on interventions proposed to reduce maternal deaths in developing countries, thus enabling interventions to be classed accordingly:

a) Beneficial (suitable for implementation; no further research required)
b) Likely to be beneficial (may be suitable for implementation with close monitoring of outcomes; further research may be required)
c) Trade off between benefits and harm (may be suitable for implementation according to local circumstances and priorities. Implementation ideally carried out in the context of research; further research required
d) Unknown effectiveness (not for implementation; may be suitable for research if existing data indicative of benefits)
e) Unlikely to be beneficial, or likely to be harmful (not for implementation; not for research)

Due to the scale of existing interventions that have been conducted in developing countries to reduce maternal mortality, only those that were deemed to be the most promising were focused on. Ten interventions and clinical situations have been reviewed. The selection of the interventions to be reviewed in this thesis were not pre-defined when the thesis commenced. Alternatively the interventions evolved through discussions with experts and clinicians with experience in maternal health in developing countries, in conjunction with publication of new evidence, and revelation of new information on maternal health.

Initially a scoping literature search was performed within the following databases MEDLINE, EMBASE, Reproductive Health Library and The Cochrane library. Experts were contacted to discuss the various interventions identified that aimed to reduce maternal mortality in developing countries. The types of interventions identified were

initially planned to be grouped in the following categories. As there is no universally recognised classification of interventions, the classifications that were used were developed following consultation with a range of stakeholders; including obstetricians, midwives, researchers and experts in the area. The purpose of the classifications was to group the intervention into meaningful categories to aid the reader.

A Single interventions

B Packages or strategies

C Behavioural or educational interventions

D Organisational interventions

E Policy and programmatic interventions

This is shown in Table 2 (Examples of Interventions from Research Proposal)

The best possible evidence available is included in the systematic reviews to evaluate the interventions. Where possible, level one evidence, data from RCTs are used in the reviews. In the absence of sufficient data from such trials, data from quasi-experimental and observational studies will be included. For example where RCTs are not available, the next level of available evidence was included. This hierarchy of evidence will be followed (22) to ensure the inclusion of the highest level of evidence available is included within the reviews.

This provisional list was subject to development and change as the reviews were conducted. The initial categories given in the provisional list above evolved as part of the iterative review process, giving the list that features in Table 3 (Interventions reviewed in the thesis). Many of the interventions reviewed spanned more than one

category in the provisional list, but fit the new classifications more appropriately. The new classifications are as follows:

a) Community based interventions

b) Task-sharing / Task-shifting interventions

c) Clinical interventions

In the absence of a universally recognised intervention classification scheme, the above classifications were used to group the interventions into meaningful categories to aid the reader.

The aim of this thesis was to systematically review the evidence on interventions to reduce maternal mortality in developing countries. The aim was achieved through the following objectives:

a) Review, synthesise and assess the literature on community based interventions

b) Review, synthesise and assess the literature on task-sharing interventions

c) Review, synthesise and assess the literature on clinical interventions

d) Make recommendations for practice

e) Make recommendations for research

The questions addressed in the thesis and the interventions that have been systematically reviewed in this thesis are shown in Table 3. A cost effectiveness assessment of the interventions reviewed was not formally considered in the thesis, however it is recognised that the cost of interventions does need consideration, particularly when considering implementation. Cost effectiveness of various interventions to reduce maternal mortality is available in the literature (23-25).

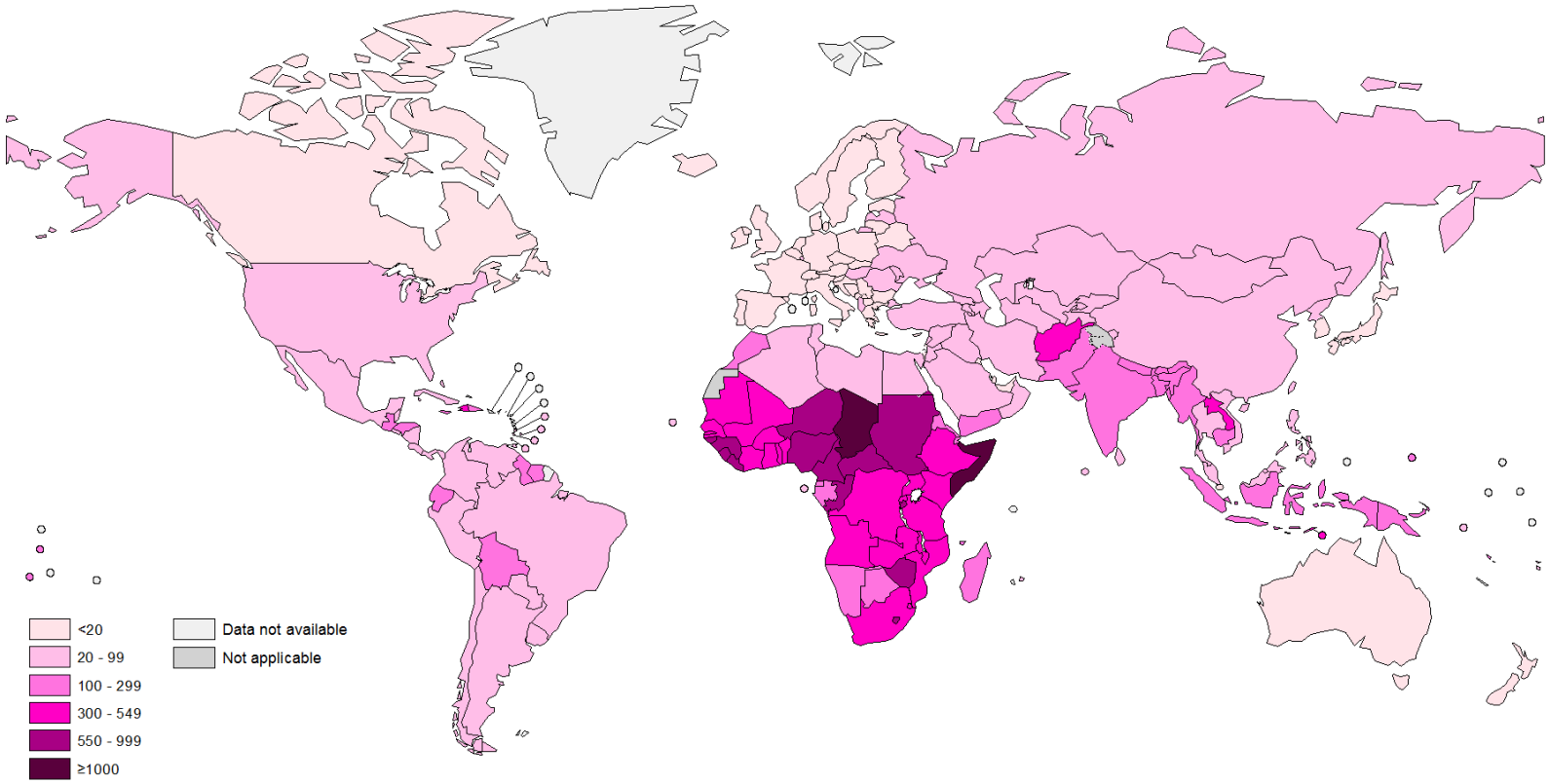


Figure 1 Maternal mortality ratio (per 100,000 live births) in 2010, as per WHO

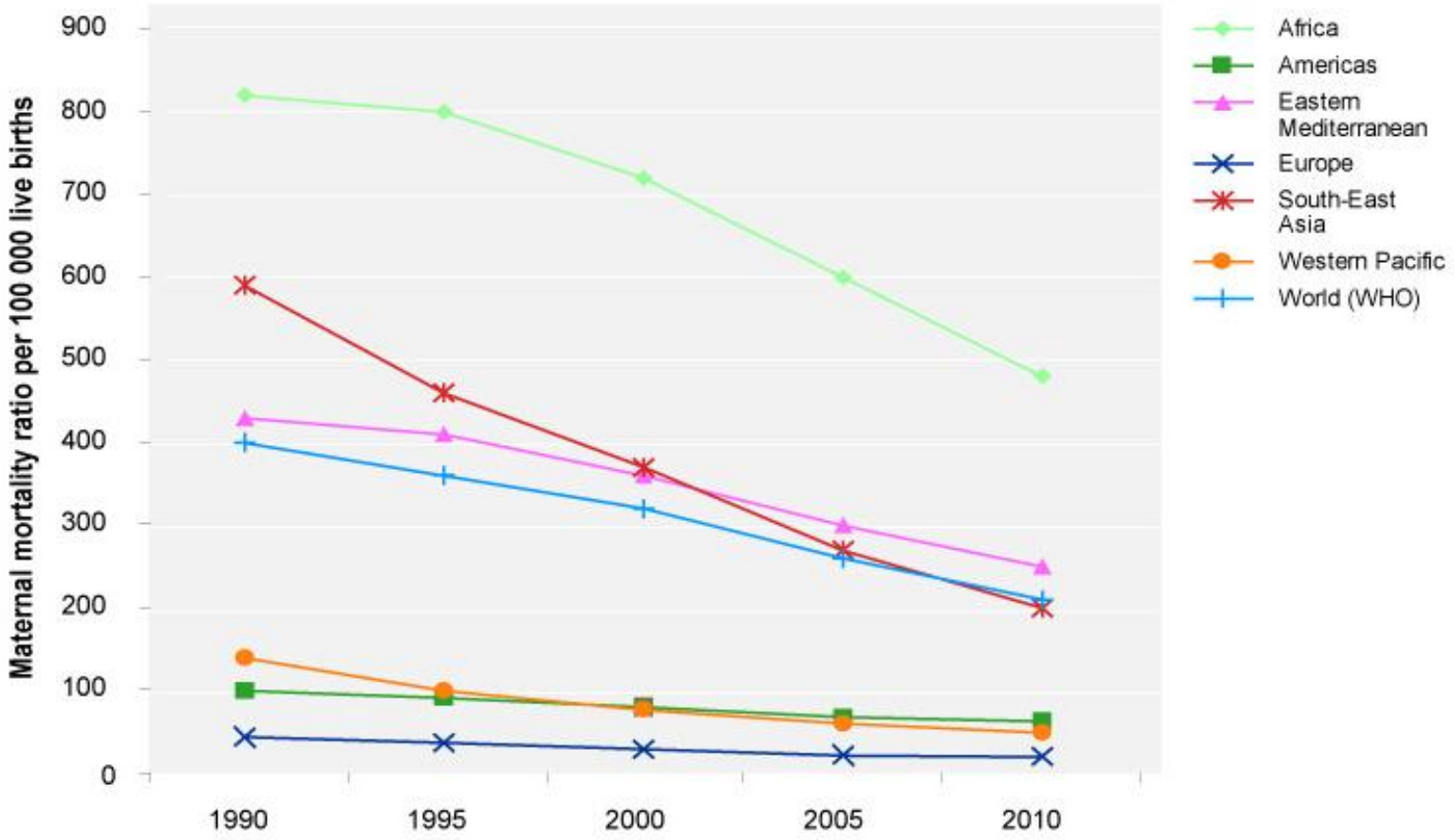


Figure 2 Maternal mortality ratio per 100,000 live births by region (1990-2010)

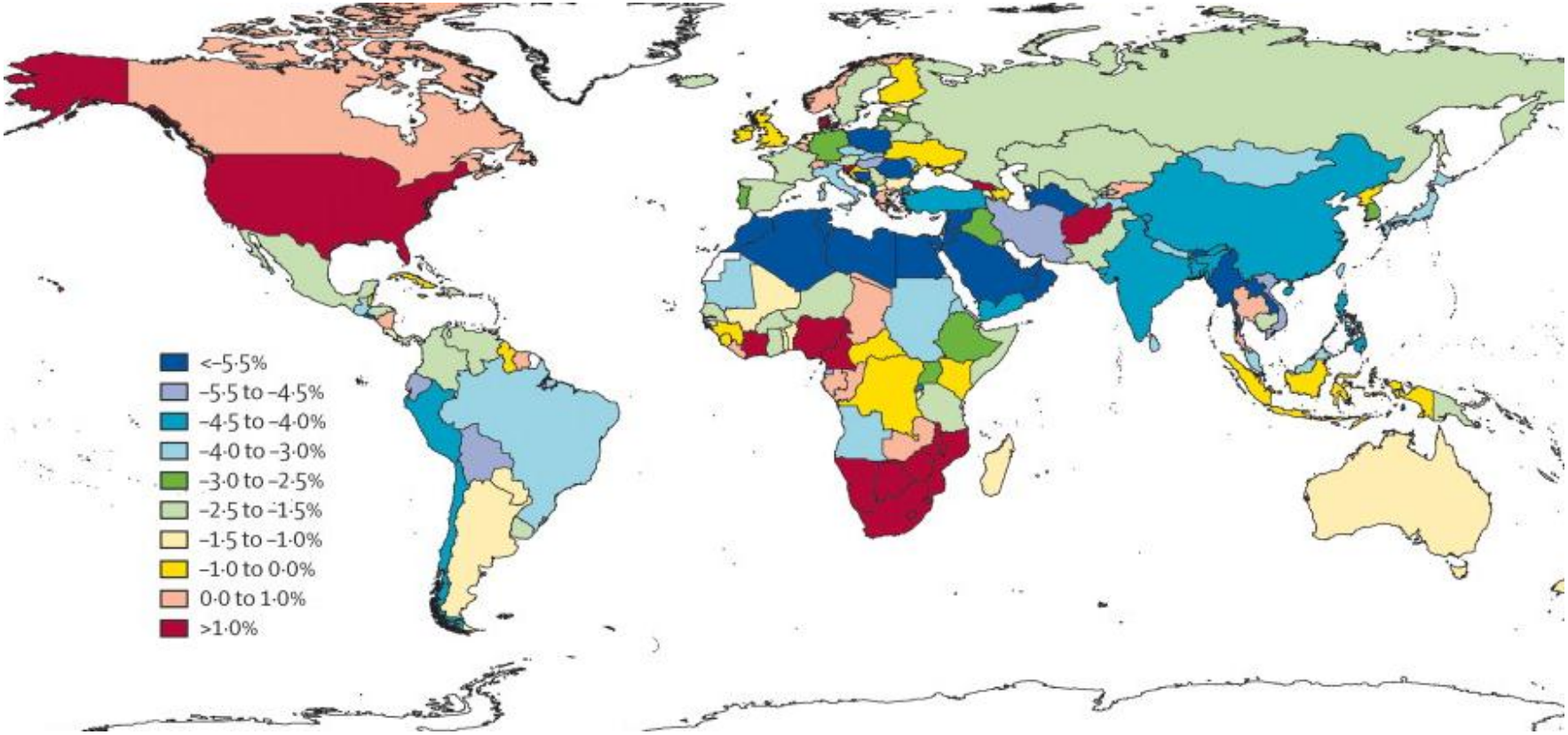


Figure 3 Yearly rate of decline in maternal mortality ratio, 1990–2008

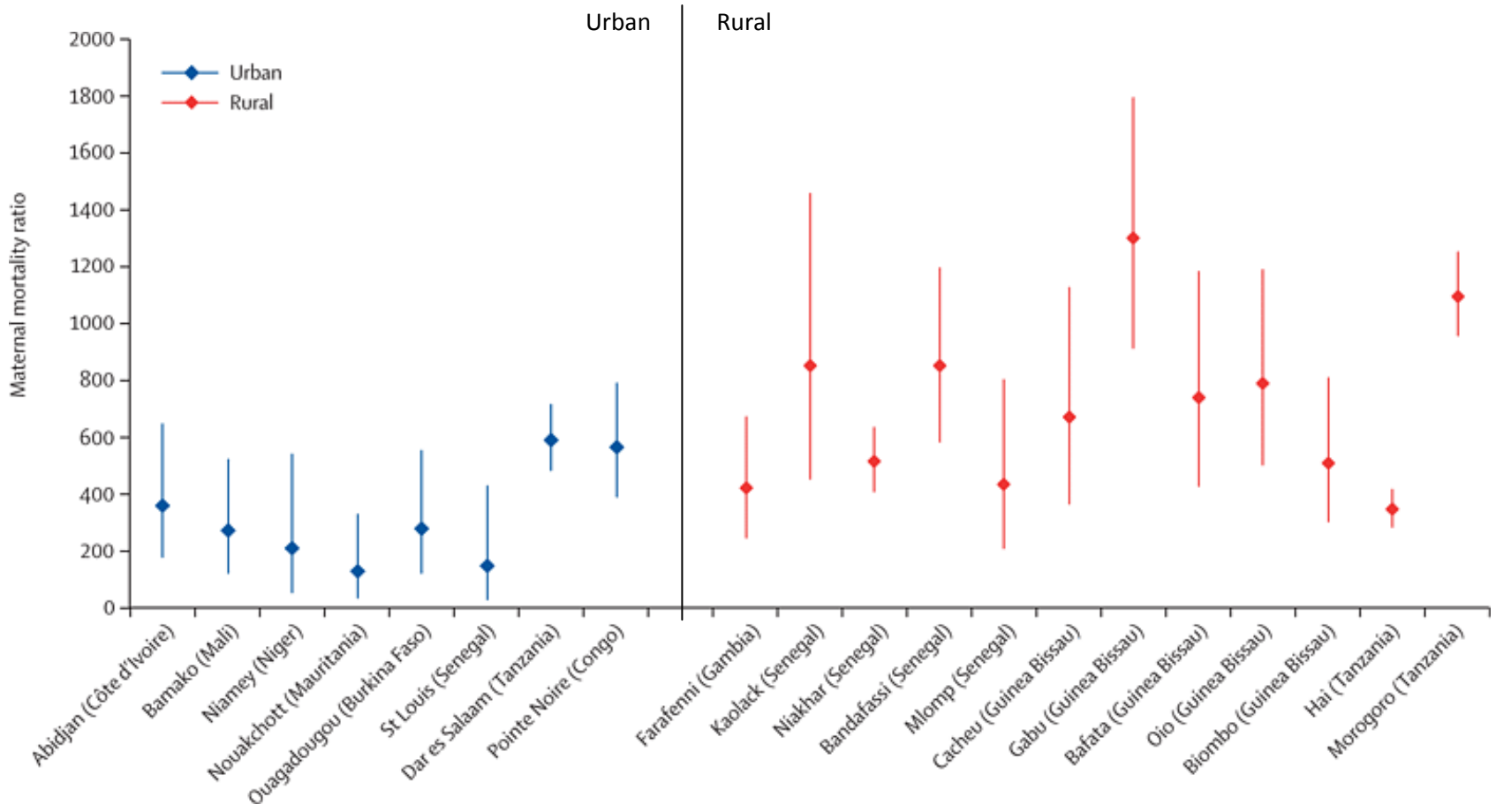


Figure 4 Maternal mortality ratios in urban and rural sites in sub-Saharan Africa (26)

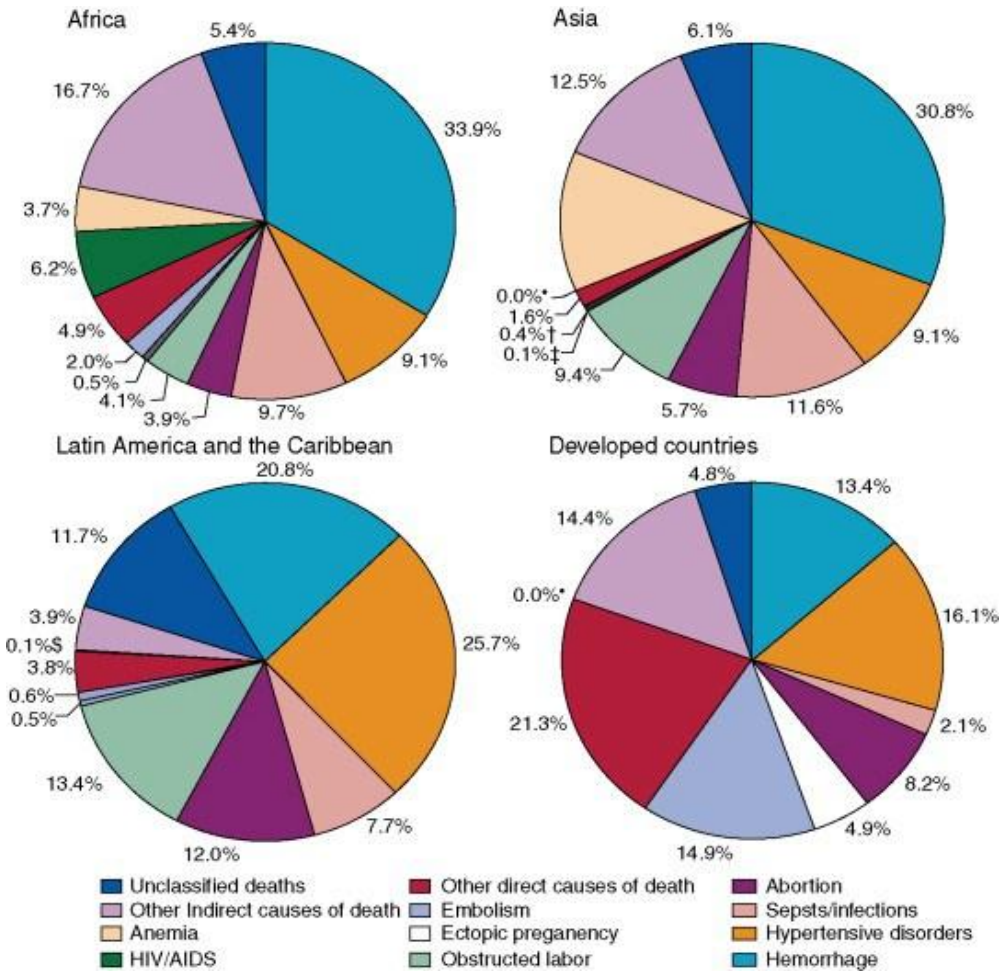


*Figure 5 Geographical variation in distribution of causes of maternal deaths *Represents HIV/AIDS. †Represents embolism. ‡Represents ectopic pregnancy. §Represents anaemia*

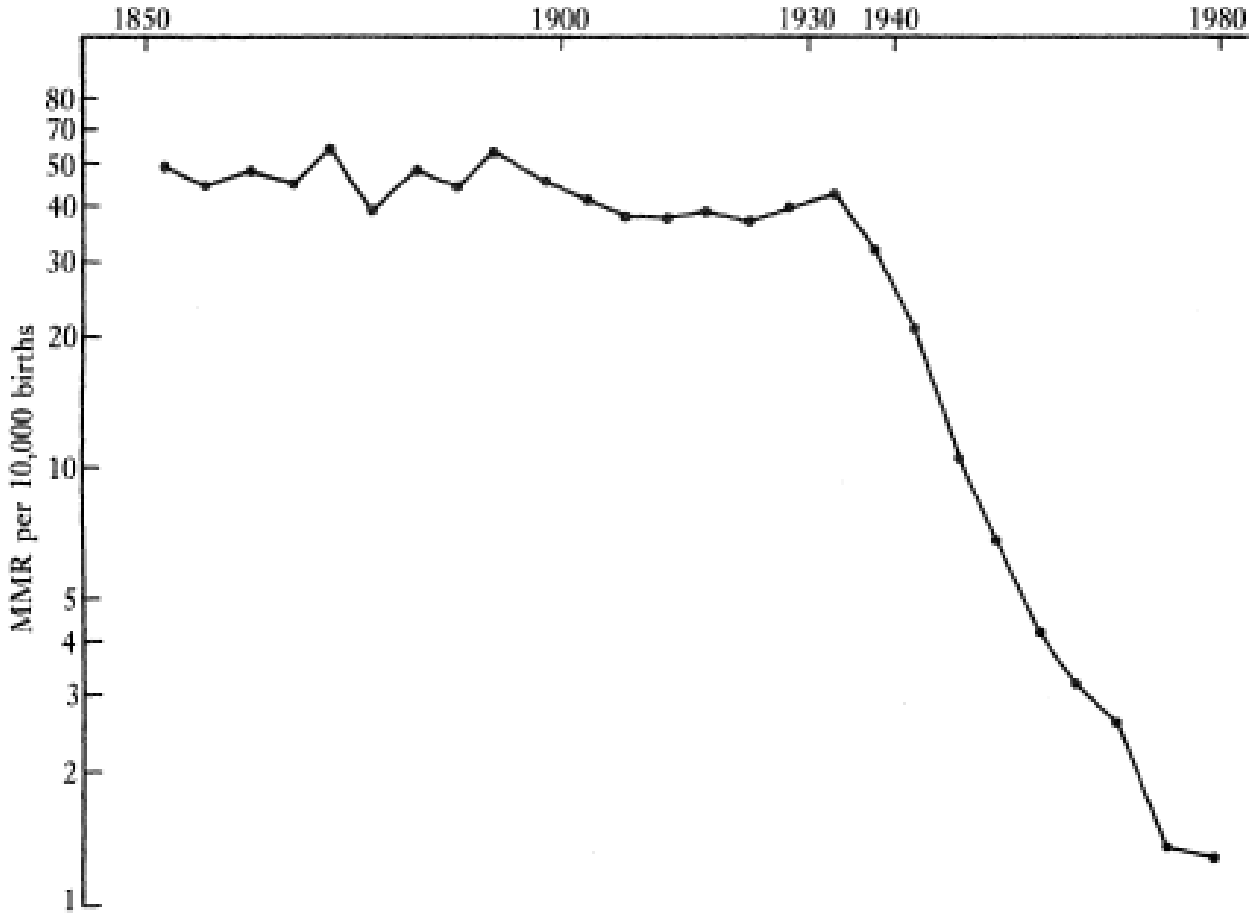


Figure 6 Maternal mortality rates in England and Wales 1850-1980 (five year averages

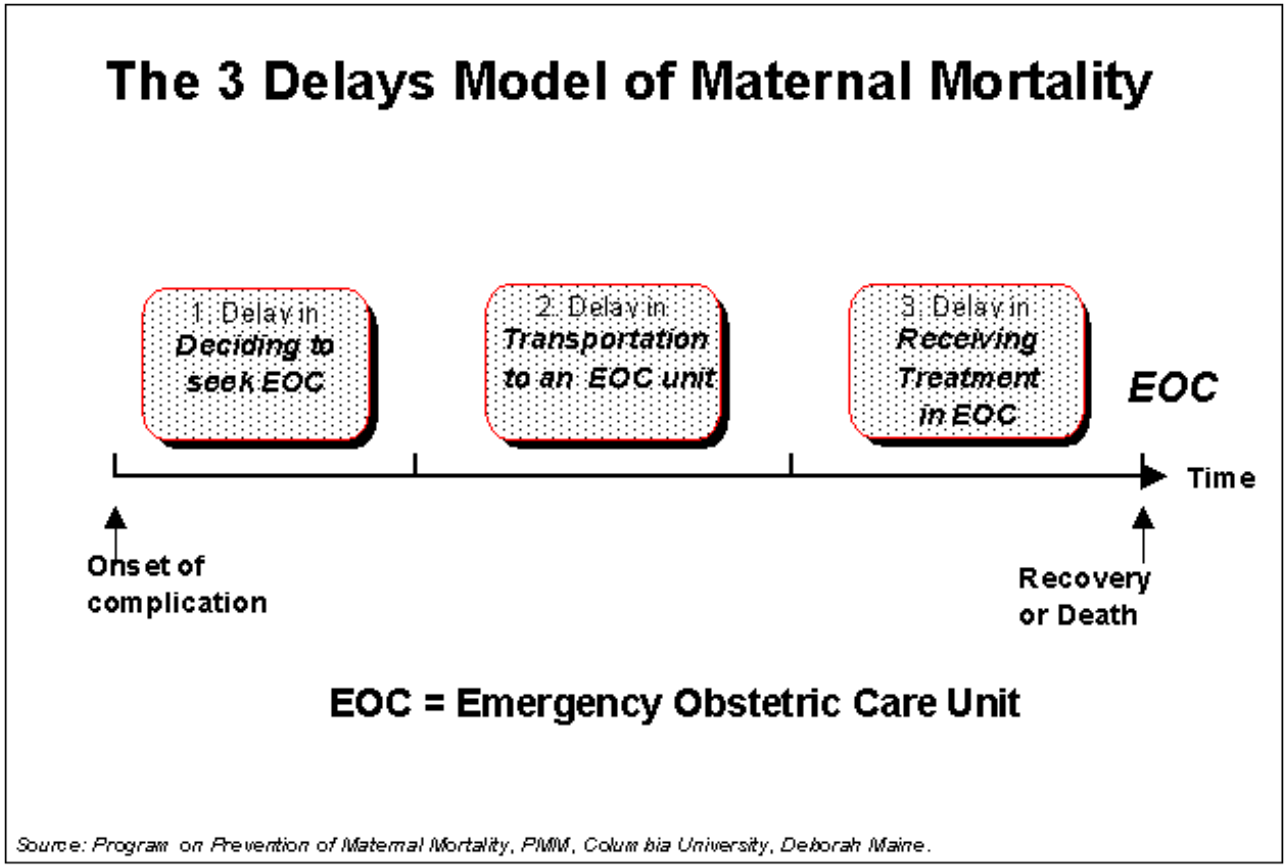


Figure 7 Three delays model

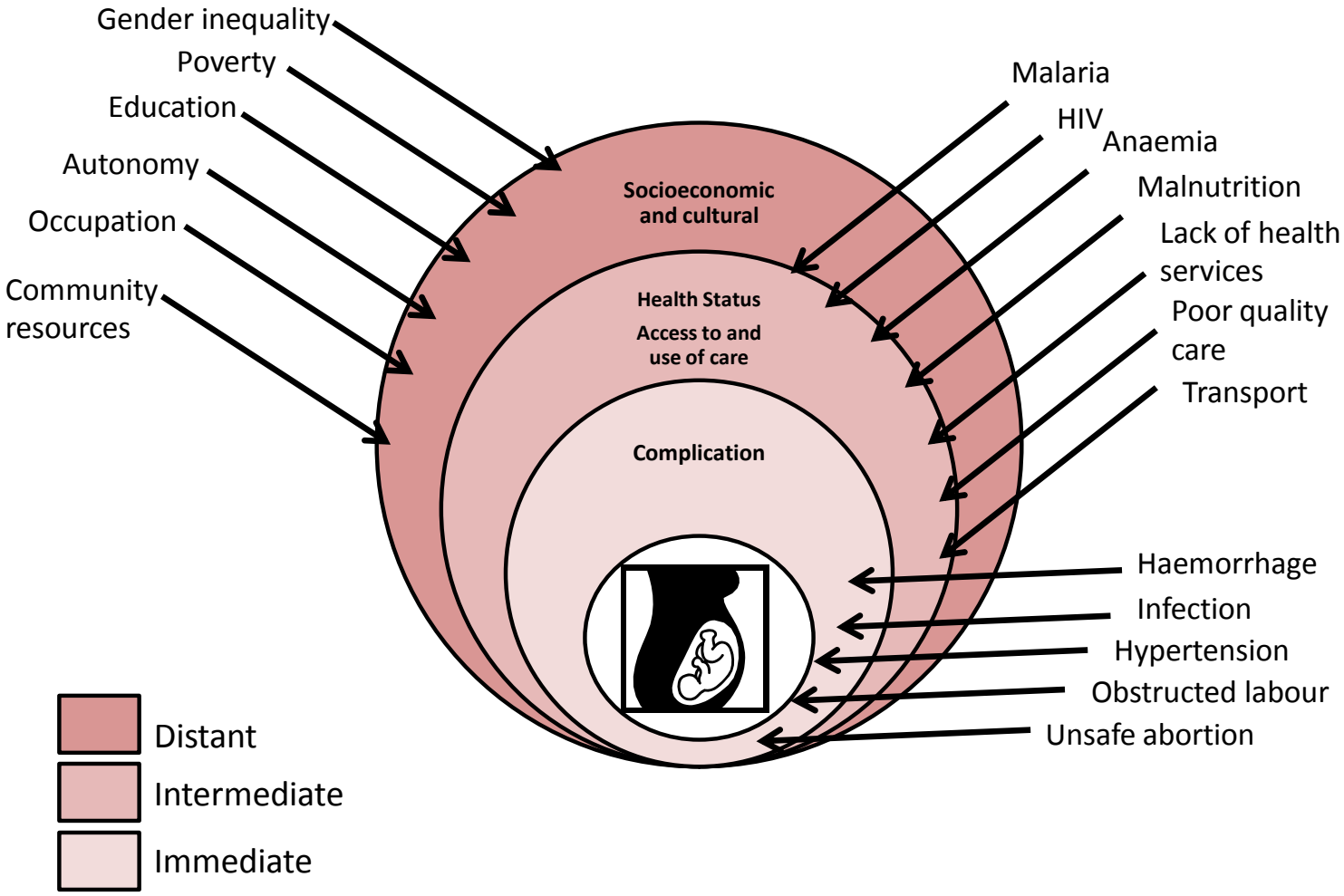


Figure 8 Immediate, intermediate and distant determinants of maternal health

Table 1 Millennium Development Goals

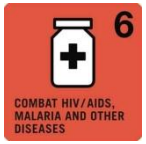
Millennium Development Goals			
	Eradicating extreme poverty and hunger		Improving maternal health
	Achieving universal primary education		Combating HIV/AIDS, malaria, and other diseases
	Promoting gender equality and empowering women		Ensuring environmental sustainability
	Reducing child mortality rates		Developing a global partnership for development

Table 2 Examples of Interventions from Research Proposal

Single Interventions			
Problem Population	Intervention	Outcome	Examples of Existing Research
A1. Obstructed Labour. Labouring women. Healthcare professionals caring for labouring women	Partograph	Correctly completed documentation, referral rate, Vaginal exams, oxytocin use, c/s, prolonged labour, complications, correctly completed documentation	Fahdhy, 2005 (27) (Indonesia) Assessing effectiveness of promoting WHO partograph by midwives. RCT (i) trained in Partograph (ii) normal care. Comparing birth outcomes, health centres referral, prolonged labour, c/s. Fawole, 2007 (28) (Africa) Retrospective review of 445 patient records. Audit use of partograph and how influences decision making
A2. Eclampsia. Pregnant women with pre-eclampsia	Anticonvulsant therapies (Magnesium sulphate, diazepam etc)	MMR, occurrence of convulsions	The eclampsia collaborative group 1995 (29) (India, Sub-Sahara Africa, Latin America) Multicentre (25) RCT sample: 198 women, comparing magnesium sulphate with diazepam or phenytoin or lytic cocktail
A3. Sepsis. Labouring and Postnatal Women	Vaginal chlorhexidine during labour	MMR, peri-partum infection	Lumbiganon, 2004 (30) (Pakistan, Zimbabwe, South Africa) Cochrane review. 3 RCT's placebo controlled. Assessing if vaginal chlorhexidine washes during labour prevents maternal and neonatal infections excluding Group B Streptococcal and HIV
A4. Hypertensive Disorders. Pregnant women <34/40 gestation	Calcium supplementation	MMR, pre-eclampsia, raised blood pressure, serious morbidity	Hofmeyr , 2006 (31): Cochrane review, 12 RCT's: 15,206 women. Calcium supplementation >1g prevent hypertensive disorders & associated problems
A5. Syphilis. Antenatal women	Benzyl-penicillin	Cases of active syphilis, female education, abortion, MMR	Hira, 1990 (32) (Zambia) Comparing pre/post intervention. 3 centres involved. 491 women from study centres. 434 from control. Syphilis intervention project: (i) implement screening, (ii) treating active cases, (iii) demonstrate improvements in outcomes. Guinness, 1988 (33) (Swaziland). Survey 283 deliveries. Examining influence of syphilis screening on perinatal mortality
A6. Malnutrition also see A7 C3. Pregnant women and Postpartum women up to 12 weeks	Vitamin A supplements	MMR, anaemia, vitamin A deficiency, maternal sepsis, night blindness, maternal infection markers	Van den Broek, 2010 (34) (Nepal, Indonesia, Malawi). Cochrane review. 5 randomised/quasi randomised trials. 23,426 women. Effectiveness of vitamin A supplementation during pregnancy, alone or in combination with supplements on maternal, newborn clinical, laboratory outcomes
A7. Anaemia also see A6.	Iron supplementation +/- Folic acid	Hb concentration	Pena-rosas, 2006 (35). Cochrane review, RCT/quasi randomised trials (i) Iron alone 29 trials (ii) Iron with folic acid. 8 trials (iii) intermittent iron

Pregnant women			supplementation vs. daily iron. 2 trials (iv) intermittent iron with folic acid vs. daily iron with folic acid 7 trials. Assessed (i) use of daily iron supplements (+/- folic acid) vs. placebo (ii) intermittent use of iron supplements (+/- folic acid) with daily supplements (iii) intermittent use of iron supplements (+/- folic acid) with placebo
A8. Postpartum haemorrhage prophylaxis	Syntometrine Syntocinon Misoprostol Carbetocin	Risk of severe PPH, use of additional uterotonics, blood transfusion, need for uterine massage following both caesarean delivery, blood loss, need for therapeutic uterotonic agents, adverse effects, hypertension	Tuncalp, 2012 (36) 72 trials (52,678 women). Oral or sublingual misoprostol vs. placebo. Compared conventional injectable uterotonics and oral misoprostol. Measured risk of severe PPH, use of additional uterotonics, blood transfusions, shivering, temperature above 38º. Su, 2012 (37)11 studies (2635 women) Carbetocin vs. oxytocin. Outcomes were blood loss, need for therapeutic uterotonic agents, risk of adverse effects such as nausea and vomiting, incidence of postpartum hypertension, cost-effectiveness
Strategies or Packages			
B1. Unsafe Abortion. Women requiring abortion	Safe surgical procedures to complete abortion	Efficacy of procedure, procedure duration, EBL, analgesia, MMR	Kestler, 2002 (38)(South Africa , Zimbabwe) RHL Commentary. 25 studies identified. 2 studies meeting criteria – most not randomised. Comparing safety and efficacy of surgical methods for incomplete abortion
B2. Inaccessible Health Care and Drugs. also see D1 Childbearing women	Health facility strengthening. Improved drug provision via antenatal care and CHWs. Improved community drug based provisions via female volunteers in villages. Financial reimbursement for eligible women and health care professional.	MMR, skilled birth attendance, haemorrhage, sepsis, referral of high risk cases, number of vouchers distributed and used.	Pagel, 2009 (39) (Malawi, Sub Sahara Africa). Mathematical model applied comparing 3 packages: combat key events to maternal mortality and effectiveness of drugs within model in 3 packages (i) ensuring health facilities supplied with oxytocin and antibiotics (ii) package (i) plus misoprostol and antibiotic distribution to CHWs (iii) package (i) plus (ii) plus misoprostol and antibiotics and advice via female volunteer outreach workers. Ir, 2010 (40) (Cambodia) Assessing effectiveness improving access to skilled birth attendants for poor women using targeted vouchers and health equity funds. 5,611 deliveries, 3 Operational health districts. Qualitative data collected through focus groups, discussions, in-depth interviews with key informants of users/non users of the scheme quantitative data collected from health information system on deliveries, contraception prevalence
B3. Poor Maternal Health. Women of reproductive age	Women's groups	MMR, women participating in women's organisations, antenatal care, skilled birth attendance.	O'Rouke, 1998 (41) (Bolivia).Before and after intervention initiated. Questionnaires. Included 50 communities total population 15,000. Evaluating impact of organising women's groups on PMR. Included interventions focused on (i) strengthening women's organisations, (ii) developing skills in problem identification and prioritisation (iii) training community members in

			safe birth techniques
B4. Poor Quality Maternity Care also see C2 D1. Pregnant women and lay health workers	Training of lay health workers. Disposable delivery kits. Links with established health services and professionals. SBA. Training TBAs	MMR, place of delivery, complications, referral to health centres, skilled birth attendance, use of safe delivery kits, antenatal care uptake	Jokhio, 2005 (42) (Pakistan). Cluster RCT, 7 sub-districts, 3 assigned to intervention, 4 to usual care. 10,114 women in intervention, 9443 women in control. Assess impact of intervention on PMR/MMR. Intervention is training TBAs, issuing disposable delivery kits, linking TBAs with establishes services, documenting processes/outcomes. Outreach clinics by obstetric teams.
B5. Postpartum Haemorrhage also see A8	Pharmacological: Misoprostol, Ergometrine, Syntometrine, Carbetocin, oxytocin Surgical: Uterine packing, trans-cervical catheter, ligation of uterine arteries, uterine tamponade	MMR, EBL, continued bleeding and unsatisfactory response, maternal Hb concentration, serious maternal morbidity, hysterectomy, need for therapeutic uterotonic agents, risk of adverse effects such as nausea and vomiting, incidence of postpartum hypertension, cost-effectiveness	Mousa, 2007 (43) (South Africa) Cochrane review. 3 studies, 462 participants, 2 RCT compared misoprostol with placebo. Assess efficacy/safety of pharmacological, surgical/radiological interventions used for treatment of PPH Su, 2012 (37)11 studies (2635 women) Carbetocin vs. oxytocin. Outcomes were blood loss, need for therapeutic uterotonic agents, risk of adverse effects such as nausea and vomiting, incidence of postpartum hypertension, cost-effectiveness
B6. Unsafe Birthing Practices. also see C1. Pregnant women of varying educational and economic status	Antenatal care	Skilled birth attendance incidence, uptake antenatal care	WHO, 2005 (12) (India) WHO report. Household surveys, demographic/health surveys, Survey & interviews using Delphi method Socio-demographic data collected. Skilled attendant at birth estimates. Bloom, 1999 (44) Cohort study. Association between antenatal care/safe delivery; care utilisation & visit frequency
Behavioural or Educational Interventions			
C1. Unsafe Birthing Practices. also see B6. Pregnant Women, Members of Community, TBA	Training TBA. Encouraging links with health care facilities. Education, information on safe childbirth. Focus group discussions.	Referral to health centres, complications (sepsis, haemorrhage, prolonged labour), antenatal care, iron supplementation, location birth, skilled birth attendance, hygienic practices employed, TBAs supporting monitoring	Smith, 2000 (45) (Ghana) Multi-component design, qualitative & quantitative methods, cross sectional surveys, questionnaire, interviews. Random sample survey of 1961 clients TBAs. Outcome evaluation TBA Training, specifically maternal/neonatal morbidity and mortality. Barnett, 2006 (46) (Bangladesh) Retrospective cross sectional survey collected data about pregnancy, childbirth, postnatal period via interviews; socio-demographic, economic data. 6,875 women interviewed. Examine prevalence maternal, newborn care practices among women who gave birth Sibley, 2007 (47) Cochrane review. Training TBAs for improving health

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		standards, maternal mortality, vitamin A supplements, malaria & tetanus prophylaxis, contraceptive use.	behaviours and pregnancy outcomes. Assess effects TBA training on health behaviours and pregnancy outcomes. Published, unpublished randomised control trials. Controlled before/after and interrupted time series studies comparing trained/untrained TBAs for women cared for/living in areas served by TBAs. Four studies. 2000 TBAs. 27,000 women
C2. Inadequate Knowledge/Training/Skills for Health Care Professionals also see B4 D1 Health care workers	Life saving skills training. Strengthening links between major health care facilities. Assessment of training. Creating links between major health care facilities, educating importance	Perceptions/attitudes to healthcare, referrals to appropriate health services, awareness of signs/symptoms of pregnancy complication, knowledge of cause/ treatment, life saving skills training, knowledge counselling, knowledge emergency care, knowledge partogram use knowledge contraception	Okafor, 1994 (48)(Nigeria) Report of safe motherhood programme. Focus group discussions. Interviews. Examining pregnancy related knowledge, attitudes, and practices of community members, and women's use of community maternal health services. Ijadunola, 2010 (49)(Nigeria) 152 health workers; doctors, nurses, midwives, community health extension workers. Self administered semi structured questionnaires. Non participant observation checklist. Assessment of knowledge maternity unit operators at primary and secondary levels of care about concept of emergency obstetric care and contents of antenatal care
C3. Poor Nutrition also see A6. Pregnant women Members of the community	Food supplementation. Dietary advice. Addressing cultural taboos. Pregnancy nutrition education	MMR with maternal anaemia prevalence, maternal deaths due to anaemia, causes of anaemia associated with maternal mortality, weight improvement, improvement in health outcome.	Lindmark, 2003 (50) Dietary interventions assessed for benefit to the infant or the mother. Reproductive health library commentary of Cochrane review (i) nutritional advice (ii) balanced energy/protein supplementation (iii) high protein supplementation (iv) isocaloric protein supplementation (v) energy/ protein restriction in overweight or high weight gain women
C4. High Fertility Rates. Women of childbearing age. Postnatal women	Family planning education. Education on postponing early marriage. Readily available family planning	Incidence contraceptive use, knowledge contraception, incidence unplanned pregnancies, attendance family planning clinic, literacy of women, access and acceptability family planning	Hiller, 2002 (51) (Lebanon, Peru, Nepal) Cochrane review. RCT/quasi-randomised trials. 5438 women giving birth more than 20 weeks gestation. Assess effects of education about contraceptive use to postpartum mothers (i) unplanned pregnancy (ii) attendance at family planning clinics (iii) use of contraception (iv) knowledge of contraception (v) breast feeding (vi) satisfaction with postnatal care.

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C5. Inappropriate health services for service users, Village development committees	Women's group meetings. Discussion of problems, possible strategies. Prioritise strategies. Assessment of factors relating to performance of health services	MMR, women assessing antenatal/ delivery care, skilled birth attendance, assessment current health facilities	Manandhar, 2004 (52) (Nepal) Cluster RCT. 28,931 births. 42 village development committees matched pairs. Questionnaires. Interviews. Assess effect of participant intervention of women's groups on birth outcome
Organisational Interventions			
D1. Poor Quality Health Care. Poor delivery of care. Barriers to accessing healthcare also see A2 E4 Childbearing women. Service users. Service providers. Wider community	Employ effective strategies to prioritise maternal health. Employ strategies to coordinate levels in delivery and fragmentation of care. Skilled birth attendance	MMR, utilisation of services, efficacy of health care strategies in targeting service users, deaths due to illegally induced abortion, literacy rate, skilled birth attendance	Prakash, 1991 (53) (India) Professional opinion of retrospective data collected. Incidence deaths linked to direct causes. Incidence preventable deaths. Status, strategies for maternal mortality reduction: (i) Prioritise maternal, child health services, integrate vertical problems (ii) attention to labour/ delivery care (iii) community based delivery huts and maternity waiting homes (iv) improve quality of maternal/child health care at rural community level (v)improve quality of care at primary health care level (vi) include postpartum programme maternal child health, family planning services (vii) examine feasibility of blood transfusion network (viii) improve transportation (ix) educate girls on heath/sex (x) informally educate masses on maternal, child health (xi) focus obstetrics and gynaecology training in practical skills management (xii) research reproductive behaviour (xiii) ensure women right to safe motherhood.
D2. Poverty-deficient maternal health infrastructure budget. Healthcare providers. Financial personnel in the health facility	Assessment effective interventions. Evaluate new interventions, technologies	Improvement in maternal health, acceptability and cost of interventions to reduce MMR, intervention success, intervention feasibility, near misses of interventions or lack of resources	Filippi, 2006 (54): Professional report reviewing progress of MDGs. Broader context of maternal mortality, Economic, social vulnerability of pregnant women, importance of concomitant strategies.
D3. Ineffective interventions. Ineffective addressing of interventions. Ineffective deployment of interventions Childbearing women	Assessment of interventions	Interventions success, economic viability of intervention, correct intervention deployment, MMR, MMR improvement, time of death, timing of effective interventions,	Tsu, 2004 (55): Report from maternal health experts, organisations from Bellagio workshop. Evaluation of utilising and developing new and underutilised technologies to reduce MMR. Developing a set of priority actions for reducing MMR (i) obstacles to the successful use of health technologies (ii) accelerating the use of high priority technologies (iii)beyond technology (iv)recommendations. Ronsmans et al, 2006 (26): Examining maternal mortality: (i) who dies,

		place of deaths, correcting placing of interventions, health inequalities	comparing women from developed and developing countries (ii) when, at what point in pregnancy and childbirth (iii) where, comparing developed and developing world (iv) why, causes of death. Literature review on maternal death and life time mortality risk comparing women in developed and developing countries.
D4. Isolated healthcare facilities. Healthcare professionals	Links with other healthcare facilities. Communication	Improvement in services offered	JHPIEGO 2005 (56): Save the Children professional report. WHO evidence based. Development of a household to hospital continuum of care – utilising the gap tool analysis to bring care closer to mothers and newborns in rural communities. Examining different levels of care
Programmatic and Policy Level Interventions			
E1. Social vulnerability of women- breach in women's human rights. Women. Wider community. Government bodies	Verbal autopsy interviews. Education. Women's groups. Advocacy. Governmental accountability. Legal support	MMR, reporting and documentation accuracy of maternal mortality, maternal death investigation, complications, women's health improvement, human rights recognition	Hoj, 1999 (57) (Guinea-Bissau) Structured interviews. Data collected from pregnancies - cohort of 100 clusters of 100 women of fertile age over a 6 year period (15,832). Examined use of verbal autopsy reported in multi-ethnic population. Interviews with filter questions to close female family members who experienced maternal mortality about cause of death, relation to childbirth. Gruskin, 2008 (58) WHO bulletin. A proposed practical approach to improve maternal health using human rights. Development of maternal mortality as public health concern including history and connections with human rights and MMR
E2. Early age pregnancy Wider community	Prohibiting early marriage	MMR, age at the first pregnancy, obstructed labour	World Health Organisation, 2004 (59): Systematic review randomised/non randomised control trials. Examines incidence of adolescent pregnancies, social background, possible health problems, clinical management. Recommendations for practice.
E3. Female Genital Mutilation Wider community	Prohibiting Female Gestation Mutilation Education	Female Genital Mutilation Attitudes. Female Genital Mutilation Incidence. obstructed labour	Banks, 2006 (60): (Burkina, Faso, Ghana, Kenya, Nigeria, Senegal, Sudan) Prospective study 28,393 women attending 28 obstetric units. Follow up information gathered until discharge, interviews performed. Comparison of female genital mutilation with obstetric outcome, included: (i) operative delivery (ii) episiotomy (iii) perineal damage (iv) birth weight (v) apgar score (vi) NMR and MMR (vii) extended hospital stay
E4. Poor organisation of health facilities. Barriers to healthcare assess. Delays in care. Inaccurate/Out dated policies. Lack of policies.	Interaction between care providers and patients. Engage multiple practice organisations. Communication between private/public services and	Services offered, delivery of services, utilisation of services, staff recruitment/ retention, MMR, changes in care delivery, improvements in health	Ronsmans, 1997 (61) (Bangladesh) Analysis of demographic surveillance data of MMR. Comparing before and after intervention implementation. Data between 1976-1993. Incidence and causes examined related to intervention of maternal and child health programme. Comparisons made with trends of MMR in presence or absence of project. Services included: Trained TBAs, essential obstetric emergency care from government district hospital and

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Lack of professional and/or government support. also see D1. Healthcare providers. Senior healthcare staff. Community. Governmental bodies	organisation Implementation of guidelines/policies. Implementation of support mechanisms for staff. Employing accountable personnel. interaction between care providers and patients	outcomes, policy changes, improvement of services offered, improvement in antenatal care	private clinics, tetanus immunisation, contraception access and advice. Kidney, 2009 (62) Systematic review of effect of community level interventions. 5 cluster RCTs. 8 cohort studies. Review effectiveness of community level based interventions to reduce MMR. Community level intervention, intervention locally accessed at woman's home, village, school or local clinic to be delivered by any person within the community.
E5. Poor maternal and female health. Malnutrition also se A7 C3 Females	Female nutrition programmes. Health education programmes. Greater financial input into maternal health improvements. Community health and nutrition programmes. Policies prioritising female health	MMR, health of female population, anaemia in childbearing women, accuracy of cause of mortality	Rush, 2000 (63) Literature review relating nutritional status to pregnancy related deaths in developing countries. Examines maternal mortality links with: (i) historical trends (ii) social status (iii) antisepsis (iv) other causes. Explores common problems with MMR: (i) underestimation of problem (ii) national, social, environmental. Association with anaemia and effects. Association with obstructed labour

Table 3: Interventions reviewed in the thesis

Question	Population	Intervention	Comparison	Outcome
Community Based Interventions				
Does training and supporting TBAs reduce maternal, neonatal and perinatal mortality in developing countries?	Pregnant women seeking labour care in developing countries	Training, supporting and linking TBAs	Standard care plus additional enhancements (vary between studies)	Maternal, perinatal and neonatal mortality
Do women's groups practising participatory learning and action cycles improve maternal and neonatal outcomes in developing countries?	Women of reproductive age in developing countries	Participatory learning and action cycles with women's groups	Standard care plus enhancements (vary between studies)	Maternal, neonatal mortality and stillbirth
What are the barriers and facilitators of emergency transportation for pregnant women in developing countries?	Pregnant women in developing countries seeking emergency transportation to access emergency obstetric care	Emergency transport	None	Experiences and opinions of pregnant women or stake holders. Barriers and facilitators of emergency transport for pregnant women.
Can motivational interviews reduce the unmet need for contraception in developing countries?	Women of reproductive age	Motivational interviews	Standard care	Effective contraceptive use, subsequent pregnancy or birth
Task Sharing Interventions				
Are clinical officers as safe and effective as medical doctors at performing caesarean section?	Pregnant women in developing countries requiring caesarean section	Clinical officers performing the caesarean section	Medical doctors performing caesarean section	Maternal and neonatal mortality, wound infection and dehiscence
Clinical Interventions				
Do prophylactic antibiotics reduce infectious morbidity in surgical abortion and miscarriage surgery?	Women having surgical abortion and women having miscarriage surgery	Antibiotics	Placebo or no drug	Infectious morbidity
Is cell salvage a safe alternative to homologous blood transfusion in caesarean section	Women having caesarean section and blood transfusion	Cell salvage	homologous blood transfusion	Pre and post operative haemoglobin, blood loss, use of additional homologous blood, length of hospital stay, serious

				adverse effects
Is cell salvage a safe alternative to homologous blood transfusion in surgery for ruptured ectopic pregnancy	Women having surgery for ruptured ectopic pregnancy and blood transfusion	Cell salvage	Homologous blood transfusion	Pre and post operative haemoglobin, blood loss, use of additional homologous blood, length of hospital stay, serious adverse effects
Is symphysiotomy a safe alternative to caesarean section in developing countries	Women with obstructed labour in	Symphysiotomy	Caesarean Section	Maternal mortality, neonatal mortality, pain, infection, haemorrhage, incontinence, pyrexia
Can the anti-shock garment, improve outcomes for women with postpartum haemorrhage in developing countries	Women with post-partum haemorrhage	Anti-shock garment	Standard care	Blood Loss, blood transfusion, maternal morbidity and mortality

CHAPTER 2: METHODS FOR SYSTEMATIC REVIEWS, META-ANALYSIS AND META-SYNTHESIS

Systematic reviews are vital in healthcare and clinical practice; they can assist clinicians with decision making and guide policy makers. A systematic review is a research article that identifies relevant evidence, appraises the quality of the evidence and summarises the results of the evidence included to draw conclusions and explore new findings using a rigorous, systematic methodology. Systematic reviews provide the reader with an up to date, comprehensive, balanced summary of the literature on a particular topic. Systematic reviews are preferred to traditional literature reviews as they are not biased by the author's opinion. Systematic reviews are based on balanced inferences generated from the evidence collated through the steps that are undertaken in the review process.

A systematic review involves five key steps in the identification, appraisal and application of the evidence, which consist of the following:

1. Framing the question
2. Identifying the relevant literature
3. Assessing the quality of the literature
4. Summarising the evidence
5. Interpreting the findings

All of these steps will be discussed in the context of this thesis.

Step 1: Framing the question

This is an important part of the review, as consideration of the components within the question are required to perfect what is it that the review is aiming to address. Each of the subsequent steps in the review will flow more efficiently and effectively if the question is framed accurately. The four components that should be included when framing the question are the population, intervention, comparison, outcomes and study design. The benefit of the question containing the prescribed components is that this structured approach is more clear and explicit than a free form question. The question should be formulated prior to the search. It is important to consider how the following components may vary among the existing literature (22).

The *population* that is to be studied is the group of patients or participants with the specific health problem or requirement in the healthcare setting, about whom the evidence is being sought. In this thesis the population is generally pregnant women or women of reproductive age (64) or health care providers (65).

The *intervention* (or the exposure) that is to be examined is the main action that is being considered in the population; in this thesis there are ten interventions that have been considered, for example women's groups practising participatory action and learning cycles.

The *comparison* (if applicable) of the intervention examined; this is often the standard care provided which the intervention is compared to; in this thesis an example of this is the standard care that women receive, or the standard behaviour in the absence of women's groups practising participatory learning and action cycles.

The *outcomes* that are to be examined are the measures of what the population wishes to achieve, such as the changes in health that a woman experiences; in this thesis the key clinical outcomes were selected, predominately maternal mortality. In some reviews in the thesis where the key clinical outcomes were less apparent, an initial scoping search was conducted to examine the reported outcomes. These were determined by reviewing the articles obtained, and if outcomes were repeated and measured in a similar manner, they were selected as key outcomes for the review and used within the review protocol.

The *design* of the studies that are to be included in the review to answer the question posed is an important consideration. An example from this thesis is the randomised trials included in the review that examined women's groups' practising participatory action and learning cycles. In this thesis the highest level of evidence was used in the reviews, where possible data from RCTs. In the absence of sufficient data from RCTs, data from lower levels was included. For example in the case where RCTs were not available, the next level of available evidence was included in the review in the order as follows, quasi-randomised studies, non-randomised controlled studies, before and after, cohort studies, case-control studies, case series, case reports and expert opinions. This hierarchy of evidence was followed to ensure the inclusion of the highest level of evidence available within the reviews. For example there were no randomised controlled trials comparing clinical officers and medical doctors performing caesarean section, so the highest level of evidence available was used. In this review it was comparative cohort studies. Another example of this is demonstrated in the anti-shock review. As there was an absence of randomised data and sufficient data from cohort studies, all available studies were included (quasi-experimental studies, case series case and reports) as there.

Step 2: Identifying the relevant literature

This step is often an iterative process of many stages. The aim is to capture the maximum number of relevant studies possible from electronic and manual searches in a quantitative systematic review. Firstly the search terms were defined; this was often guided by an initial scoping search to explore the terms used in the current literature. Previously conducted systematic reviews were explored for search terms utilised. The breadth of search terms used within the reviews differed with each topic. A wide variety of search terms were used in some reviews, such as strategies incorporating the training and support of traditional birth attendants. In this case numerous search terms used were necessary to capture all of the studies that included traditional birth attendants, as the name of this cadre varies widely across cultures and countries. Some of the reviews used minimal search terms, because there was little diversity in the terms used for the intervention being examined, for example symphysiotomy.

The aim in this thesis was always to conduct the most comprehensive search possible, and therefore include as many relevant studies as possible. Some reviews did not include a pregnancy specific search term (as in the clinical officer systematic review), in order to increase the sensitivity of the search, and to ensure all relevant studies were identified. By not including a pregnancy related search term, a study would be identified even if the title or keywords were not pregnancy related. Pregnancy related data may be contained in the main body of the paper and this study may have been missed in the search. Most of the reviews however had pregnancy specific search terms, for example symphysiotomy, traditional birth attendant, miscarriage and abortion.

The search process differed in the systematic review of qualitative studies, where the search terms were selected iteratively through scoping searches. The aim here was to

conduct a comprehensive search, and to obtain a purposive sample of studies for interpretive explanation (66).

No language restrictions were applied to any of the searches. Articles that were not in English were translated into English.

Multiple databases were searched in all reviews in this thesis to ensure all relevant studies were obtained. The popular databases that were used for each review were decided on by the type of journals that they included. All searches involved the use MEDLINE, as this is a generic database containing biomedical literature. However the database psycInfo was used in the search of the review on motivational interviews, but not the antishock garment. This was because this database contains records of literature on psychology and related behavioural and social sciences, thus not relevant to interventions such as anti-shock garment. Different databases were used in the emergency transport review, compared to the other reviews, as this review included only qualitative literature, therefore databases with a qualitative focus, such a QUALIDATA were utilised in addition to generic databases such as MEDLINE.

In keeping with good practice the electronic search results were scrutinised by multiple reviewers for each of the systematic reviews in this thesis. The titles and abstracts were initially reviewed for inclusion by each reviewer against the inclusion and exclusion criteria developed when defining the question. Full manuscripts of relevant studies were then acquired and scrutinised against the criteria. Final decisions on inclusion or exclusion of the articles were made after inspection of these manuscripts by the reviewers, with the addition of another reviewer if necessary to resolve any disagreement. Reasons for the exclusion of studies were noted on a database by the reviewer. All of the reviews apart from the qualitative review included only studies with

quantitative data. The qualitative review included studies that contained qualitative data alone or both qualitative and quantitative data.

In conjunction to searching databases, reference lists and grey literature were searched to increase the scope of the search, and to search for articles that may not have been indexed or have been indexed inaccurately. Discussions with experts in the field were also undertaken at this stage to explore possible studies that had not yet been published. Review of the grey literature and reference lists was more extensive in the qualitative review.

Step 3: Assessing the quality of the literature

This step appraises the aspects of the study design, conduct and analysis. The quality of a study can be defined as the degree to which it aims to minimise bias and error. Standardised tools have been developed to aid the quality assessment of studies, which are reporting checklists or criteria and risk of bias assessment tools. These tools can help guide the reviewer with making a judgement on the internal validity of a study, thus the degree to which the results of the study are likely to be free of bias. There are several key forms of bias that the tools consider; selection bias (whether the study participants were randomly allocated, and was the allocation concealed); performance bias (was the care for both intervention and control group standardised, and was it blinded to the patient and provider); measurement bias (were the outcome assessors blinded); attrition bias (was a description of the patient that withdrew provided, was an intention to treat analysis conducted).

The tools that have been used in this thesis are ones commonly used in the quality assessment of systematic reviews previously by credible groups such as Cochrane

(67). The quality assessment tool that were used, were specific for the study design of each article. The tools were completed independently by multiple reviewers.

Reporting checklists: Independent assessment of the reporting checklist criteria was performed by multiple reviewers in accordance with good practice. The checklist specific to the study design of the articles was used. Randomised controlled trials were assessed for methodological quality using the CONSORT checklist, with the extension statement added to account for the cluster effect if required (68). These studies were assessed for randomisation and sequence generation, baseline comparability, blinding, appropriate statistical analysis and accounting for cluster effect if necessary. Cohort studies were assessed for adequacy of reporting using the STROBE checklist (69). The STROBE statement is a checklist of 22 items considered essential for sound reporting of observational studies. The items included relate to the article's title and abstract, the introduction, the methods, the results of the study and the discussion section. Other information such as funding is also featured. The checklist differs slightly for reporting case-control studies, cohort studies and cross sectional studies. The STROBE statement assesses adequacy for reporting on setting, participants, variables, bias, quantitative variables, statistical methods and generalisability. Case series were assessed using the MINORS checklist (70), this assesses for reliability, consistency and validity. The items are scored between 0 and 2 for the adequacy of the reporting, with the ideal score being 16.

Risk of bias: There are two risk of bias assessment tools that are designed for randomised and non-randomised studies that have been used in this thesis. RCTs were assessed for risk of bias using the Cochrane Collaboration's tool, which assesses the risk of bias through examining the following items: random sequence generation, allocation concealment, blinding of participants, personnel, and of the outcome

assessment, completeness of outcome data, selective reporting and any other bias within the studies. Non-randomised studies were assessed for methodological quality using the Newcastle Ottawa Scale (71). The studies were evaluated for representativeness of the cohorts, selection of the cohorts, ascertainment of the intervention and the outcome, comparability of the cohorts, as well as the length and adequacy of follow-up. The risk of bias within a study was deemed low if a study obtained four stars for selection, two stars for comparability and three stars for ascertainment of exposure (71). Medium risk of bias was suggested to exist in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was classed as having high risk of bias. Qualitative studies were assessed using the COREQ framework for reporting qualitative research. This framework aims to assess the trustworthiness and transparency of studies within their settings, by focusing on the research team and reflexivity, study design, and data analysis and reporting (72).

Step 4: Summarising the evidence

This step involves collating the findings of the individual studies included in the review. It is however more than a summary of the studies included. It involves deeper exploration of the pooled evidence in the review to generate a greater level of understanding and insight than what was obtained from the primary studies alone in both quantitative and qualitative studies. In the reviews in this thesis, the information on the characteristics from included studies was extracted by two reviewers independently. It was then presented in a table of study characteristics (this is included in each review) and contained details on the population that has been studied, the interventions and the outcomes, and details on the designs of the studies. Tabulating the characteristics of the studies enables the reviewer to identify similarities and differences across the studies, thus identify the presence of any clinical heterogeneity.

If substantial heterogeneity is not identified from the narrative summary of the studies, then it could be decided if a meta-analysis is suitable, however a meta-analysis or meta-synthesis is not always deemed appropriate. Numerical data was also extracted by two reviewers and tabulated in each systematic review.

Tabulating and examining the study characteristics was essential for evaluating and explaining the presence of heterogeneity in the systematic reviews. In the thesis this was particularly useful when examining the differences in effect size between the trials included in the women's groups' systematic review. From examining the characteristics of each study, it was apparent that studies conducted in a rural location with more than 30% of pregnant women participating in the group had a great effect. It was also useful when trying to understand the presence of statistical heterogeneity.

This thesis examined complex interventions as well as discrete interventions. Complex interventions are often associated with greater heterogeneity when compared to discrete interventions. They have multiple components that are often highly context specific. Complex interventions cannot be treated in the same way as discrete interventions when considering heterogeneity, as what is considered as significant heterogeneity varies with the complexity of the intervention. Furthermore, what constitutes reasonable heterogeneity is always a judgement. This judgement was made by multiple reviewers in each of the systematic reviews in this thesis.

Quantitative synthesis of findings

Determining if a meta-analysis was suitable was an iterative process. The decision to pool effect measures was widely discussed within the research team. However the general principle was that the level of clinical and statistical heterogeneity was considered in depth before the decision of pooling was made. When the value of pooling was suspect, disaggregated data were made available in the reviews, so that

interpretation could be made without reference to the pooled findings. If a meta-analysis was deemed appropriate in cases where substantial heterogeneity was present, the relevant model was chosen to account for this. The addition of sub-group analysis was used if deemed appropriate. An example of this from the thesis is the systematic review on strategies incorporating training and support of traditional birth attendants. There was substantial clinical heterogeneity in the interventions of the studies, as each contained multiple components that were highly specific to the context of the study setting. The random effects model was used in this case to account for the variability within the intervention, and the characteristics examined to explain the differences and similarities between the interventions. If sufficient numbers of studies were included in the systematic reviews, formal exploration of heterogeneity would be conducted, in the form of a meta-regression (22) or other methods, however this was not possible with any of the reviews due to the limited number of studies included. A sub-group analysis was performed to examine the effect in studies that had the greatest difference in training and support between the intervention and control group.

Meta-analyses were appropriate to be conducted for the majority of the systematic reviews in the thesis. These analyses involved pooling the risk ratios or odds ratios that were reported in the primary studies, and using the appropriate model to pool the data. In reviews that reported data from both randomised and non-randomised studies, these were pooled separately. In the absence of heterogeneity the fixed effects model was used. This model was used once in this thesis due to the level of heterogeneity involved in many of the reviews.The random effects model was most commonly used in this thesis to pool the risk ratios or odds rations from individual studies. The random effects model was used to account for the clinical heterogeneity within the studies. The fixed effects model was not deemed suitable in most reviews as this model is only suitable when there is a single source of variability within the included studies (73).

In the meta-analyses of cluster randomised controlled trials, data were pooled differently. Data for effect estimates and corresponding 95% confidence interval were extracted directly from cluster RCT reports after assuring that the analyses performed had taken into account the cluster nature of the trial design. If the intra-cluster correlation coefficient was reported this figure was used in the analysis. In the case of a trial reporting the effect estimate without accounting for cluster design, the standard error of the effect estimate from the analysis without clustering was inflated by multiplying by the square root of the estimated cluster effect (73). These effect estimates and their 95% CI were then meta-analysed using the generic inverse-variance method using a random effect model. This type of analysis was used to account for the cluster effect within the trials, to allow for the variability of responses in the sample, and to detect the true differences between the intervention and control arms. Account for the cluster effect allows a comparison within-group variance and between-group variance.

Statistical tests were used to measure the heterogeneity of treatment effects using forest plots, chi square tests and its magnitude determined by computing I^2 statistic. The I^2 statistic measures the variation between the studies; therefore heterogeneity was assessed to be low if the I^2 statistic was equal to or less than 25%, moderate if the I^2 statistic was less than 25% and equal to or less than 50%, and high if the I^2 statistic was equal to or above 75% (74).

Qualitative synthesis of findings:

Methods for the synthesis of qualitative literature in the form for a meta-synthesis are much less well developed than the synthesis of quantitative data (meta-analysis). The findings of qualitative research studies are intended to be applicable to specific setting in which it was conducted, thus not generalisable. However when a meta-synthesis is conducted in addition to a systematic review, it can offer more insight on a variety of

settings, contexts and participants. It can explore concepts not reported in primary studies.

Meta-synthesis is based on the qualitative methodology meta-ethnography (75) and involves identifying key concepts from studies and translating them into each other (76). This process involves recognising key concepts within a single study and identifying similar concepts in other studies, even though the expression of the concept may be not reported identically. In the meta-synthesis in this thesis, thematic synthesis was used for analysis through examination and translation of common elements across the studies that explored transport in emergency obstetric care, as this is the suggested method of analysis in systematic reviews (77-79).

The first and second stages of the thematic synthesis is to code the text and develop descriptive themes (76). This was developed by identifying quotes from respondents and relevant texts in all studies. Extracted data were then labelled to develop a code (80). Initial codes closely reflected the quotes from the manuscript. Codes were continuously refined and altered as more quotes were added. Codes then lead to the development of themes and a thematic framework was constructed. In the third stage (76) the thematic framework was developed and implored to develop a 'line of argument', that concepts could be tested against (81). Having applied the thematic framework to individual manuscripts, in order to build up a picture of the data as a whole and to consider the range of each theme, the data was charted. Charts were developed using themes against individual manuscripts. This method sought to develop an analytical framework, ensuring that the themes built up were cross-checked with other data within and then between studies, so that the validity of emerging explanations was tested and improved. The third stage is suggested to be the most controversial stage in thematic synthesis as it is subject to the reviewer's judgments and insights (76). Multiple reviewers were involved in this stage to reduce the likelihood

of this. Furthermore, the development of themes was presented in a tabulated form, in addition to a discussion in the text, to demonstrate how the themes were developed in a more transparent manner.

Step 5: Interpreting the findings

Systematic reviews aim to guide practice and policy, therefore this step is important when considering how to translate the findings obtained from the systematic review into meaningful conclusions about the question addressed. This step aims to determine the strength of the review findings. It involves consideration of the reviews strengths and weaknesses. The key points that should be considered are the adequacy of the searches, the presence of bias (publication or other), the quality of the studies, and the significance of the effects (22).

One of the most relevant points for this thesis is the quality of the included studies. Although it is preferable to draw inferences on good quality experimental data, such as double blind randomised controlled trials, this is not always available. However, it may still be important to assess the body of evidence that is available as this too can guide practice, policy and further research funding. The evidence, taking account of the level of study design, must be assessed for credibility and trustworthiness. The applicability and transferability of clinical practice should also be assessed.

In this step conclusions on sub-groups of the population compared to the total population examined can also be drawn. An example of this in this thesis is demonstrated in chapter four (women's groups practicing participatory action and learning cycles). Further exploration of a sub group analysis discovered that where groups contained more than 30% of pregnant women (per group), living in a rural location, and a greater reduction in maternal mortality was seen.

There are several factors that need to be taken into consideration with the reviews in this thesis. The main factor is the quality of the available studies for the particular reviews. Chapter 3 (strategies incorporating the training and support of TBAs) and chapter 4 (women's groups practising participatory action and learning cycles) both draw inferences from reviews involving large cluster randomised controlled trials. However most of the other reviews contained studies providing much lower levels of evidence, thus the inferences drawn from these reviews will be subject to greater bias. It is important to take this into consideration when this evidence is used to guide policy and practice.

The second significant factor in this thesis is the level heterogeneity in some if the reviews. This is particularly applicable to the review on strategies that incorporate traditional birth attendants. The interventions varied within the complex package of care. However despite the variation, almost all studies suggested a benefit, providing a consistent message that regardless of the exact approach to involving TBA's, strategies that incorporate TBA's were effective. However, such heterogeneity in the intervention means it is difficult to provide one clear approach for programme development. The specific approach for programmes will need to be considered within the local context and constraints.

The third pertinent factor in this thesis is the limited number of events that are contained in the outcomes of some of the meta-analyses. In chapter 11 (symphysiotomy for obstructed labour) the tentative conclusions on outcomes such as fistulae, haemorrhage and infection, were based on a limited number of events. With small numbers it is difficult to make firm inferences on the likelihood of the outcome developing in a larger population, than those included in the review.

The fourth important factor considered in this thesis was the origins of the data. Most of the reviews contained data from studies originating from developing countries only, but some contained data from only developed countries, since this was all that was available. In the case where all of the included studies in the review were from developed countries, the transferability of the intervention obviously had to be considered. An example of this is chapter 10 (cell salvage in caesarean section), where due to the complexities and costs associated with the training and resources required for this procedure, the applicability of this type of cell salvage in a low resource setting would need careful consideration.

The interpretation of the systematic reviews findings have been discussed in each chapter. Recommendations for further research and recommendations for policy and practice have also been provided. There is however a formal process for grading evidence to make recommendations for practice. The GRADE approach classifies evidence to the extent to which it can be applied to clinical practice. This classification involves consideration of the bias present within the study. The GRADE approach also considers the directness of evidence, the variability (heterogeneity) within the evidence, the precision of effect estimate, and the risk of biases such as publication bias. The GRADE approach allows the recommendation to be downgraded or up graded as a result of these criteria. The GRADE approach was not applied to the interventions reviewed in this thesis (82).

COMMUNITY BASED INTERVENTIONS

CHAPTER 3. EFFECTIVENESS OF STRATEGIES INCORPORATING TRAINING AND SUPPORT OF TRADITIONAL BIRTH ATTENDANTS ON PERINATAL AND MATERNAL MORTALITY: META-ANALYSIS

ABSTRACT

Background: Despite the drive to increase skilled birth attendance in the developing world, more than 50% of births are attended by TBAs (TBA). However, there is uncertainty about the effectiveness of including TBAs in strategies to improve perinatal and maternal health. We have therefore systematically reviewed and meta-analysed the effectiveness of strategies incorporating TBAs.

Methods: A systematic review with meta-analysis was conducted. MEDLINE, EMBASE, AMED, BNI, Cochrane library, CINAHL, BIOMED Central, PsycINFO, LILACS, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index (inception-2011) were searched without language restriction. Studies of randomised and non-randomised controlled design were selected, with the outcomes of perinatal, neonatal and maternal mortality. Studies were assessed for risk of bias and adequacy of reporting. Relative risks (RR) from the individual studies were pooled separately for the randomised and non-randomised controlled studies, using random effects model.

Results: Six cluster RCTs (n=138,549), and seven non-randomised controlled studies (n=72 225) were identified. All six randomised trials found a reduction in adverse perinatal outcomes; meta-analysis of the randomised trials showed significant reductions in perinatal death (RR 0.76, 95% CI 0.64, 0.88; p<0.001) and neonatal death (RR 0.79, 95% CI 0.69, 0.88; p<0.001) with strategies incorporating TBAs. The findings of the non-randomised studies were consistent with the above findings. Six studies reported on maternal mortality, and five found no significant difference with strategies incorporating TBAs; meta-analysis of three cluster randomised trials found a

relative risk of 0.79 (95% CI 0.53, 1.05; p 0.12) and three non-randomised studies a relative risk of 0·80 (95% CI 0.44, 1.15; p 0.26) for maternal mortality.
Conclusion: Perinatal and neonatal deaths are significantly reduced with strategies incorporating TBAs.

Impact of review: Publication in BMJ, presentation at international conference (FIGO)

Citation of published work on which this chapter is based

Amie Wilson, Ioannis D Gallos, Nieves Plana, David Lissauer, Khalid S Khan, Javier Zamora, Christine MacArthur, Arri Coomarasamy. Effectiveness of strategies incorporating training and support of traditional birth attendants on perinatal and maternal mortality: meta-analysis. **BMJ** 2011;343:d7102

3.1 BACKGROUND

It is estimated that around 60 million births occur outside healthcare facilities in developing countries (83), with 52 million births occurring without the assistance of a Skilled Birth Attendant (SBA)(83). According to the WHO, an SBA is an accredited health professional (midwife, doctor or nurse), which has been educated and trained in the skills needed to competently manage uncomplicated pregnancies, childbirth and the immediate postnatal period. An SBA is also trained to identify, manage and refer women and newborns if complications arise.

Many interventions have been implemented with the aim of reducing perinatal and maternal mortality, yet these have often focused on skilled birth attendants, or been targeted at health facilities. However, there is a global deficit of skilled birth attendants, particularly within developing countries (21), so many women do not receive skilled birth attendance. Furthermore, there are also limited healthcare resources in the

majority of many developing countries, so the ideal prospect of all births taking place within a health facility, with skilled birth attendance, is yet to materialise.

At present it is estimated that more than 50% of births within developing countries are attended by TBAs (TBA), with incidence being as high as 90% in some countries (2). A TBA is a person who assists the mother during childbirth; their roles vary accordingly to local customs, interests, and expertise. The tasks TBAs conduct range from provision of intrapartum and postnatal care, to domestic chores. TBAs acquire their skills by delivering many babies or through an apprenticeship with other TBAs. In many regions they are known and respected for their knowledge and experience, they are not usually salaried, but paid in-kind.

There are many reasons for women not having an institutional birth with skilled birth attendance. Women give birth outside of health facilities with the help of a TBA for financial reasons because they are unable to afford the care, or the transport to access the care; for geographical reasons, because the health centre maybe difficult to reach, or too great a distance to travel. Instead many women utilise the services of TBAs for a more accessible, more culturally sensitive approach.

TBAs were previously supported, and training programmes began over 60 years ago in regions where maternal mortality rates were high. In 1994 it was estimated that over 85% of developing countries had some form of TBA training (84). However support for training TBAs diminished due to the lack of evidence of effect on perinatal and maternal health. In 2009 a Cochrane review described the potential of TBA training in reducing perinatal and maternal mortality as ‘promising’ (47), yet the analysis contained only a single cluster randomised trial, as no further randomised trials had been conducted at this time.

In response to the International Safe Motherhood Initiative, TBA training was adopted as part of the maternal health policy in many developing countries in the 1970s and 1980s (85). However, it is suggested within the literature that traditional birth attendants should have never been expected to reduce maternal and perinatal deaths directly, for example in cases of obstetric emergency. Yet they could be utilised in weak health systems, often where literacy levels among women are low, and have insufficient schooling to be trained as midwives, to prevent complications through using safe birth kits, and preventing sepsis, and referring women to a higher level of care when complications arise (86, 87). However, it was not only due to lack of evidence on the effect on traditional birth attendant training as to why the support for training traditional birth attendants was withdrawn in the late 1990's, it was also due to an ongoing debate of cost effectiveness of this cadre, and whether resources could be utilised with in a more effective manner elsewhere (88-93). It was suggested that training TBAs would have limited benefit as they often worked in poor resource settings, where availability and access to quality obstetric services was restricted (47, 88). Therefore with a lack of systematic evaluation and rigours cost effectiveness analysis, cumulatively these factors contributed to the removal of TBA training from the safe motherhood project.

Given the uncertainty about the effectiveness of TBAs on perinatal and maternal outcomes, we have systematically reviewed and meta-analysed the effectiveness of strategies incorporating TBAs.

3.2 METHODS

Data sources and searches

The databases that were searched were MEDLINE, EMBASE, AMED, BNI, Cochrane library, CINAHL, BIOMED Central, PsycINFO, LILACS, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index (from database inception to April 2011). Databases were searched for literature evaluating

strategies that incorporated TBAs in developing countries. Electronic searches were complimented with hand searching, and reference lists were checked. The search terms that were used were 'Birth attend*', 'traditional midwife',' lay birth attendant', as well as 'Dais' and 'Comadronas'. No language restrictions were applied to the search.

Study selection and data extraction

RCTs and non-randomised controlled studies were selected. Primarily the electronic searches were scrutinised and full manuscripts of relevant studies were acquired. Final decisions on inclusion or exclusion of manuscripts were made after inspection of these manuscripts by the author and another reviewer (AW and AC). Information was extracted from each article independently on study characteristics, quality and outcome data by the author and multiple reviewers (AW, CM, IG, NP, JZ). The outcomes deemed most clinically relevant were focussed on, the objective outcomes of perinatal, neonatal and maternal mortality. Morbidity outcomes such as postpartum haemorrhage, obstructed labour and neonatal apnoea were not extracted, as they were subjectively assessed, in a non-standardised manner, between the two study groups. For example post-partum haemorrhage was described as "bleeding"(94) "haemorrhage"(42) "heavy bleeding"(95) "significant bleeding that soaked more than two kangas"(96), and was assessed by TBAs, SBAs or by women themselves. The outcomes that were selected were the key clinical outcomes. These were decided by reviewing the articles obtained from an initial scoping search. This was used to examine the reported outcomes. If outcomes were repeated and measured in the same manner, they were selected as key outcomes for the review and used within the review protocol. The systematic search for the review was then conducted. The outcomes in the individual studies were then synthesised from the included studies.

Methodological quality assessment

The cluster randomised studies were assessed for methodological quality using the CONSORT statement extension (68), to accommodate for the cluster effect within the data. These studies were assessed for randomisation and sequence generation, baseline comparability, accounting for cluster effect, blinding and appropriate statistical analysis. Risk of bias was assessed using the Cochrane collaboration's tool, which assesses the risk of bias through examining the following items, random sequence generation, allocation concealment, blinding of participants, personnel, and of the outcome assessment, completeness of outcome data, selective reporting and any other bias within the studies.

The non-randomised studies were assessed for methodological quality using the Newcastle Ottawa Scale(71). The studies were evaluated for representativeness of the cohorts, selection of the cohorts, ascertainment of the intervention and the outcome, comparability of the cohorts, as well as the length and adequacy of follow-up. The risk of bias within a study was deemed low if a study obtained four stars for selection, two stars for comparability and three stars for ascertainment of exposure (71). Medium risk of bias was suggested to exist in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was classed as having high risk of bias.

Statistical Analysis

The data from randomised and non-randomised studies were pooled separately to reduce methodological heterogeneity. Non-randomised studies were included to examine the overall effect of strategies incorporating training and support of TBAs on perinatal and maternal outcomes, to see if there was any difference between the randomised and non randomised data. Data for effect estimates (Risk Ratios) and corresponding 95% confidence interval were extracted directly from cluster RCT

reports after assuring that the analyses performed had taken into account the cluster nature of the trial design. If the intra-cluster correlation coefficient was reported this figure was used in the analysis. In the case of a trial reporting the effect estimate without accounting for cluster design, the standard error of the effect estimate from the analysis without clustering was inflated by multiplying by the square root of the estimated cluster effect. These effect estimates and their 95% CI were then meta-analysed using the generic inverse-variance method using a random effect model. This type of analysis was used to account for the cluster effect within the trials, to allow for the variability of responses in the sample, and to detect the true differences between the intervention and control arms. Accounting for the cluster effect allows a comparison within-group variance and between-group variance. Heterogeneity of treatment effects was evaluated using forest plots, chi square tests and its magnitude determined by computing I^2 statistic. The I^2 statistic measures the variation between the studies, therefore heterogeneity was assessed to be low if the I^2 statistic was equal to or less than 25%, moderate if the I^2 statistic was less than 25% and equal to or less than 50%, and high if the I^2 statistic was equal to or above 75%.(74) Analyses were performed using STATA 11.0 statistical software.

3.3 RESULTS

The process of literature search conducted, and the study selection process is given in Figure 9. Six cluster RCTs, with a total of 138,549 participants, were included in the review. Seven non-randomised controlled studies, with a total of 72,225 participants, were also identified. The characteristics of the included studies are shown in Table 4, and the details of the care package in the intervention and control clusters are reported in greater detail in Table 5.

Study Characteristics

All six cluster RCTs included women of child bearing age, one trial by Jokhio et al included pregnant women specifically (42), whereas all of the other trials included newly delivered mothers. All trials included women from rural regions: Jokhio et al excluded city residents where healthcare access was better (42), Azad et al excluded temporary residents (97) and Carlo et al trials excluded infants and still births with a birth weight under 1500kg (98) and Jokhio et al excluded maternal deaths due to injury or accident (42). All of the trials included women from communities with poor health systems with a high proportion of home births. In the trials that reported the age of the women, the mean age was 26.7 and 26.6 years old in Jokhio et al (42), and 25.3 years old in Gill et al (99), with the majority of women aged between 20-19 years in Azad et all (97). The majority of women in the trials by Jokhio et al, Azad et al, Gill et al and Bhutta et al had limited or no education (42, 97, 99, 100).

All of the included trials examined the effect of TBAs on perinatal and maternal mortality; however the TBAs encompassed a variety roles, and were incorporated within wider interventional strategies with a multitude of components (e.g. neonatal resuscitation, umbilical cord care). For example, the trials by Jokhio et al and Carlo et al incorporated a three days training course for TBAs in the intervention arm, in which they were trained in neonatal resuscitation (42, 98) and clean delivery techniques (42). Other trials did not report the length of the training, but reported that the training consisted of similar components, such as neonatal resuscitation (97, 99, 100), recognising danger signs in mothers and babies (97, 99, 101), and clean delivery (97, 101). The trials by Jokhio et al and Midhet et al did not provide any TBA training in the control arm (42, 101), but trials by Azad et al, Carlo et al, Gill et al and Bhutta et al included minimal TBA training in the control arm (97-100). In all of the included trials TBAs in the intervention arm were supported by staff; however the type of support staff varied in the trials. In the trials by Jokhio et al and Bhutta et al TBAs were supported by lady health workers (42, 100), in the other trials they were supported by female peer

facilitators (97, 101), health management staff (99) and community leaders (98). Clean delivery kits were supplied to both arms in all trials except in the trial by Jokhio et al, where clean birth kits were only supplied in the intervention arm (42).

Study quality

The six cluster randomised trials were assessed using the consort extension statement, and the majority of trials adequately reported on the appropriateness of randomisation, cluster comparability, accounting for the cluster effect within the data, and that no clusters were lost to follow up (Table 6). The cluster randomised trials when assessed using the Cochrane collaboration tool (102) were found to have low risk of bias in random sequence generation, allocation concealment, incomplete outcome data, selective reporting and other bias in most studies. There was high risk of bias in blinding of participants and personnel and blinding of outcome assessment in most studies (Table 7) The seven non-randomised studies were assessed to have low to medium risk of bias for selection, low risk of bias for comparability and low risk of bias for outcome assessment on the Newcastle Ottawa scale (Table 7)(71).

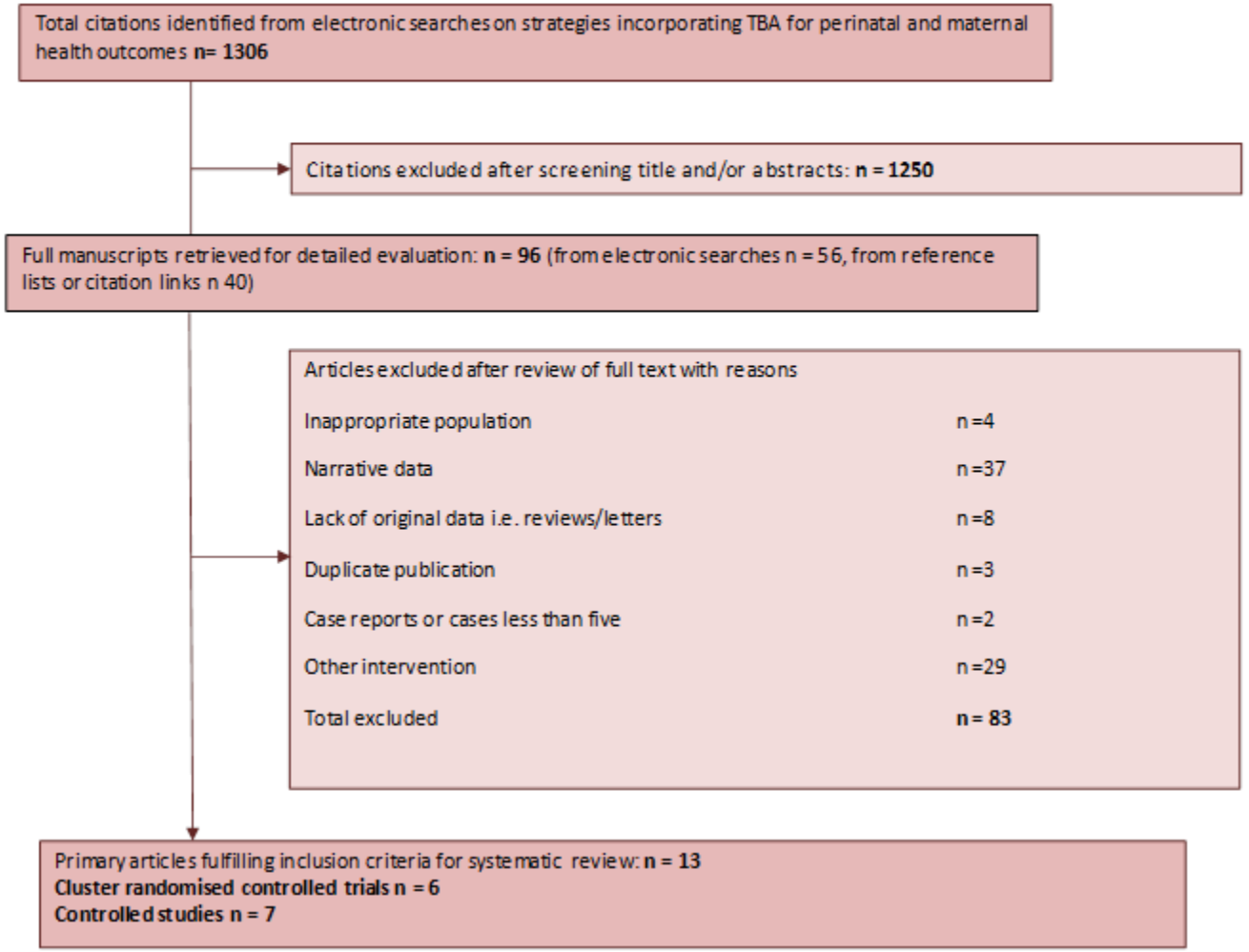

Figure 9 Flowchart of study selection in strategies incorporating TBAs for maternal and perinatal health outcomes

Table 4 study characteristics of included studies in strategies incorporating TBAs for maternal and perinatal health outcomes

Study population &method of allocation	Intervention (n= number of clusters)	Control(n= number of clusters)	Outcome
Cluster RCTs Jokhio: 2005 (42) 19,557 pregnant women in rural Pakistan: Excluded: City residents, multiple pregnancies excluded from perinatal outcome. Maternal deaths due to injury or accident. Cluster randomisation, computer generated.	(3) Mean age 26.7 years, mean parity 3.5, mean years education 1.1. Mean distance 2.7 km from health centres.	(4) Mean age 26.6 years, mean parity 3.7, mean years education 1.4, 2.5 km mean distance from health centres.	PMR, NMR, MMR
Carlo: 2010 (98) 63,324 mothers, 63,729 infants > 28 weeks of gestation delivered in rural sites, Congo, Guatemala, India, Pakistan, Zambia. Excluded: infants & stillbirths with birth weight <1500 grams. Poor health systems & high rate of home births assisted by TBAs. Birth attendants in birth clusters randomly assigned to neonatal resuscitation program.	(43) characteristics not provided. 83.5% of neonates weighed at birth >2500g, 5% suffered birth apnoea.	(45) characteristics not provided. 85.2% of neonates weighed at birth >2500g, 5.2% suffered apnoea at birth.	PMR & NMR
Azad:2010 (97) 25,714 home births of women aged 15-49 in rural districts Bangladesh. Excluded: Temporary residents. Each district constituted a stratum & each union a cluster. 18 unions selected. Unions randomly allocated to either intervention or control groups via names written on pieces of paper, folded & placed in a bottle. The randomised clusters were then further randomly assigned by same method to TBA intervention or control clusters	(9) 65% 20-29 years, 50% no education.	(9) 60% 20-29 years, 48% no education.	NMR
Midhet: 2010 (101) 2,561 women in 32 village clusters in Khuzar rural district in Pakistan. Each cluster contained 5-15 villages with an average population of 2000, all within 80mk from a central town where a district hospital was located (8 clusters containing couples excluded in our analysis to reduce heterogeneity within the intervention arm). Randomisation separately within each of 3 zones, equal number of village clusters randomly allocated to intervention or control sites.	(8)(8 couples clusters excluded in analysis to avoid heterogeneity). Socioeconomic & demographic characteristics similar age, parity & education, higher proportion with electricity & telephone.	(16) socioeconomic &demographic characteristics similar age, parity & education (couples could not be removed from control arm in analysis).	PMR, NMR
Bhutta: 2011 (100) 23,834 births Hala & Matiari subdistricts, Pakistan 16 clusters 23,834 births. Restricted, stratified randomisation. 3 strata on basis of size & number of LHW per 1000 population, 126 random allocations resulted in similar population sizes in two groups, similar numbers of live birth and NMRs, similar ratios of LHW to population, similar proportions of women delivering in hospital. From list of balanced allocations, one scheme selected using random	(8) 83% illiterate. Lady Health Worker programme is National program introduced 1994 to strengthen primary care & preventative services	(8) clusters. 80% illiterate. Lady Health Worker programme is National program introduced 1994 to strengthen primary care & preventative services.	MMR, NMR, PMR

number.	(including family planning).		
Gill: 2011 (99) 3559 newborns, mothers attended by 127 TBAs in Zambia. Randomisation by compiling 120 allocation slips, 60 control & 60 intervention, selected by participants.	(60) Mean age 25.3. 68.9% some primary education, 89% married.	(67) Mean age 25.3. 69.3% some primary education, 90.1% married.	MMR, NMR, PMR
Non- Randomised Controlled Studies			
Janowitz:1988 (103) 1160 Women delivered in Brazil. Included deliveries by TBAs, family or neighbours, & deliveries that took place in hospital	69.2% aged 20-34, 49.6% parity 1-4, 54% 1-3 years of education.	61.9% aged 20-34, 50.0% parity 1-4, 54.2% 1-3 years education.	PMR
Greenwood: 1990 (104) 2738 women aged 15-44 in 41 villages & hamlets in Gambia. Villages selected if population >400. Villages where primary health care programme was not introduced were control group. Participants were women who resided within villages that were selected.	Other changes in study area were increase in town size, transport networks improved, increased number of taxis & frequency of buses. New health centre opened 1983, staffed with 2-4 doctors, increased visits to local dispensaries. No blood transfusion or major surgery services.		MMR, PMR, NMR
Alisjahbana: 1995 (94) 3275 pregnant women in West Java, intervening distance 60km to reduce possible contamination. Data collected on women who were pregnant, parturient or postpartum during 12 month period	27.1% aged <20 or >35. 83.4% mothers <6 years education. 6.5% had > 5 children.	26.8% aged <20 or >35. 11.7% had > 5 children. 82.9% mothers < 6 years education.	PMR
Ronsmans: 1997 (61) 24,059 births of pregnant women in Bangladesh. Intervention area had received extensive family planning & health services previously), comparison area received no intensive health inputs.	Main income sources are rice growing or fishing. Low literacy rates. Geographical ease to access services varies across area: Access most difficult in north of control area (>4hrs travel). Access most simple in south of control area (<2hrs) Extensive services in health & family planning since 1977 with government TBA training		MMR, PMR, NMR
Bang 1999 (92) 2264 births in 86/100 villages in India. 14 villages excluded due to small population size and lack of suitable female worker to assist with study. 100 villages, births & child deaths recorded in 39/53 villages in intervention area (14 villages not included due to population size of <300, or inability to identify a suitable woman to be trained), 47 villages in control.	37.9% female literacy rate, 35.6% lowest caste.	33.0% female literacy rate, 41.2% lowest caste.	NMR, PMR
Gloyd: 2001 (105) 4169 Pregnant women, 3616 completed pregnancies from 65 rural zones of Mozambique (612 women who delivered at health post by midwife were excluded from our analysis to reduce heterogeneity). 40 rural zones where trained TBAs resided, 25 zones were randomly selected proportional to population size from census estimates. further comparison group comprised of 9 villages/ town in study area served by health facilities with trained	Mean age 26.6 yrs. 32% completed 4th grade education.	Mean age 27.3. 31% of women completed 4th grade education.	NMR

nurses/midwives			
Bhutta: 2008 (106) 34,560 women of reproductive age, 5,134 birth from subdistricts in Pakistan. 24 village clusters identified, each cluster contained basic health centre. 8 clusters randomly selected for pilot	(4) No information on age, education or parity. 86.3% home owners, 86.7% electricity, 56.9% functioning dry toilet, 66.6% water pump in village.	(4) No information on age, education or parity. 79.2% home owners, 69.5% electricity, 67.5% functioning dry toilet, 55.9% water pump in village.	MMR, NMR, PMR

Table 5 Details of Intervention

Component	Intervention	Control
Jokhio: 2005 (42)		
TBA strategy	3 day training course by obstetricians and paramedics. Involved picture cards containing advice on antenatal, intra-partum & postpartum care, clean delivery, care of newborn including basis resuscitation. TBAs visit each woman >3 times in pregnancy (3/6/9mths) to check danger signs. Register all pregnant women.	None specified
Support workers	LHW trained to support TBAs & record data. Obstetric teams offered outreach clinics. LHW followed all pregnant women in catchment area with normal monthly visits to women & children	LHW followed up all pregnant women in catchment area by normal monthly visits to women & children. No outreach clinics.
Resource support	Disposable delivery kit: sterilised disposable gloves, soap, gauze, cotton balls, antiseptic solution, umbilical cord clamp, surgical blade.	No delivery kits.
Referral support	Trained to refer a woman for emergency obstetric care & recognition of danger signs. Links with primary care facilities. Improved contact with LHW &primary care centres	No links facilitated.
Carlo: 2010 (98)		
TBA strategy	3 day course, included routine neonatal care, initiation of breathing & resuscitation (bag and-mask ventilation), thermoregulation, breast-feeding, kangaroo (skin-to-skin) care, care of small babies, recognition of danger signs & initial management of complications. Modified for illiterate participants. Also received neonatal resuscitation program, 3-day course, refresher course given 6 months. Hands-on training in basic knowledge & skills of resuscitation, resuscitation & bag-and-mask ventilation, not chest compressions, endotracheal intubation, administration of medications	3 day course, included routine neonatal care, initiation of breathing &resuscitation (bag and-mask ventilation), thermoregulation, breast-feeding, kangaroo (skin-to-skin) care, care of small babies, recognition of danger signs & initial management of complications. Course modified for illiterate participants.
Support workers	Government officials & community leaders facilitated training & collection of data.	Government officials & community leaders facilitated training & collection of data
Resource support	Ventilation bags & masks, spring scales, &clean delivery kits were distributed after training	Ventilation bags & masks, spring scales, clean delivery kits distributed after training
Referral support	No information is provided	No information is provided.
Azad:2010 (97)		
TBA strategy	Basic training in undertaking clean & safe deliveries, recognising danger signs in mothers & infants, making emergency preparations, mouth to mouth resuscitation. Additional training in neonatal resuscitation with bag & mask valve.	Basic training in clean & safe deliveries, recognising danger signs in mothers & infants, making emergency preparations & mouth to mouth resuscitation. No additional training in neonatal resuscitation with bag & mask valve.
Support workers	Female peer facilitator to act as a catalyst for community mobilisation in random half of clusters	Female peer facilitator to act as a catalyst for community mobilisation in random half of clusters
Resource support	Safe delivery kits & information on efficient use of available resources were provided	Safe delivery kits, information on efficient use of available resources were provided

Referral support.	Received health services strengthening. Referral support Improving referral systems & links between the community & health service & between different levels of health service. TBAs accompany women to facilities.	Received health services strengthening. Improving referral systems & links between the community & health service & different levels of health service. TBAs accompany women to facilities.
Midhet: 2010 (101)		
TBA strategy	Trained in clean delivery, recognising common obstetric & neonatal emergencies. TBAs introduced to medical staff	None specified
Support workers	Support workers leading support groups for women on family planning, nutrition, danger signs in pregnancy & labour. Six sessions. Facilitators encouraged to hold sessions in villages not directly trained by project staff. Advance training given to obstetricians, paediatricians & anaesthetists in district hospital. Training for health care providers in primary healthcare settings on clinical skills for neonatal & obstetric care	Training health care providers in primary healthcare settings on clinical skills for neonatal & obstetric care
Resource support	Pictorial booklets, audio cassettes	None specified
Referral support	Facilitated timely referral, transportation of obstetric & newborn emergencies to district hospital, Local transport owners & public transport drivers trained in stretcher use, orientation to hospital, introducing doctors & medical staff. Wireless telecommunication used. TBAs & drivers linked with healthcare facilities	None specified
Bhutta: 2011 (100)		
TBA strategy	Lady health worker programme continued to function as usual included regular refresher training according to standard national lady health worker programme curriculum & monthly debriefing sessions in public sector health facilities. Extra 6 days to lady health worker training. Encouraged LHW to identify pregnant women, provide basic antenatal care, work with TBAs. LHW trained in mouth-to-mouth resuscitation. LHW encouraged to visit mothers in pregnancy & after birth. Additional visits encouraged after birth. LHW performed group education sessions. 3 day training programme for TBAs in basic newborn care including basic resuscitation. Attendance voluntary, TBAs informed about training sessions through LHW & community health committees encouraged to attend lady health worker. Led community education sessions.	Lady health worker programme continued to function as usual included regular refresher training according to standard national LHW programme curriculum & monthly debriefing sessions in public sector health facilities. Basic training on promotion of antenatal care, iron folate use in pregnancy, immediate newborn care, cord care, breastfeeding. No extra training sessions
Support workers	Promotion of liaison & linkage between TBA with LHW. Each provides antenatal care, contraceptive advice, growth monitoring, &immunisation. Village health committees linked with LHW &TBAs	No attempt made to link TBAs with lady health worker or communities or change usual lady health worker activity
Resource support	Clean delivery kits provided to LHW, no resuscitation equipment or injectable antibiotics provided	Clean delivery kits provided to LHW. No resuscitation equipment or injectable antibiotics provided
Referral support	Emergency transport fund, use of vehicles using local resources Emphasis on recognition &referral rather than home-based management. Links facilitated with community health committees to promote maternal &newborn care	Emphasis on recognition & referral rather than home-based management.
Gill: 2011 (99)		
TBA strategy	Training received in basic obstetric & newborn care (including mouth to mouth assisted breathing). Training on record keeping & importance of regular contact with mother & infant post delivery. Training workshop, modified from neonatal resuscitation protocol. Various techniques used to teach	Training received in basic obstetric & newborn care (including mouth to mouth assisted breathing). Training given on record keeping, importance of regular contact with mother

	required skills, drying & warming baby, ensuring clear open airways & evaluating respiration on manikins. TBAs trained to recognise signs & symptoms of possible sepsis. Drugs &chest compressions not taught. Assessment took place following the course. TBAs took part in refresher courses.	& infant post delivery. TBAs took part in refresher courses
Support workers	Lufwanyama district health management team	Lufwanyama district health management team
Resource support	Clean delivery kits for each birth. single dose of amoxicillin. intervention supplied with resuscitator mask, bottle with chlorinated water, absorbent blankets, soft rubber bulb syringe, equipment to administer antibiotics to infant. Received reference cards summarising neonatal resuscitation protocol, trigger conditions for antibiotics with facilitated referral.	Clean delivery kits for each birth
Referral support	Refer all high risk pregnancies for delivery at health centres. Formal link with health sector maintained & facilitated referral of infants to health centre.	Required to refer all high risk pregnancies for delivery at health centres. Formal link with health sector maintained.
Non- Randomised Controlled Studies		
Janowitz:1988 (103)		
TBA strategy	TBAs with 5 meetings & practical experience at mini-maternity unit. training orientation & supervision in prenatal care identification of high-risk pregnancies, assistance in normal deliveries postpartum care, identification of complications & hospital referrals	No TBA training
Support workers	None specified	None specified
Resource support	Health program including setting up of mini-maternity units	No health program set up
Referral support	None specified	None specified
Greenwood: 1990 (104)		
TBA strategy	Instructed to administer malaria prophylaxis. Selected women received 10 week training course & support & supervision from government employed community health nurses.	None specified
Support workers	Village health workers selected to be trained	No added support although have access to health centres & hospitals, subject to constraints of transport
Resource support	Obstetric pack containing clean dressings, scissors, string, oral ergometrine, disinfectant, colour coded spring balance for weighing newborn babies. Given chemoprophylaxis	None specified
Referral support	No added support although have access to health centres & hospitals, subject to constraints of transport	None specified
Alisjahbana: 1995 (94)		
TBA strategy	8 month of preparation & training to improve knowledge, skills & practices of TBAs & health personnel in facilities for preparing birthing homes. Trained in detection of pregnancy complications & making referrals.	None specified
Support workers	None specified	None specified
Resource support	None specified.	Area without maternal &neonatal health program.

Referral support	None specified	None specified
Ronsmans: 1997 (61)		
TBA strategy	government training of TBAs	No TBA training
Support workers	None specified	None specified
resource support	Extensive services in health & family planning since 1977	No such services
Referral support	None specified	None specified
Bang 1999 (92)		
TBA strategy	Trained & supported TBAs in distribution of iron & calcium, clean delivery, treat reproductive tract infections.	Not given in control area.
Support workers	Trained & supported male & female village health workers trained in neonatal care &illness, managing birth asphyxia, premature birth, low birth weight, hypothermia & breast feeding problems. Diagnosed & treated neonatal sepsis. Case management of children with pneumonia & neonatal sepsis	Management of pneumonia in children not given by study health workers in control area, done by government health services
Resource support	Distribute iron & calcium tablets & treatment for reproductive tract infections. Reproductive health education program for adolescents, management by village health workers for minor health problems such as malaria, scabies. Prenatal care at referral clinic. Village health worker provided with neonatal care kit containing, flip chart for health education, nail brush, torch, wristwatch, mucus sucker, tube & mask for resuscitation, spring balance for weighing, thermometer, photo album with reference points, baby clothes & head cover, blanket, sleeping bag, breast pump for inverted nipples, spoon, record & files, soap, cotton, spirit, sodium hypochlorite solution, gentian violet, disposable syringes & needles, gentamicin vials, co-trimoxazole syrup, paracetamol tablets, vitamin k ampoules. No evidence of resources for TBAs	Reproductive health education program for adolescents, management by village health workers for minor health problems & prenatal care at the referral clinic.
Referral support	No added referral care than what already present at government health facilities.	No added referral care than what already present at government health facilities.
Gloyd: 2001 (105)		
TBA strategy	Access to trained TBA with 3 week training program, promoted pre-natal care, family planning, immunisation, hygienic management of birth, risk recognition.	No access to TBA
Support workers	None specified	Not given in control area.
Resource support	Clean birth kits.	None specified
Referral support	None specified.	None specified
Bhutta: 2008 (106)		
TBA &lady health worker	3 day voluntary training programme in basic newborn care including basic resuscitation & immediate newborn care. Encouraged to attend LHW led community education sessions. Special	Not offered to TBAs, however special training in basic & intermediate newborn care to all public-sector rural health

strategy	training in basic & intermediate newborn care offered to public-sector rural health centre &hospital-based medical &nursing staff.	centre & hospital-based medical &nursing staff. Referral support
Support workers	Community health committees set up support from two community mobilisers	No attempt to link LHW with TBAs or to set-up community health committees.
Resource support	All health-care facilities provided basic & intermediate newborn care equipment. Enhanced 6 day module of LHW training programme, covering community mobilisation, basic newborn care, group counselling. LHW encouraged to work with TBAs to identify when births would occur, visit mothers twice during pregnancy & following birth. No resuscitation equipment or injectable antibiotics were provided to the LHW or TBAs.	LHW training programme continued as usual, regular refresher sessions. All health-care facilities provided with basic &intermediate newborn care equipment. No resuscitation equipment or injectable antibiotics provided to the LHW or TBAs.
Referral support	Assistance to establish emergency transport funds for mothers &newborns	None specified.

Table 6 Consort extension statement reporting checklist for cluster randomised trials in strategies incorporating TBAs for maternal and perinatal health outcomes

Item	Checklist item	Jokhio	Carlo	Azad	Midhet	Bhutta	Gill
Title and abstract							
	Identification as RCT in title	N	N	Y	Y	Y	Y
	Structured summary of design, methods, results, conclusions	Y	Y	Y	Y	Y	Y
Introduction							
Background objectives	Scientific background and explanation of rationale	Y	Y	Y	Y	Y	Y
	Specific objectives or hypotheses	Y	Y	Y	Y	Y	Y
Methods							
Trial design	Description of design including allocation ratio	Y	Y	Y	Y	Y	Y
	Changes after trial commencement with reasons	n/a	n/a	n/a	n/a	n/a	n/a
Participants	Eligibility criteria for participants	Y	Y	Y	Y	Y	Y
	Settings and locations where data collected	Y	Y	Y	Y	Y	Y
Interventions	Interventions per group with details	Y	Y	Y	Y	Y	Y
Outcomes	Pre-specified primary and secondary outcome measures	Y	Y	Y	Y	Y	Y
	Changes to outcomes after commenced	n/a	n/a	n/a	n/a	n/a	n/a
Sample size	Sample size determined: Method of calculation, number of clusters(s) cluster size, coefficient of intracluster correlation, indication of uncertainty	Y	Y	Y	Y	Y	Y
	When applicable, explanation of interim analyses and stopping guidelines	n/a	n/a	n/a	n/a	n/a	n/a
Randomisation:							
Sequence generation	Method to generate random allocation sequence	Y	Y	Y	Y	Y	Y
	Randomisation; details of any restriction	Y	Y	Y	Y	Y	Y
Allocation concealment mechanism	Random allocation sequence, steps taken to conceal sequence until interventions assigned	Y	Y	Y	Y	Y	Y
Implementation	Random allocation sequence and enrolled participants enrolment	Y	Y	Y	Y	Y	Y
	Who generated random allocation sequence, enrolled clusters, assigned clusters to interventions	Y	Y	Y	Y	Y	Y
	Mechanism by which individual participants were included in clusters for purposes of trial	Y	Y	Y	Y	Y	Y

	where consent was sought and whether consent was sought before or after randomisation	N	N	N	N	N	N
Blinding	who blinded after assignment to interventions, how	N	N	N	N	N	N
	description of similarity of interventions	N	N	N	N	N	N
Statistical methods	Statistical methods to compare groups primary/secondary outcomes	Y	N	Y	Y	Y	Y
	additional analyses	Y	Y	Y	Y	Y	Y
Results							
Participant flow	numbers randomly assigned, received intended treatment, analysed for primary outcome	Y	Y	Y	Y	Y	Y
	losses and exclusions after randomisation, reasons	N	N	N	N	N	N
Recruitment	Dates of recruitment and follow-up	Y	Y	Y	Y	Y	Y
	Why trial ended or was stopped	N	N	N	N	N	N
Baseline data	table baseline demographic, clinical characteristics	Y	Y	Y	Y	Y	Y
Numbers analysed	participants included in each analysis and whether analysis was by original assigned groups	Y	Y	Y	Y	Y	Y
Outcomes and estimation	primary and secondary outcome, results and the estimated effect size and its precision	Y	Y	Y	Y	Y	Y
	binary outcomes, presentation of both absolute and relative effect sizes is recommended	Y	Y	Y	Y	Y	Y
Ancillary analyses	Results of other analyses performed, including subgroup analyses, adjusted analyses, distinguishing pre-specified from exploratory	Y	Y	Y	Y	Y	Y
Harms	important harms or unintended effects in group	X	X	X	X	X	X
Discussion							
Limitations	Trial limitations, addressing sources of potential bias, imprecision, if relevant, multiplicity of analyses	**Y**	Y	Y	Y	Y	Y
Generalisability	Generalisability of trial findings	Y	Y	Y	Y	Y	Y
Interpretation	Interpretation consistent with results, balancing benefits and harms, considering relevant evidence	**Y**	Y	Y	Y	Y	Y
Other information							
Registration	Registration number and name of trial registry	N	N	N	N	N	N
Protocol	full trial protocol can be accessed, if available	N	N	N	N	N	N
Funding	funding and other support role of funders	**Y**	Y	Y	Y	Y	Y

Y = Reported N = Not Reported N/A = Not Applicable

Table 7 Newcastle Ottawa Scale for assessing risk of bias in non-randomised studies

Cohort Studies		Janowitz 1998	Greenwood 1990	Alisjahbana 1995	Ronsmans 1997	Bang 1999	Gloyd 2001	Bhutta 2008
Selection	Representativeness	Y	Y	Y	**Y**	Y	N	Y
	Selection on comparison	Y	Y	Y	Y	Y	Y	Y
	Ascertainment of exposure	Y	Y	N	Y	Y	N	Y
	Demonstration of outcomes	Y	Y	Y	Y	Y	Y	Y
Comparability (maximum of two is available)	Comparability	YY	N	YY	N	N	YY	YY
Outcome	Outcome assessment	Y	Y	Y	Y	Y	Y	Y
	Follow up length	Y	Y	Y	Y	Y	Y	Y
	Adequacy of follow up	Y	Y	Y	Y	Y	Y	Y

Y = Reported N = Not Reported

Table 8 Risk of Bias assessment of randomised studies in strategies incorporating the training and support of TBAs

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Jokhio						
LOW: Page 2092:simple cluster randomisation computer generated	LOW: Page 2092: computer generated	UNCLEAR: Not reported	UNCLEAR: Page 2094: LHW recorded outcomes could not be blinded to intervention but were not aware of study objective or outcome measures.	LOW: Figure 1: all accounted for	LOW: Table 3 & 4: all outcomes reported	LOW: no other sources of bias
Carlo						
UNCLEAR: Page 616: randomly assigned, no further details	UNCLEAR: Not reported	UNCLEAR: Not reported	UNCLEAR: Page 617: The birth attendants/community coordinators obtained written informed consent from mothers and collected data on standardized data forms.	LOW: Figure 1: all accounted for	LOW: Table 1 & 2: outcomes reported	LOW: no other sources of bias
Azad						
LOW: Page 1194: Unions randomly allocated to intervention or control groups by district in presence of project staff and external individuals. Randomisation process done before collection and analysis of baseline data.	LOW: Page 1194: Cluster names written on pieces of paper, folded and placed in bottle. Project manager drew papers from bottle. allocation sequence decided upon by project team before drawing papers and based on clusters not individuals. Clusters had been pre-identified by team on basis of previously mentioned criteria.	HIGH: Page 1195: None of staff attending randomisation process had previous knowledge of health and socioeconomic status of chosen union clusters. Neither study investigators nor participants masked to group allocation.	HIGH: Page 1195: Neither study investigators nor participants were masked to group allocation. No details given for analysts	LOW: Page 1198:Interviews completed for 84% and 82% of births in intervention and control arm	LOW: Page 1199: outcomes reported; table 2 & 3	HIGH: Page 1194: control clusters included 3 areas worse health & socioeconomic indicators than rest of area. In these areas, surveillance started late due to entry restrictions.

Midhet						
UNCLEAR: Page 1183: external observer drew folded papers with numbers corresponding to clusters with existing groups from basket.	LOW: Page 1183: first four clusters drawn from basket allocated to intervention group, rest to control group.	HIGH: Page 1183: Because of nature of intervention, neither team nor participants were masked to group assignment.	HIGH: Page 1183: Because of nature of intervention, neither intervention team nor participants were masked to group assignment. No details on blinding of analysts	LOW: Page 1187: Loss to follow up was <1% and 2% in intervention and control clusters.	LOW: Page 1187: outcomes reported: table 2 & 3	LOW: Page 1191: No incentives or disincentives for under or over reporting deaths and births, several mechanism in place to detect errors
Bhutta						
LOW: Page 6: clusters allocated to both or no intervention with random number sequence generated.	LOW: Page 6: concealment of intervention allocation, identification numbers assigned for each cluster and random number generated for each. Sequence used to allocate to each of four intervention groups. Sequence concealed until interventions assigned.	HIGH: Page 6: Neither participants nor those administering interventions blinded to group assignment.	HIGH: Page 6: Those assessing outcomes not blinded to group assignment	UNCLEAR: Page 10: 29% lost to follow up, observed birth rates in study matched expected crude birth rate within 3%, little difference in loss-to-follow-up between arms.	LOW: Page 10: outcome reported, table 2-6	LOW: None reported
Gill						
LOW: Page 8: random number sequence	LOW: Page 8: Randomization done after collection, before entry and analysis, of baseline data. Study personnel allocated clusters to intervention groups.	HIGH: Page 8: nature of interventions made masking of allocation impossible at participant level.	LOW: Page 8: Masking at level of analysis and trial monitors. Data collected independently of programme implementation, no results were back to inform interventions	LOW: Figure 4: Participants lost to follow up accounted for	LOW: Page 17: outcomes reported, table 3-6	LOW: None reported

Perinatal mortality:

Five cluster randomised trials reported on the outcome perinatal mortality. All individual studies showed a reduction in perinatal mortality, with three studies (42, 100, 101) showing a statistically significant reduction with strategies that incorporate the training and support of TBAs. Study level meta-analysis of the five cluster randomised trials showed a significant reduction in perinatal death (RR 0.76, 95% CI 0.64, 0.88, p<0.001, Figure 10). There was statistical heterogeneity between the studies, that was assessed to be moderate (I^2 = 65.7%). Non-randomised studies also demonstrated a very similar reduction in perinatal death with strategies that incorporate the training and support of TBAs (RR 0.70, 95% CI 0.57, 0.84, p<0.001, Figure 10). There was evidence also of moderate heterogeneity within this analysis (I^2 = 40.2%).

Neonatal death:

All six cluster randomised trials individually showed a reduction in neonatal mortality, with three studies (42, 99, 100) showing a statistically significant reduction. Meta-analysis of the six studies showed a significant reduction in neonatal death with strategies that incorporate the training and support of TBAs (RR 0.79, 95% CI 0.69, 0.88, p<0.001, Figure 11). There was moderate level of heterogeneity between the studies (I^2 = 40.5%). Non-randomised studies also showed a reduction in neonatal mortality (RR 0.61, 95% CI 0.48, 0.75, p<0.001, Figure 11). There was evidence of low heterogeneity within this analysis (I^2 = 19.3%).

Maternal mortality:

Three cluster RCTs (42, 99, 100) reported on this outcome and found no significant difference in maternal mortality with strategies incorporating TBAs (RR 0.79; 95% CI 0.53, 1.05, p=0.12, Figure 12). There was no evidence of heterogeneity within this analysis (I^2=0%). Three non-randomised controlled studies (61, 106, 107) also showed no significant difference (RR 0.80, 95% CI 0.44, 1.15, p=0.26: Figure 12), there was no evidence of heterogeneity in the analysis (I^2=0%).

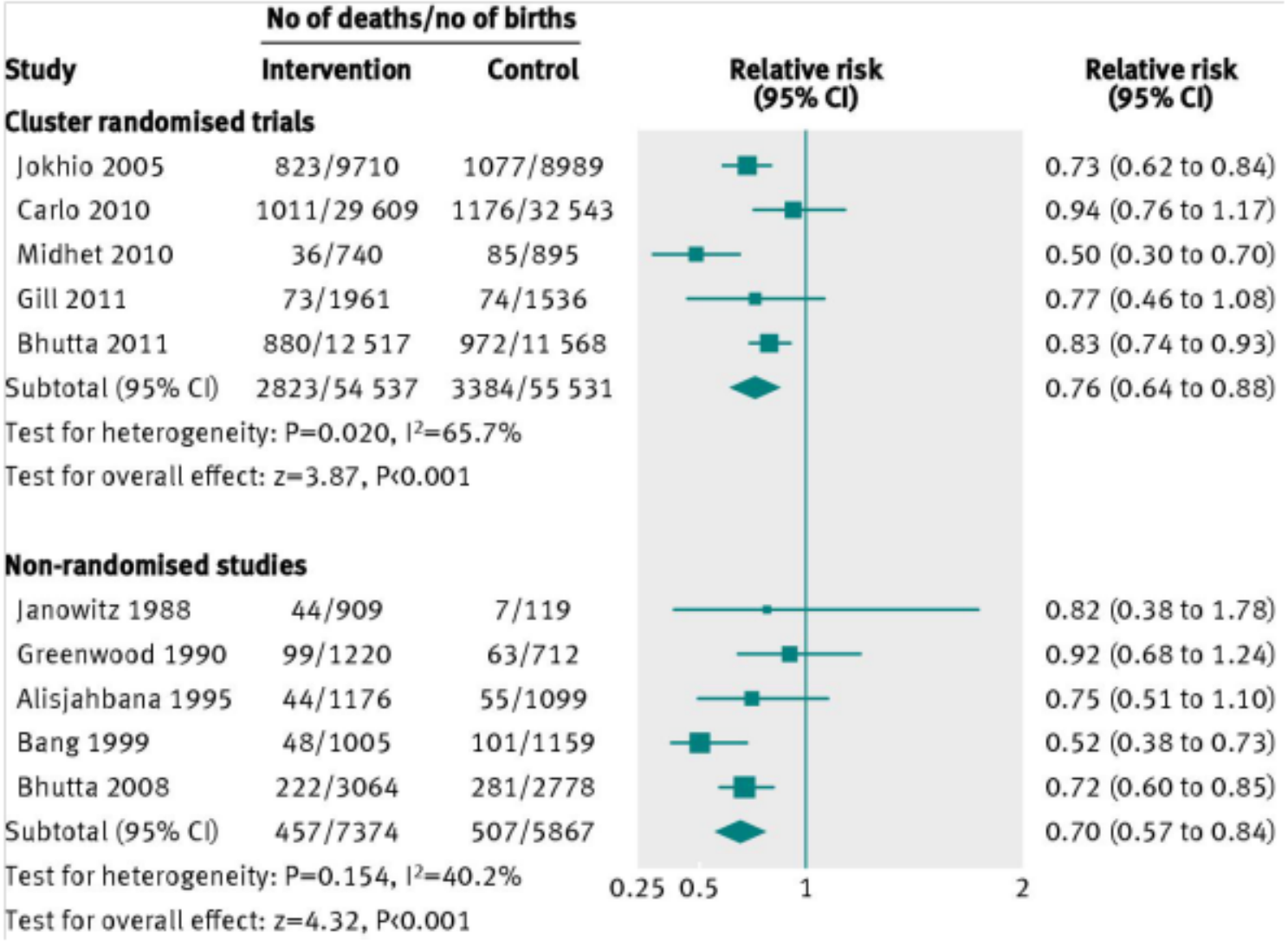

Figure 10 Perinatal mortality in areas that incorporated the training and support of TBAs compared to the control

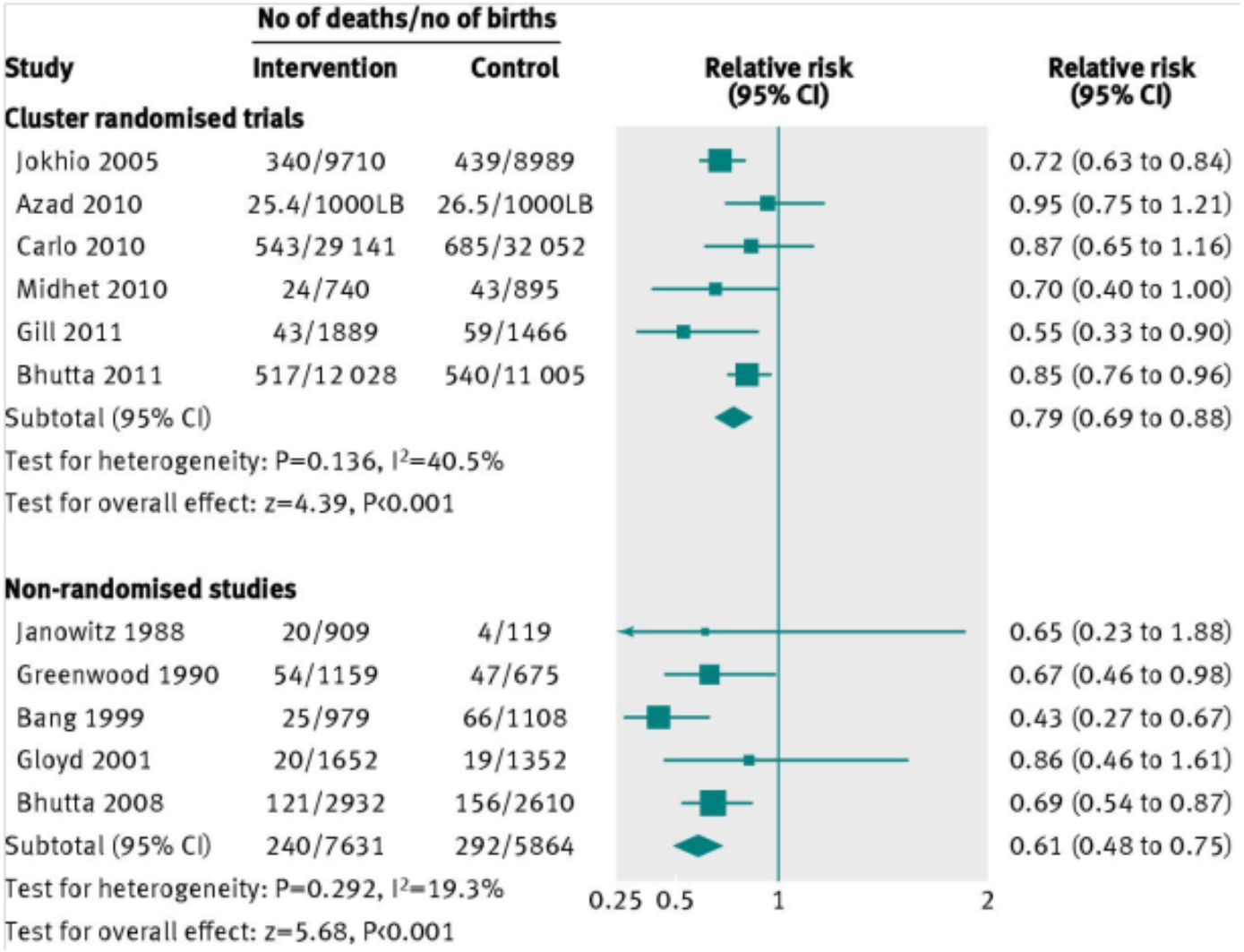

Figure 11 Neonatal mortality in areas that incorporated the training and support of TBAs compared to the control

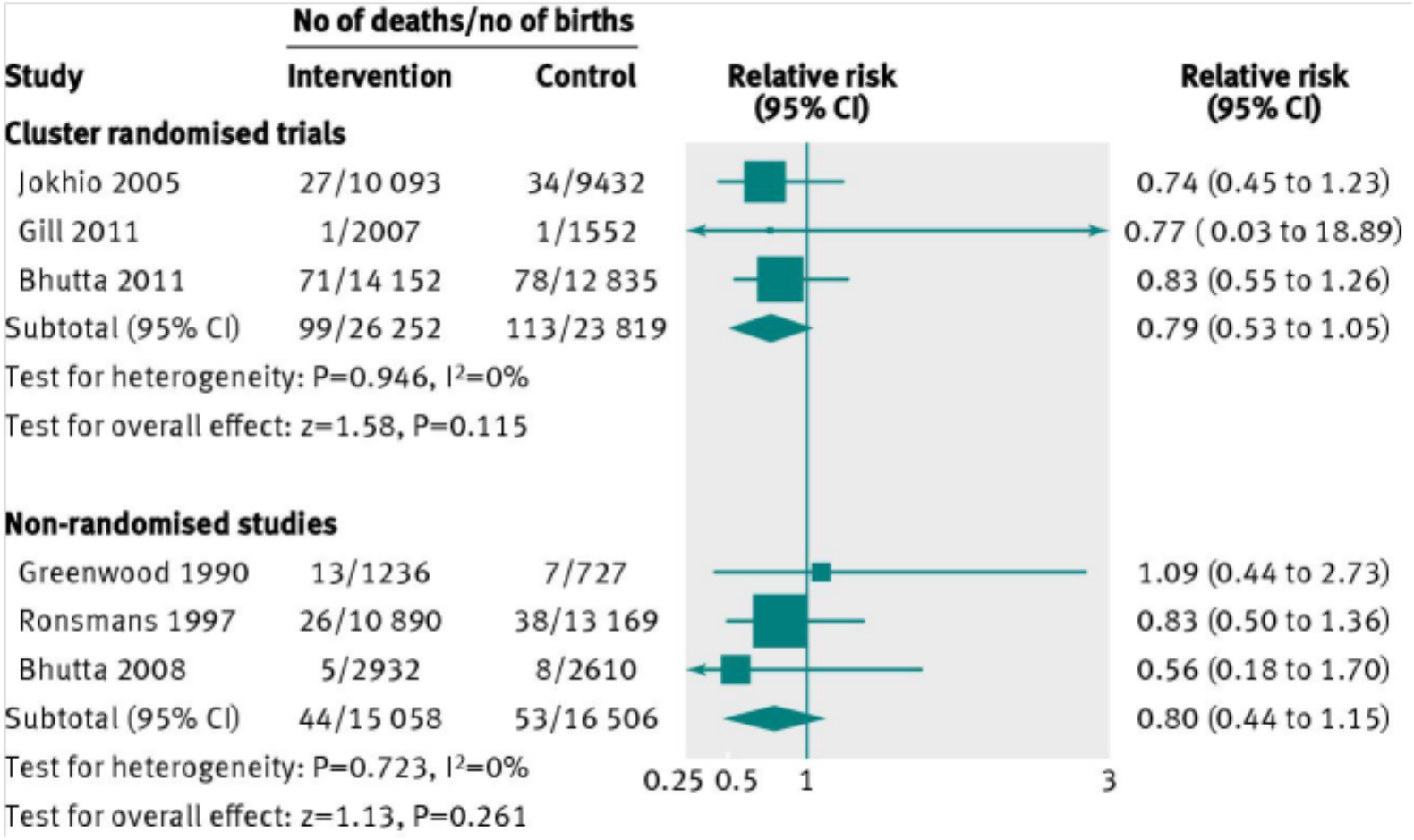

Figure 12 Maternal mortality in areas that incorporated the training and support of TBAs compared to the control

3.4 DISCUSSION

Findings

The meta-analysis of cluster RCTs showed that perinatal and neonatal deaths were significantly reduced with interventions incorporating the training and support of TBAs. The findings from non-randomised studies were entirely consistent with the findings of the cluster randomised trials. There was statistical heterogeneity in the analysis for perinatal death and neonatal death; however, all cluster randomised trials and all non-randomised studies showed a reduction in these two outcomes. The heterogeneity thus represents differences in the magnitude of the favourable effect found across all studies, rather than suggesting opposing effects. The estimated effect is large enough to contribute to a substantial improvement in perinatal and neonatal outcomes in the developing world.

Meta-analysis of the cluster RCTs showed no significant difference in maternal mortality, with the non-randomised studies following a similar trend. There was no evidence of heterogeneity identified for this outcome within the studies.

Limitations

All trials included within the systematic review evaluated highly complex interventions with a range of components. There was substantial variation in the role of the TBAs, the support staff involved, the resources that they were provided with, and the referral pathways that were incorporated (Figure 13). None of the trials included provided a direct comparison between trials that involved TBAs versus trials that did not include TBAs, rather it included trials that provided a comparison of strategies that incorporated additional support of TBAs, against strategies that did not. Some trials supported TBAs in both intervention and control arms, but the level of support was enhanced within the intervention group; for instance, Gill et al (99) supplied clean delivery kits to all TBAs, in conjunction with providing basic training on newborn care and resuscitation. Their addition for the intervention arm was providing training and protocols on higher level resuscitation and recognition of signs of neonatal

sepsis. In the study by Carlo et al (98), the there was limited difference in the TBA involvement between the two trial arms; interestingly, this was also the study that showed the smallest difference in perinatal death. In contrast, Jokhio et al (42) and Midhet and Becker (101) trials had the largest difference in TBA involvement between the trial arms, and these trials showed the largest improvement in perinatal mortality with the intervention. However, one cannot infer that the greater the support for TBAs, the better the perinatal outcomes, as within a complex package of interventions, it is not possible to separate out the role played by enhanced TBA support against other components in achieving the observed improvements.

Notwithstanding, the primary question in the included trials, and for our review, was whether the complex interventions incorporating TBAs, as a whole, resulted in an improvement in outcomes. The consistency in the findings, despite the heterogeneity in the populations, settings (countries), health systems, interventions and comparisons, contributes to the generalisability of the findings. This is likely to be important for policy making.

Existing evidence

The effect of incorporating TBAs into perinatal and maternal mortality reduction programmes was examined in a Cochrane review (47) in 2009. As there was only one cluster randomised trial at the time of the review, firm inferences could not be drawn resulting in the suggestion that "TBA training had promising potential to reduce perinatal and neonatal mortality when combined with health services; however the limited number of studies included did not provide the evidence needed". Our meta-analysis, consisting of six cluster randomised trials and seven non-randomised studies, allows firm inferences to be drawn. Another Cochrane review (108) evaluated the full range of 'community based intervention packages' which included strategies as wide as nurse-led nutrition counselling, stimulation exercises to improve psychomotor development in infants (109), distributing supplementary foods to poor families (110), and providing preschool education. This review identified 11 cluster

randomised and 8 quasi-randomised trials or controlled studies; however, only one RCT incorporated TBAs as an interventional strategy, a further two trials involved TBAs as the type of health worker involved for delivery of the intervention. Darmstadt et al (83) reviewed the evidence for community based skilled and TBAs, as well as CHWs in improving perinatal and intrapartum related outcomes. This review included a single cluster randomised trial with TBAs as the intervention, as this is all that existed at the time of the review (42). Their findings on TBAs were consistent with our review findings.

Practice and policy implication

Deployment of TBAs without an appropriate package of training, support and resources is unlikely to be effective. Potentially important components that support strategies incorporating TBAs include support from health care professionals, continued skill development, access to resources such as clean birth kits, and effective referral pathways. Although the optimal intervention to improve perinatal and maternal outcomes is to increase the proportion of births attended by *skilled* birth attendants, the economical, geographical, political and social realities have limited the ability of national and international efforts for all births to be attended by SBAs. This has therefore resulted in critical coverage gaps, and 52 million women give birth without skilled birth attendance (83). Therefore, other cadres of health workers may need to be considered to extend the coverage of maternal and neonatal care to help improve outcomes. TBAs are on location, culturally acceptable, and can improve care coverage, and evidence from this meta-analysis suggests that TBAs can be a component of strategies to improve perinatal outcomes. TBAs often represent a more feasible, culturally acceptable and an accessible option for women in developing countries (95).

Unanswered questions and future research

It is suggested that the incorporation of TBAs in the absence of an appropriate training package, or without appropriate and adequate support and resources is likely be ineffective.

As this intervention is a complex intervention package that has several interacting components, it is important to understand the processes involved as well as evaluating the outcome. Evaluating complex interventions can be problematic due to the practical and methodological difficulties that arise with complex intervention packages. The Medical Research Council framework can be used to offer guidance with evaluation, however it is suggested that it is necessary to understand the change process, as well as the evidence base and the developing theory (111). Currently however, detail lacks on the exact effect of the components of each of these elements. Therefore further research is needed to examine the components in greater detail, and attempt to establish an understanding of which components contribute to more successful incorporation of TBAs, and maternal and newborn health outcomes. A qualitative synthesis of existing studies may offer greater insight into the practical and methodological challenges of implementing complex interventions, as well as the possible barriers and facilitators of this process. However, as complex interventions are suggested to be most effective when they are tailored to local circumstances, rather than being completely standardised, it may be more effective to conduct this research in a variety of settings, to develop a firm theoretical understanding of how the intervention causes change, so fragile links in the causal chain can be identified and strengthened (111). Further primary research may also provide greater insight (112, 113).

3.5 CONCLUSION

Our systematic review and meta-analysis provides good quality evidence showing a 24% reduction in perinatal death rates with strategies incorporating TBAs. Enhancing access to care during pregnancy and labour, in areas where coverage by skilled birth attendants is poor, can form part of the solution to meet MDGs 4 (reducing child mortality) and 5 (improving maternal health).

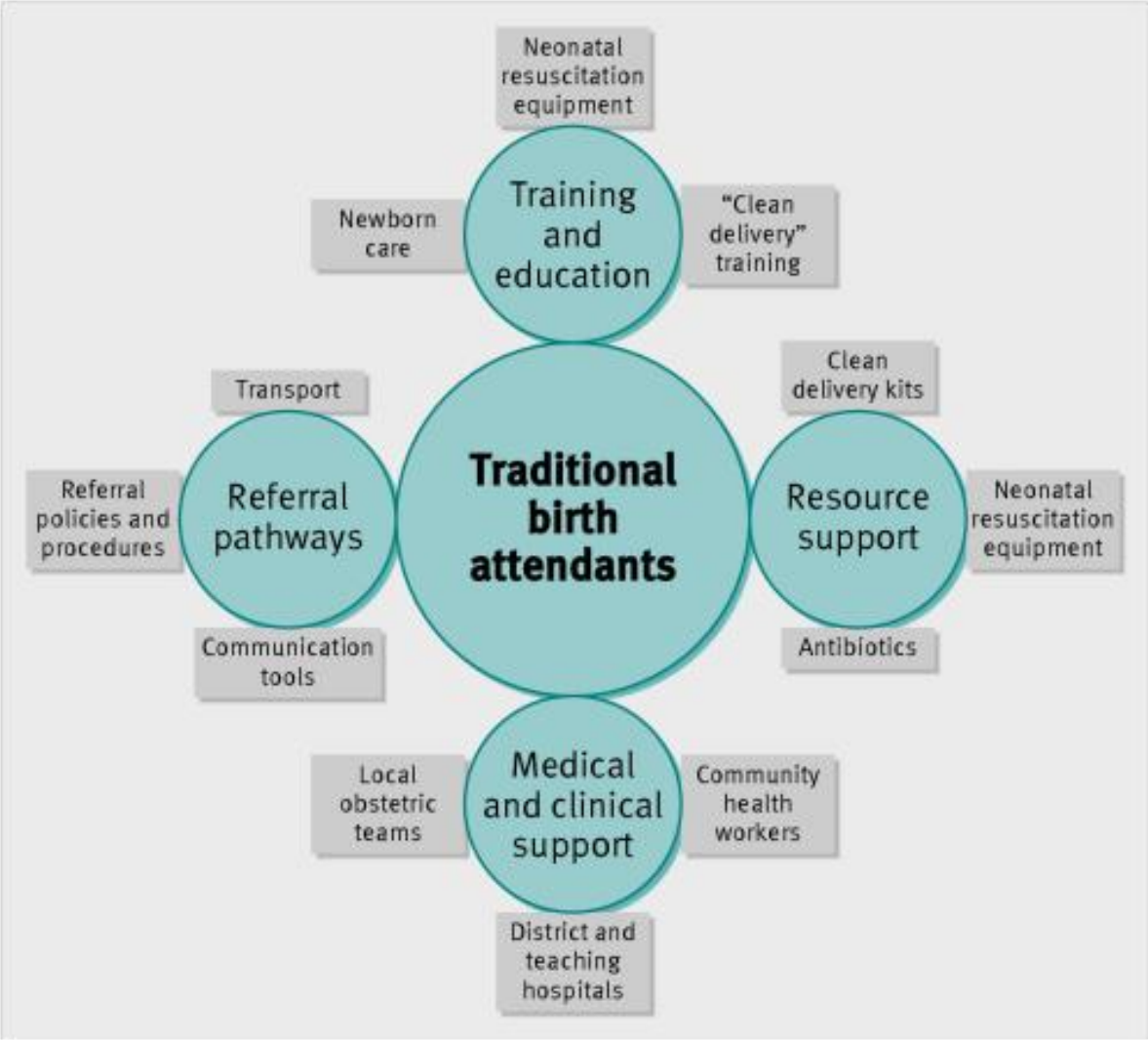

Figure 13 Optimal support for TBAs as suggested in primary studies

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CHAPTER 4: WOMEN'S GROUPS PRACTISING PARTICIPATORY LEARNING AND ACTION TO IMPROVE MATERNAL AND NEWBORN HEALTH IN LOW-RESOURCESETTINGS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Participatory action research has attempted to address the impact of women's participatory action groups on maternal and neonatal health outcomes, yet results have shown conflicting findings. Therefore a systematic review and meta-analysis was performed on the impact of women's participatory action groups on maternal and neonatal health outcomes in low income settings

Methods: MEDLINE, EMBASE, Cochrane library, CINAHL, African Index Medicos, Web of Science, the Reproductive Health Library, and the Science Citation Index were searched (inception- November 2012) without language restriction. Studies of randomised controlled design were selected, with the primary outcomes of still birth, neonatal and maternal mortality. Relative risks (RR) were pooled using random effects model. A sub-group analysis was performed on groups from trials where at least 30% of pregnant women participated in the women's groups. This figure was selected as previous studies have suggested that this coverage is a key determinant of impact.

Results: Seven cluster RCTs (n= 119,443 births) were identified. Meta-analysis of the randomised trials showed a reduction in maternal mortality (OR 0.66, 95%CI: 0.33-0.99), a reduction in neonatal mortality (OR 0.77, 95% CI 0.65-0.89) and a non-significant reduction in stillbirth (OR 0.91, 95%CI: 0.79-1.03) with women's participatory action groups. Women's groups where at least 30% of pregnant women participated showed more marked effects on outcomes. Maternal and perinatal mortality were reduced further (OR 0.45, 95% CI: 0.17-0.73 and OR 0.67, 95% CI: 0.59-0.74 respectively)

Conclusion: Maternal and neonatal deaths are significantly reduced with women's participatory action and learning groups. Women's groups with at least 30% of pregnant women participating show greater reductions on neonatal and maternal mortality.

Impact of review: Published in Lancet, Presented at the Houses of Parliament

Citation of published paper on which this chapter is based

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4.1 BACKGROUND

Community-based interventions are suggested as being critical to improving maternal as well as newborn health (20) in low income settings, however packages of these interventions have demonstrated various levels of effect on maternal and neonatal mortality (108, 110, 114-117). Research suggests that increasing community participation in maternal and newborn health projects improves health outcomes and care seeking behaviours (41, 118).

A systematic review of randomised trials of various community based intervention packages published in 2010 (108) demonstrated significant reductions in neonatal mortality, but there was inconclusive evidence on the effect of maternal mortality. The interventions included

were heterogeneous, some involved home counselling visits to mothers, some enhanced referral pathways and some provided home-based care to newborns. Other intervention packages included community-level activities to strengthen newborn care practices, and women's groups using a four phase, participatory learning and action cycle.

Participatory action and learning cycles are a rigorously examined community based intervention that aims to explore and understand local health problems, possible causes and solutions (119, 120). Participatory action and learning cycles with women's groups involves identifying and prioritising problems in pregnancy, delivery and the postpartum period; planning how to address these problems through locally feasible strategies; implementing the chosen strategies; and evaluating their activities. These cycles are a form of community mobilisation that involves a group of local community members, meeting in the presence of group facilitators, often in the presence of key stake holders, to identify and discuss problems within the local community. Through this problems are addressed, the group then plan how to implement strategies to instigate change through an action plan. Once action has been taken to address the problems, the group then assess the effect of the actions, and reassess the problems initially identified, with the addition of any newly arising problems (121) (119, 122).

The concept of working with women's groups arose after the Alma Ata Declaration in a commitment to supporting the participation of local people in healthcare planning and implementation. This idea stems from the work of Pedagogue Paulo Freire. When translated into healthcare it focuses on three main notions: firstly that many health problems are rooted in powerlessness, thus social and political empowerment can therefore improve health; secondly that health education is more empowering if it is a dialogue-based process of co-learning and problem-solving rather than as 'message-giving'; and thirdly that communities can develop 'critical consciousness' to recognize and address the underlying social and political determinants of health, as well as the immediate determinants of health (123).

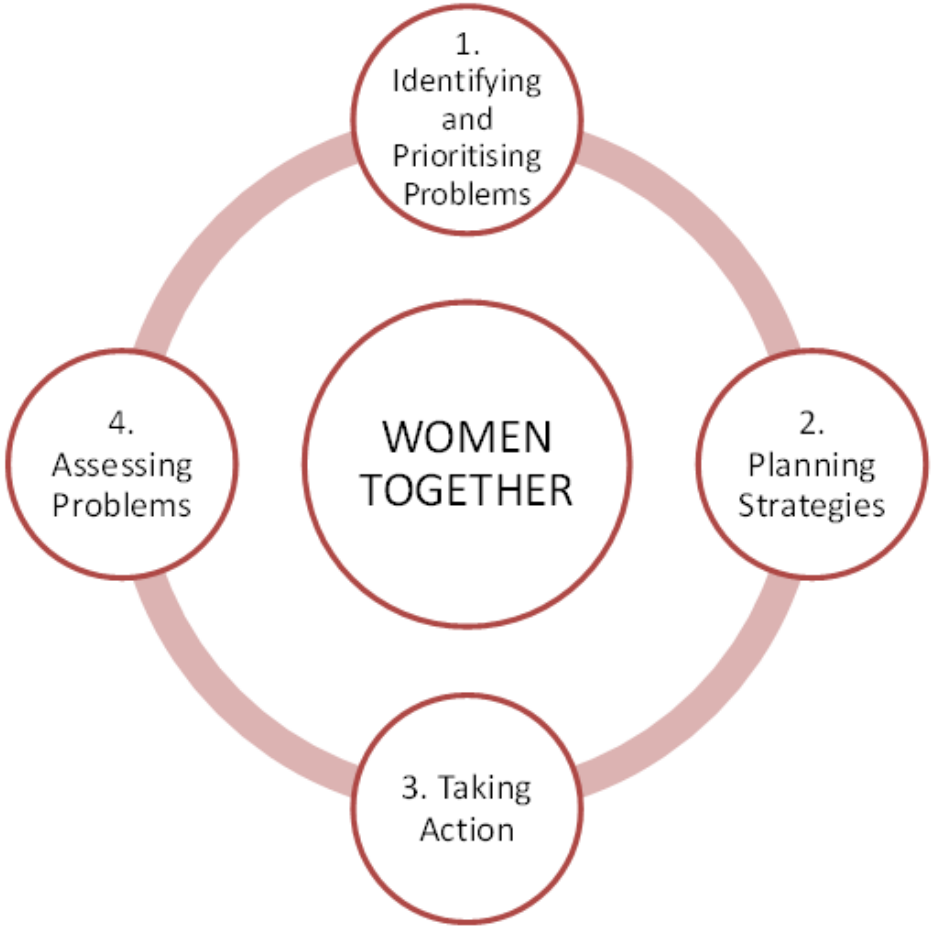

Figure 14 Process of women's participatory action and learning cycle

Participatory action is suggested to empower groups, as well as the wider community (124, 125) and encourage them to assess their own environmental situation and health needs (122). The effects of participatory learning and action with women's groups, has been assessed on maternal and neonatal health outcomes in low income settings (121, 126). Other studies have measured the impact of women's groups on behavioural change (127). Results have been conflicting (52, 97, 128), with some studies showing a reduction in neonatal death (52, 129), and others showing no effect (97). Most studies were not individually powered to show an effect in maternal mortality.

The various types of community-based interventions to improve maternal and newborn health have different ideological, organisational and economic implications. Therefore pooling their results may not be as informative for policy recommendations as analysing their impact separately, and reflecting on factors that affect their effectiveness. By conducting a systematic review of RCTs the impact of women's groups practising participatory learning and action on maternal and neonatal mortality and stillbirth could be assessed. The aims of this review were to determine the impact of women's groups on maternal mortality, neonatal mortality and stillbirths with women of reproductive age in low resource settings.

4.2 METHODS

Data sources and searches

Databases were searched for literature on women's participatory action groups in developing countries. We searched PUBMED, EMBASE, Cochrane library, CINAHL, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index (from database inception to November 2012). Hand searching complemented electronic searches, and reference lists were checked. The search terms were a combination of 'community mobilisation', 'community participation', 'participatory action', 'participatory action group*','women* group*' and 'women'. No language restrictions were applied to the search.

Study selection and data extraction

RCTs only were selected. Initially the electronic searches were scrutinised and full manuscripts of relevant studies were acquired. Final decisions on inclusion or exclusion of manuscripts were made after inspection of these manuscripts by the author and another reviewer (AW and CM). Information was extracted from each article on study characteristics, study quality and outcome data by the author and three other reviewers (AW, CM, NS, AP). Studies were excluded if they did not contain all of the stages used within a participatory action and learning cycle, if the majority of the participants were not women of reproductive age, and the study outcomes did not include maternal mortality, neonatal mortality or stillbirth. The outcomes for the systematic review were stillbirth, neonatal mortality and maternal mortality.

Methodological quality assessment

The RCT were assessed for methodological reporting using the CONSORT statement and its extension (68) as appropriate for cluster trials. These studies were assessed for randomisation and sequence generation, baseline comparability, accounting for cluster effect, blinding and appropriate statistical analysis (68). Risk of bias within individual studies was assessed using the Cochrane collaboration's tool (130).

Statistical Analysis

Odds or risk ratios were extracted from each study for each outcome using the main estimates reported in the trials. The ratios accounted for stratification and clustering, and where appropriate adjustments for other covariates reported were made. When an outcome was required for the analysis, but not reported in the outcome data, the identical methods reported as used in the original study were used to calculate an effect size from the trial datasets. Meta-analysis of the study-level data was conducted with the *metan* command in Stata (version 12.1) using random-effects model, this was because the effects seen in each trial were assumed to be taken from an underlying distribution. A-priori meta-analyses to ascertain the effect of women's groups on maternal mortality, neonatal mortality, and

stillbirths with all trials were performed. Subgroup analyses were then performed to identify population-level predictors of effect, as it was postulated that these may include the population coverage of women's groups, proportion of pregnant women within the groups, and background mortality and institutional birth rates as measured in the control areas during the trials. In previous studies, the hypothesis was that having one women's group per 450–750 population and between 30% and 50% of pregnant women attending groups would be key determinants of effect. Meta-regression analysis was used to assess whether each of the predictors was associated with intervention effects. If there was evidence of statistical heterogeneity ($I2>50\%$, $p<0.05$), the trials were separated into groups according to the results of the meta-regression analyses. Potential publication bias and small-study effects were assessed using funnel plots and Egger tests (TC, A.Cop)

4.3 RESULTS

The process of literature search and selection is given in Figure 15. Seven RCTs were included all of which were cluster randomised (52, 97, 120, 128, 130) with a total of 119,443 births. Characteristics of the included studies are shown in Table 9, and characteristics of the clusters are shown in Table 10. The studies examined the effect of women's participatory action and learning cycles on stillbirth, neonatal and maternal mortality. Four studies used these groups within a wider interventional strategy with a multitude of components, however these other components were introduced in both the control and intervention arms. Most studies effectively reported on sequence generation, randomisation, baseline comparability, accounting for cluster effect, blinding and appropriate statistical analysis (Table 11). Four studies did not adequately report the reason for a cluster design within the background of the manuscript, and five studies lack reporting on adverse outcomes. Most studies were assessed as having low risk of bias for random sequence generation (6/7), incomplete outcome data (5/7), or selective reporting (5/7). All studies had low risk of bias for allocation concealment (7/7), but high risk of bias for blinding of participants and personnel (7/7). Half

of the studies had high risk of bias in blinding of outcome assessment, and one study was assessed as high risk for other sources of bias (Table 11).

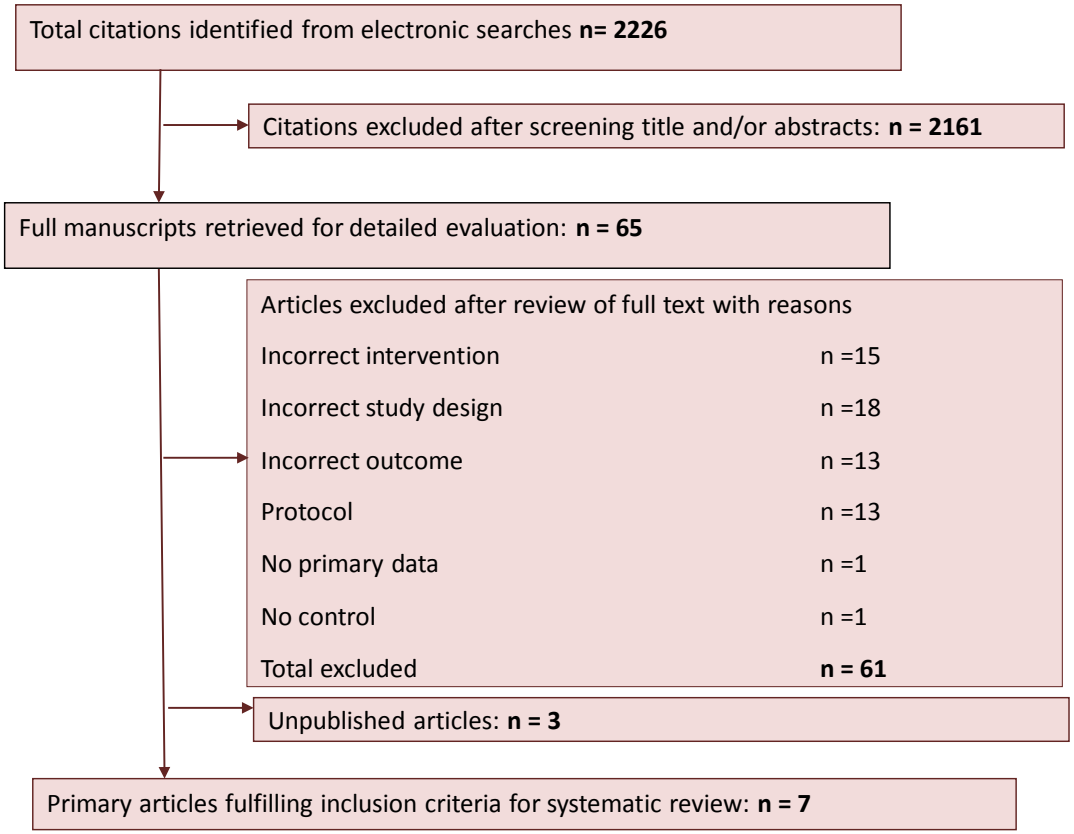

Figure 15 Results of search strategy and identification of literature included in the review

Maternal mortality

Seven cluster RCTs (n= 119,443) reported on the effect on maternal mortality. Meta-analysis of RCTs demonstrated a significant reduction of 34% in the odds of maternal mortality (OR 0.66,95%CI: 0.33-0.99: Figure 16). There was evidence of moderate and significant heterogeneity within the analysis (I^2=58.8%, p=0.015).

Neonatal mortality

Seven cluster RCTs (52, 97, 120, 128, 131) (n=119,443) reported on neonatal mortality. Meta-analysis showed a significant reduction of 23% in the odds of neonatal mortality with women's participatory action and learning cycles (OR 0.77, 95% CI 0.65-0.89: Figure 17). There was high heterogeneity noted within the analyses (I^2=64.7%, p=0.009).

Stillbirth

Seven RCTs reported on this outcome. There was no evidence of reduction in stillbirths (OR 0.91, 95% CI 0. 79–1. 03, I^2=37. 7%: p=0. 141: Figure 18).

Sub-group analysis

Maternal mortality: More than 30% pregnant women participating in groups

Four cluster RCTs (n=49,703 births) where at least 30% of pregnant women participated in the women's groups showed a significant reduction of 55% in the odds of maternal mortality (OR 0.45, 95% CI: 0.17-0.73: Figure 19). There was evidence of low heterogeneity within this analyses that was not statistically significant (I^2 = 51.3%, p = 0.104).

Neonatal mortality: More than 30% pregnant women participating in groups

Four cluster RCTs (n=49,703 births) where at least 30% of pregnant women participated in the women's groups showed a significant reduction of 33% in the odds

of neonatal mortality (OR 0.67, 95% CI: 0.59-0.74: Figure 20). There was evidence of moderate heterogeneity within this analyses that was not statistically significant (I_2=0%, p=0.844).

	Years	Livebirths	Deaths in intervention group	Livebirths in intervention group	Deaths in control group	Livebirths in control group	Percentage of pregnant women attending groups (numerator/denominator)	Population per group	Percentage of institutional deliveries in control group	Control maternal mortality ratio	Odds ratio (95% CI)	Percentage weight
Colbourn et al,[26] 2013 (Malawi)	2008–10	19986	22	10055	25	9931	10 (estimated)	1200	67	251·7	0·91 (0·51–1·63)	14·77
More et al,[24] 2012 (India)	2006–09	15703	15	7944	16	7759	2 (118/5996)	788	87	206·2	1·41 (0·51–3·87)	3·03
Azad et al,[14] 2010 (Bangladesh)	2005–07	29889	55	15153	32	14736	3 (477/15695)	1414	16	217·2	1·74 (0·97–3·13)	6·38
Fottrell et al,[27] 2013 (Bangladesh)	2009–11	17421	14	8819	23	8602	36 (3326/9109)	309	27	255·8	0·74 (0·34–1·64)	12·64
Manandhar et al,[12] 2004 (Nepal)	2001–03	6125	2	2899	11	3226	37 (1123/3036)	756	2	341	0·20 (0·04–0·91)	18·27
Tripathy et al,[13] 2010 (India)	2005–08	18449	49	9469	60	8980	37 (3544/9577)	468	20	668·2	0·70 (0·46–1·07)	22·38
Lewycka et al,[25] 2013 (Malawi)	2006–09	6338	5	3074	23	3264	51 (1273/2503)	440	47	705	0·26 (0·10–0·70)	22·53
Overall (I^2=58·8%, p=0·024)											**0·63 (0·32–0·94)**	**100·00**

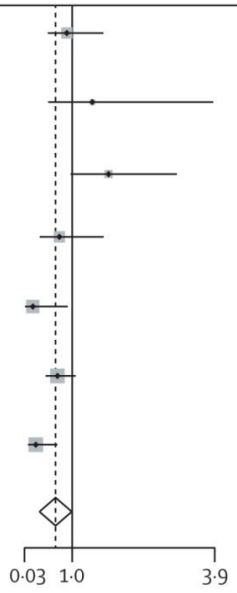

Figure 16 Maternal mortality in clusters where women's groups' practised participatory action and learning cycles compared to the control

89

	Years	Livebirths	Deaths in inter-vention group	Livebirths in inter-vention group	Deaths in control group	Livebirths in control group	Percentage of pregnant women attending groups (numerator/ denominator)	Population per group	Percentage of institutional deliveries in control group	Control neonatal mortality rate	Odds ratio (95% CI)	Percentage weight
Colbourn et al,[26] 2013 (Malawi)	2008–10	19986	286	10055	308	9931	10 (estimated)	1200	67	31·0	0·90 (0·75–1·09)	16·84
More et al,[24] 2012 (India)	2006–09	15703	132	7944	88	7759	2 (118/5996)	788	87	11·3	1·42 (0·99–2·04)	4·59
Azad et al,[14] 2010 (Bangladesh)	2005–07	29889	515	15153	557	14736	3 (477/15695)	1414	16	37·7	0·90 (0·73–1·10)	15·92
Fottrell et al,[27] 2013 (Bangladesh)	2009–11	17421	187	8819	271	8602	36 (3326/9109)	309	27	31·5	0·62 (0·43–0·89)	13·37
Manandhar et al,[12] 2004 (Nepal)	2001–03	6125	76	2899	119	3226	37 (1123/3036)	756	2	36·9	0·71 (0·53–0·95)	14·46
Tripathy et al,[13] 2010 (India)	2005–08	18449	406	9469	531	8980	37 (3544/9577)	468	20	59·1	0·68 (0·59–0·78)	21·46
Lewycka et al,[25] 2013 (Malawi)	2006–09	6338	55	3074	95	3264	51 (1273/2503)	440	47	29·1	0·59 (0·40–0·86)	13·37
Overall (I^2=64·7%, p=0·009)											**0·77 (0·65–0·90)**	**100·00**

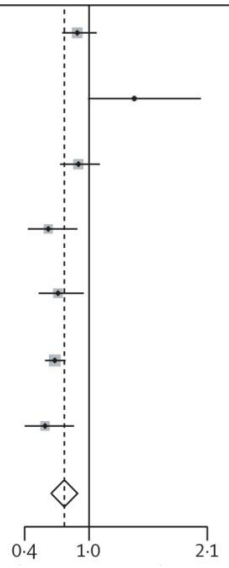

Figure 17 Neonatal mortality in clusters where women's groups' practised participatory action and learning cycles compared to the control

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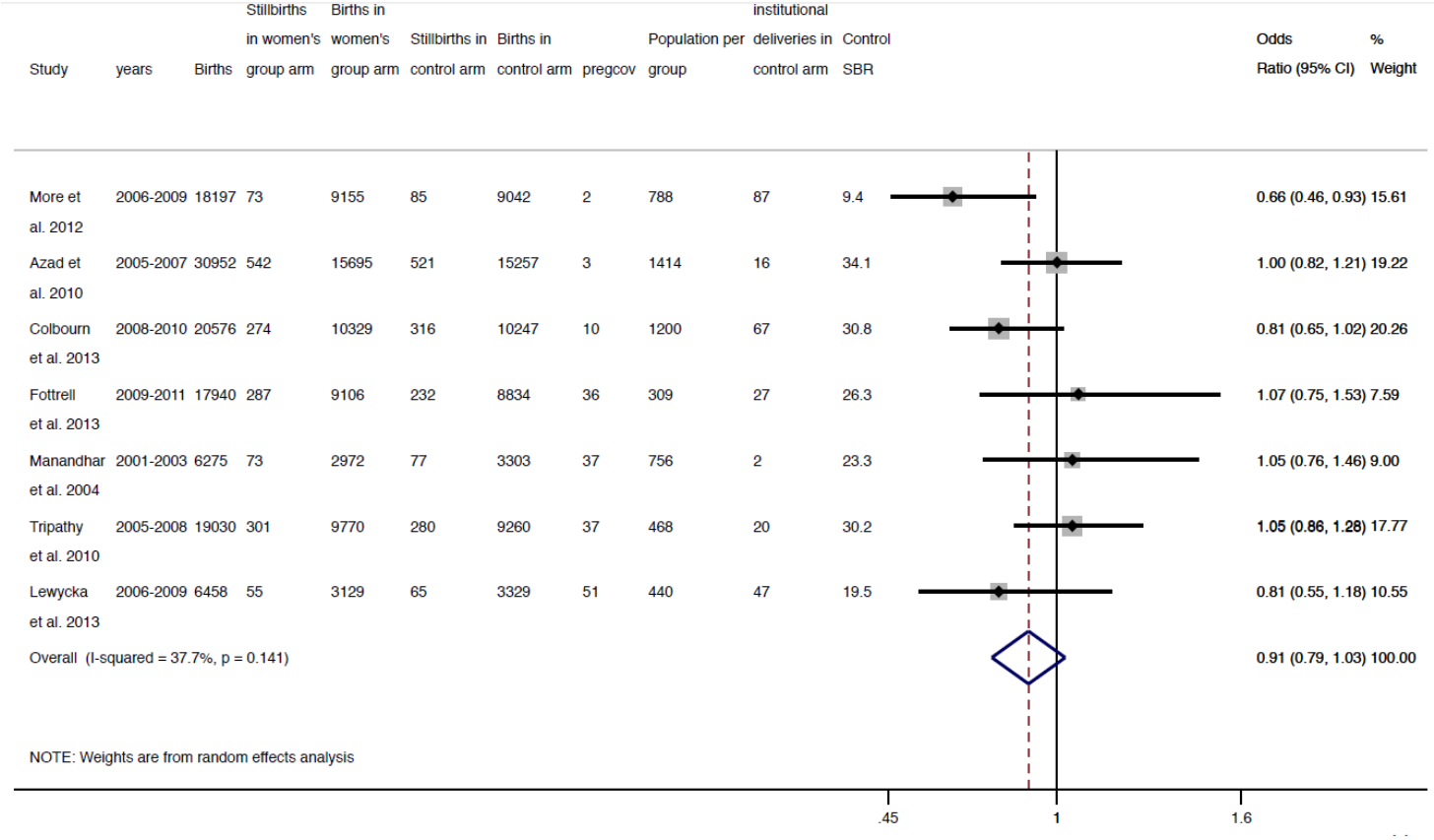

Figure 18: Stillbirth in clusters where women's groups practised participatory action and learning cycles compared to the control

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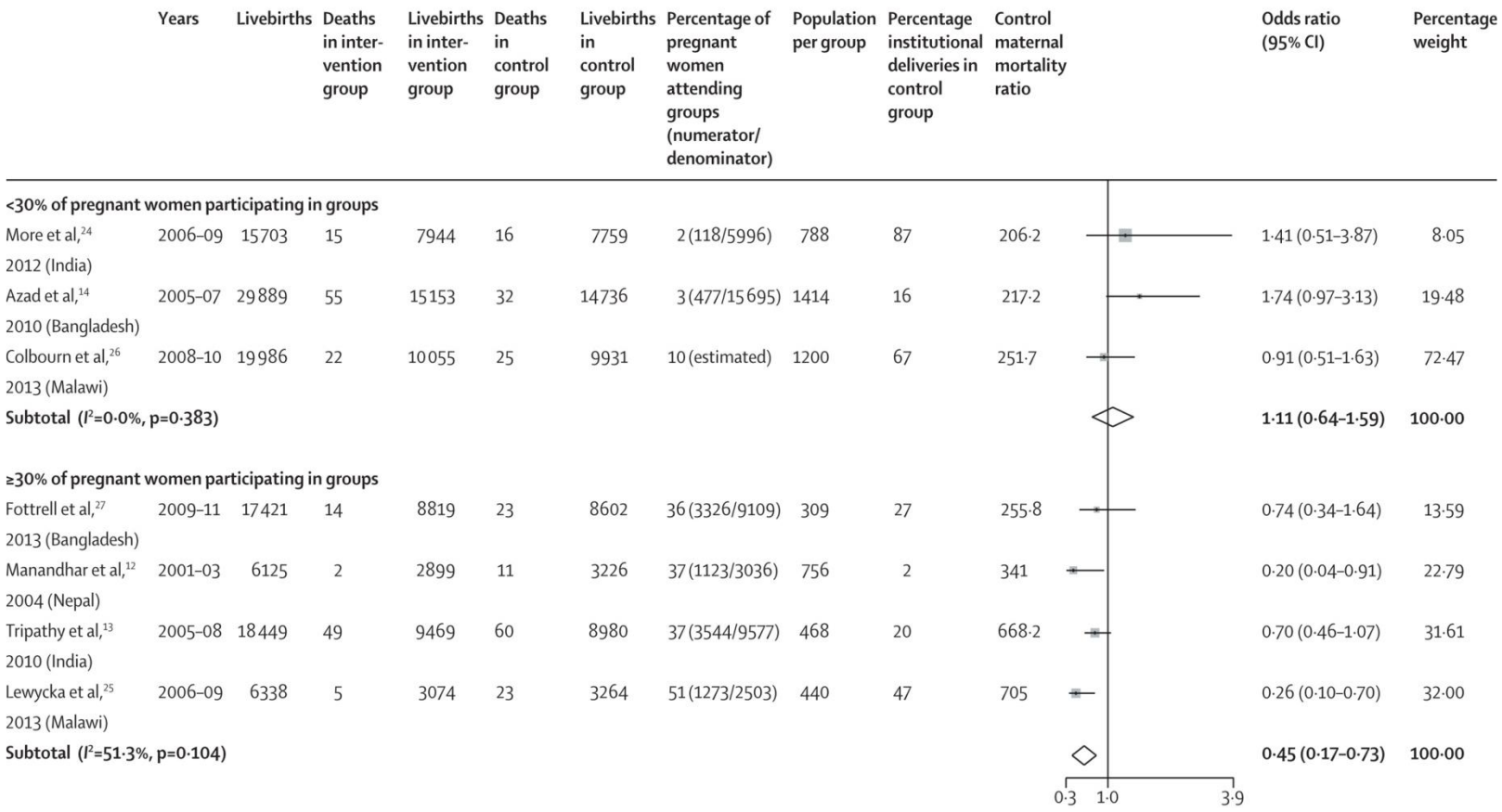

Figure 19 Maternal mortality by % of women participating in groups

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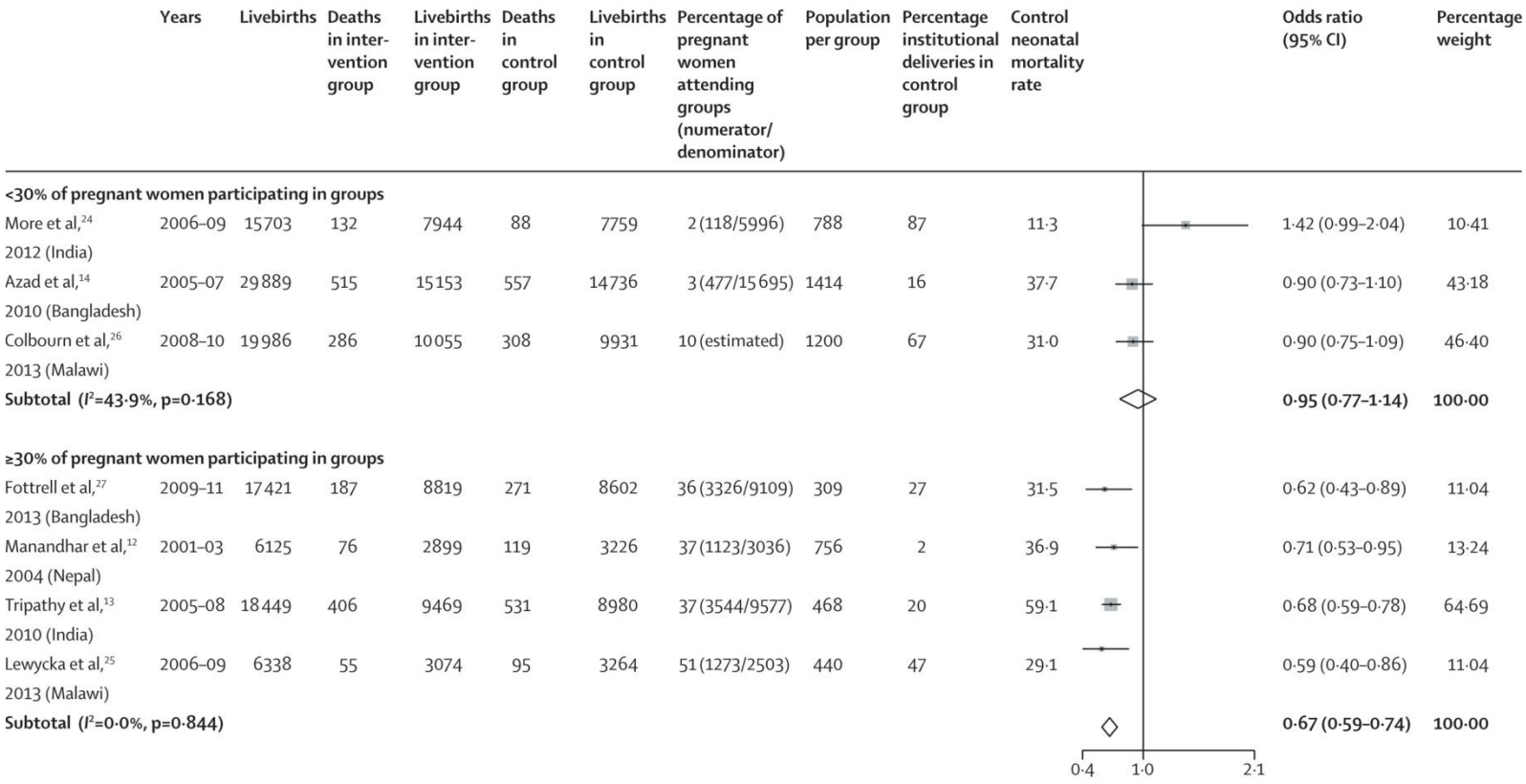

Figure 20 Neonatal mortality by % of women participating in groups

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4.4 DISCUSSION

Principal findings of the study

This meta-analysis of cluster RCTs showed a significant and substantial reduction in neonatal and maternal mortality with women's participatory action groups. There was moderate heterogeneity, but not statistically significant for both outcomes in the sub-group analysis. Participatory action and learning cycles that were conducted within a rural setting, and had a group density of more than 30% or pregnant women attending the groups showed the most marked reductions in the odds of mortality, these are demonstrated in Figure 21.

Strengths and limitations of the study

There was considerable heterogeneity within the analyses that included both rural and urban settings, with various concentrations of pregnant women attending the groups. However this heterogeneity was reduced and the effect on maternal and neonatal mortality more pronounced when data was pooled and analysed where groups from trials contained more than 30% of pregnant women. This figure was selected upon the guidance of previous studies that had hypothesised that population coverage was a key determinant of impact. Studies have suggested that the order of one group per 450–750 population, and between 30% and 50% of pregnant women attending groups, are key for impact (97, 132).

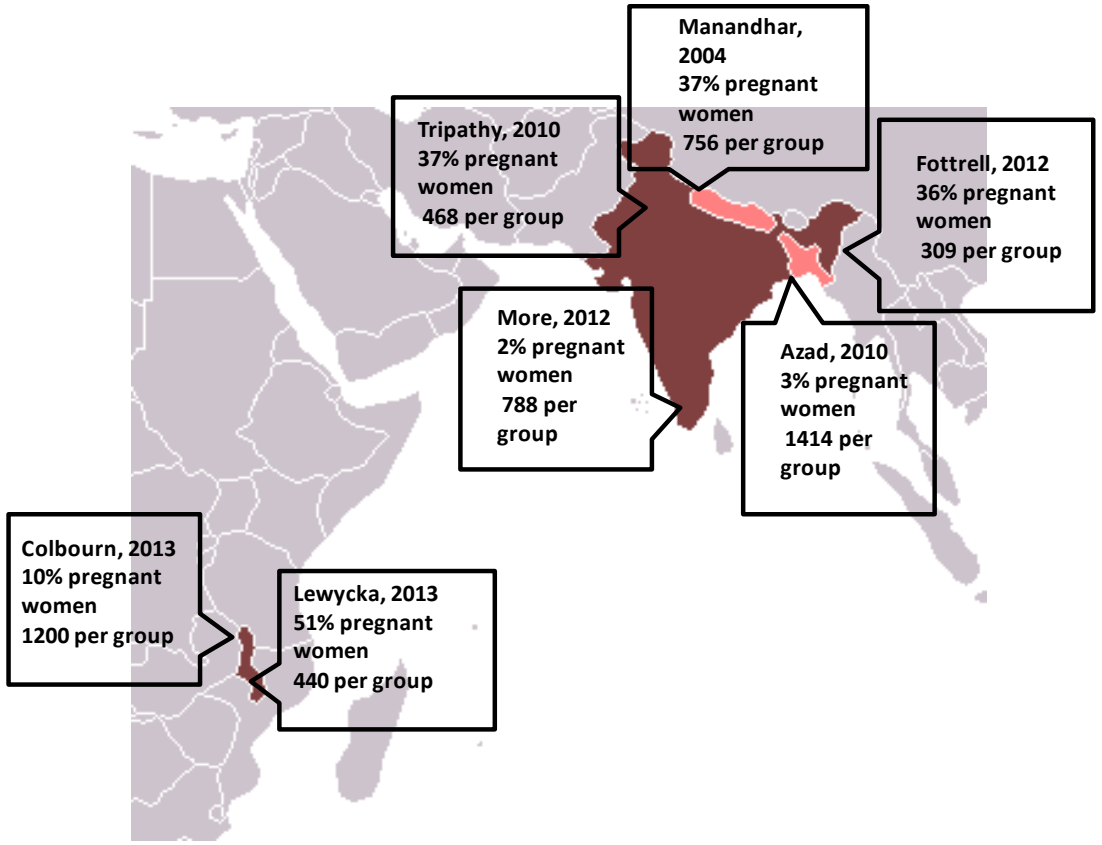

Figure 21 Map of settings of where the research on women's groups was conducted

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Comparison with other studies

To date no systematic reviews have evaluated the impact of women's groups practising participatory learning and action cycles on maternal and neonatal mortality. However two reviews (62, 108) have evaluated the effect of community based intervention packages on maternal and perinatal mortality: these assessed the full range of community interventions which included diverse strategies such as TBA training, antenatal care, nurse led nutrition counselling, distributing supplementary foods to poor families, and providing preschool education. Limited information was provided on the effects of women's participatory learning and action cycle on maternal and newborn health within these reviews.

A more recent review (133) found a significant decrease in neonatal mortality rates with community based newborn care: this systematic review contained 13 controlled trials (randomised, quasi-randomised and non-randomised) of a variety of community based neonatal care packages. Three studies from this review examined the effect of participatory women's groups, and meta-analysis found a reduction in the risk of neonatal mortality by 23% (RR 0.77 95% CI 0.61, 0.96; I^2 78.2%, p=0.010), however one randomised trial that was included was omitted from our analyses as it was not conducted in a developing country. Furthermore the effects on maternal outcomes were not examined within this review.

Policy implications

Women's participatory groups have been used to assess perceptions of maternal health issues within communities (134), as well as to measure objective quantitative outcomes such as death and disability. Women involved within participatory action

groups have shown an enhanced awareness of maternal health problems, as well as the desire and motivation to address them. It is however suggested that the process of identifying problems and implementing strategies to address the problems, may be more beneficial to the group than the strategy itself, as research suggests that interaction with the wider community may encourage greater interest and involvement of the community with perinatal health issues (121).

Activities between women's groups can vary, some studies suggest that there is no 'magic bullet' for successful community mobilisation, whereas participatory learning and action cycles often follow a 'formula' for an active women's group (121). For example it is suggested that working closely with communities and consulting them at stages in the design, planning and implementation of the participatory action group is critical for achieving favourable outcomes (135). A participatory approach is thought to have the potential to develop knowledge, skills and critical consciousness, as well as enhance community involvement beyond the women's group itself. It can target and actively recruit marginalised communities and vulnerable groups such as newly pregnant women, and achieve high population coverage (119).

Research suggests that several interrelated factors influence the interventions impact on health and care-seeking behaviour outcomes. Pregnancy and childbirth are often culturally viewed as 'women's problems', therefore the responsibility often falls with women themselves (136, 137), therefore the acceptability and feasibility of this methodology within the region should be assessed prior to implementation, especially if marginalised and vulnerable communities are being targeted. It is suggested that a detailed understanding of the context in which the participatory action group will take place is necessary to ensure successful delivery of the intervention. A planned yet

flexible approach to key implementation features, and a strong support for participatory methods from implementing agencies are recommended for scaling-up this intervention (119).

In regions where improvements in maternal health and maternal mortality are inhibited by gender inequity, empowered women's groups could give individuals the support and confidence to strive for a healthy pregnancy, and be involved with decisions about their care.

Unanswered questions and future research

As this review addressed only the objective outcomes of mortality, associated effects on morbidity or improvements in health seeking behaviours could be examined. Communications with the WHO have occurred since publication of this review to examine the effect of this intervention on such outcomes.

4.5 CONCLUSION

This systematic review and meta-analysis demonstrates the effect of women's groups practicing learning and action cycles, and provides good quality evidence showing a significant reduction in maternal and neonatal mortality. Empowering women and encouraging support for improvements in care seeking behaviours to enhance maternal and perinatal health can form part of the solution to meet MDGs 4 (reducing child mortality) and 5 (improving maternal health).

Table 9 Study characteristics of included studies in the review

Study population, setting	Intervention	Control	Outcomes
Tripathy: 2010 Open cohort women 15-49 in rural India, gave birth Jul 05-Jul 08. 6 clusters (average population 6338 per cluster).	18 clusters (9770 births): Monthly women's group meetings facilitated by local woman (20 meetings per cluster). Facilitators had 7 day residential training course. Groups followed four-phase participatory learning & action cycle. community members encouraged to participate. Strategy implementation was discussed to assess results. Information on clean delivery & care-seeking behaviour shared through stories & games. Stories, participatory games & picture cards to facilitate discussions on prevention & care-seeking in pregnancy, birth & postnatal period. Health committees formed – as control.	18 clusters (9260 births): Health committees formed, community members discuss & express opinions about design & management of local health services. Meetings held two months & structured action cycles, to discuss maternal & newborn health entitlement issues. Workshops provided for appreciative inquiry with frontline government health staff.	Primary: NMR, maternal depression scores. Secondary: Stillbirths, MMR, PMR, uptake of antenatal/delivery services, home-care practices, health-care-seeking behaviour.
Manandhar: 2004 Closed cohort married women 15-49 Jun 2000, living rural Nepal. Pregnancies registered Nov 2001 – Oct 2003. Women included: married with potential to become pregnant. Excluded separated or widowed women. 24 clusters (average population 7000 per cluster).	12 clusters (2972 births): Each cluster had local literate female facilitator, Facilitators given training in perinatal health issues. Facilitators had manual on 'Warmi project methodology'. Facilitators supported groups with meetings x10. Women's groups implemented & assessed strategies. Information through iterative design & picture card games. Health service strengthening – as control.	12 clusters (3303 births): Health service strengthening undertaken; primary health centres equipped with resuscitares, phototherapy units, warm cots, neonatal resuscitation equipment. Remedied short falls & discussed strategies for resupplies of neonatal drugs. Essential newborn care training health staff & TBAs. Community based workers received newborn care kits containing suction, resuscitation equipment, iodine gauze, wrapping cloth, pictorial manual.	Primary NMR Secondary: Stillbirths, MMR, uptake of antenatal/delivery services, homecare practices, infant morbidity, health-care seeking.

Azad: 2010 Open cohort women 15-49 in rural Bangladesh giving birth Feb 05 – Dec 07.18 clusters (average population 27953 per cluster).	9 clusters (15695 births): Women's group facilitators visited every tenth household in intervention clusters & invited married women of reproductive age to join. Mothers-in-law, adolescents, other women joined later. Groups facilitated by local female peer facilitator. Facilitators 5 training sessions that covered communication, maternal & neonatal health issues. Health service strengthening and basic training of TBAs – as control.	9 clusters (15257 births): Health service strengthening, basic TBA training, included improving referral systems & links with health services, between different levels health services. Resources & refresher clinical training maternal & neonatal care, information, education & communication materials. Training refreshing knowledge pregnancy & birth care, recognition of danger signs in mother & baby, essential newborn care, clean birth kits.	Primary: NMR Secondary: MMR, stillbirths, uptake of antenatal and delivery services, home-care practices during and after delivery, infant morbidity, health-care seeking behaviour, PMR, early NMR, late NMR
More: 2012 Women recruited Oct 06 -Sept 09 urban Mumbai slums. Excluded women from transient communities & areas of resettlement. 48 clusters (average cluster population 5865).	24 clusters (9155 births): Women's groups full-time facilitator in each (1000 households). facilitator was local woman with secondary education & leadership skills married with children. regular training on healthcare topics. Over six months each facilitator set up 10 groups. Groups met fortnightly, & facilitator weekly with other facilitators & supervisor. Women's groups followed 36 meeting cycle, attended by women, pregnant & non-pregnant.	24 clusters (9042 births):No details for control clusters	Primary: Stillbirth, NMR, PMR, perinatal care, maternal morbidity. Secondary: MMR, Antenatal care, iron supplementation, nutrition and rest, institutional delivery, breastfeeding, newborn care seeking
Lewycka: 2013 Open cohort of women 10-49. Women with permanent family planning excluded. 48 clusters (average cluster population of 8000).	24 clusters (9374 births): Women's group intervention supported by female facilitator, (20 meetings). Meetings facilitated by local literate woman aged 20-49, at least one child. trained 11 days, refresher 4 months. Strategies evaluated & plans made for future meetings. Groups restricted to females, expanded to men later. Health service strengthening – as control.	24 clusters (9749 births) strengthening of health services. Health workers from facilities had theory & practical training in essential newborn care, life-saving skills, safe motherhood, orientated two interventions. Neonatal resuscitation equipment donated to facilities. Prevention of mother to child transmission of HIV (PMTCT) project introduced	Primary: MMR, PMR, IMR. Secondary: Maternal, infant morbidity, use of SBA, postnatal services, tetanus toxoid immunization, malaria prophylaxis, insecticide-treated nets, PMTCT services, infant immunizations,

		2005, scaled to all facilities 2008	breastfeeding.
Colbourn: 2013 open cohort pregnant women from rural Malawi Oct 2008-Dec 2010. 32 clusters (average cluster population 4000 people). Cluster was catchment population of a health centre. Areas excluded if health facilities provided comprehensive emergency obstetric care or were non–functioning. Urban facilities were also excluded due to transient nature of urban communities.	15 clusters (10331 births): Participatory women's groups to mobilise communities around maternal and newborn health, using volunteer facilitators. Facilitators formed 9 women's groups. In 2009 women's groups chose maternal & neonatal health as a strategy to focus on (50%) had maternal & neonatal health task forces added to enhance antenatal coverage, maternal, neonatal health knowledge, facility delivery. .	17 clusters (10260 births): No details reported.	Primary: MMR, NMR, PMR. Secondary: Deliveries at health facility; percentage of maternal deaths subjected to maternal death audit, case fatality rates, practice of signal obstetric care functions.
Fottrell: 2013 Open cohort of women rural Bangladesh, permanent residents, delivered Jan 2009-Jun 2011. Temporary residents excluded. N.B. clusters same as Azad 2010.	9 cluster (9107 births): In addition to 162 women's groups already set up (Azad, 2010) 648 new groups formed by newly recruited facilitators to increase population coverage. Original groups continued to meet on monthly basis from late 2004-Jun 2011, focus expanded beyond maternal & newborn health to include women's health & health of under-fives. From Jan 2009 new groups had cycle of monthly meeting on maternal & newborn health. Health system strengthening initiatives – as control	9 clusters (8835 births): Health system strengthening initiatives including provision of basic medical equipment, TBA training of essential newborn care, refresher training for physicians & establishing links between communities & health services	Primary: NMR, Secondary: Stillbirth, NMR PMR, pregnancy related mortality. Facility delivery, home delivery, clean birth practice, thermal care of newborn, infant feeding, health service utilisation

Table 10 Characteristics of clusters in interventions groups of included studies

Study	Pregnant women per group %	Coverage group	Allocation	Area	Facilitators per cluster	Meeting frequency	Existing cluster activities	Education level/literacy of cluster
Manandhar 2004	37	756	Pair matched	60 km^2	1 per cluster	Monthly per ward	Some groups set up by local female community health volunteers already existed but activities were sporadic	none: 82% primary: 12% secondary or higher: 7% illiterate: 66%
Azad 2010	3	1414	stratified	NR	Each facilitator 18 groups	Month	NR	none: 50% primary: 32% secondary or higher: 18%
Tripathy 2010	37	468	stratified	NR	Each facilitator 13 groups per month	Monthly	18 clusters-172 existing women's groups involved in savings & credit activities.	none: 78% primary:6 % secondary or higher: 16%
More 2012	2	788	NR	NR	1 per cluster	fortnightly	slum women's groups existed in some clusters, focus on single issues	none:23.7 % primary: 5.2% secondary or higher:71.1%
Colburn 2013	10	1200	stratified	NR	Each facilitator:9 women's groups	NR	NR	NR
Fottrell 2013	36	309	Stratified	NR	NR	Monthly	162 women's groups already set up continued monthly meetings until June 2011	none: 25.2% primary: 36% secondary or higher:38.8% illiterate: 29.8%
Lewycka 2013	51	440	NR	NR	1 per cluster	NR	NR	none: 20% primary:73% secondary or higher: 7%

Table 11 CONSORT Checklist – Assessment of reporting in the included studies

Item	Checklist item (with extension for cluster)	Manandhar 2004	Azad 2010	Tripathy 2010	More 2012	Colburn 2013	Fottrell 2013	Lewycka 2013
Title and abstract								
	Identification as RCT in title	Y	Y	Y	Y	Y	Y	Y
	Structured summary design, methods, results, conclusions	Y	Y	Y	Y	Y	Y	Y
Introduction								
Background & objectives	Scientific background & explanation of rationale	Y	Y	N	N	N	N	Y
	Specific objectives or hypotheses	N	N	N	N	N	N	N
Methods								
Trial design	Description of design including allocation ratio	N	N	N	N	N	N	N
	Changes after trial commencement with reasons	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Participants	Eligibility criteria for participants	Y	Y	Y	Y	Y	Y	Y
	Settings & locations where data collected	Y	Y	Y	Y	Y	Y	Y
Interventions	Interventions per group with details	Y	Y	Y	Y	Y	Y	Y
Outcomes	Pre-specified outcome measures	Y	Y	Y	Y	Y	Y	Y
	Changes to outcomes after commenced	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sample size	Sample size determined: Method of calculation, number of clusters(s) size, coefficient intracluster correlation, uncertainty	Y	Y	Y	Y	Y	Y	Y
	explanation of interim analyses & stopping guidelines	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Randomisation:								
Sequence generation	Method to generate random allocation sequence	Y	Y	Y	Y	Y	Y	Y
	Randomisation; details of any restriction	Y	Y	Y	Y	Y	N	Y
Allocation concealment	Random allocation sequence, steps taken to conceal the sequence until interventions assigned	Y	Y	Y	Y	Y	N	Y
Implementation	Random allocation sequence, participant enrolment	Y	Y	Y	Y	Y	N	Y
	Who generated random allocation sequence, enrolled clusters & assigned clusters to interventions	Y	Y	Y	Y	Y	Y	Y
	Mechanism by individual participants included in clusters for purposes of trial	Y	Y	Y	Y	Y	Y	Y
	where consent was sought & whether consent sought before or after randomisation	Y	Y	Y	Y	Y	Y	Y

Blinding	who blinded after assignment to interventions	Y	Y	Y	Y	Y	Y	Y
	description of similarity of interventions	N	N	N	N	N	N	N
Statistical methods	Statistical methods to compare groups outcomes	Y	Y	Y	Y	Y	Y	Y
	additional analyses,	Y	Y	Y	Y	Y	Y	Y
Results								
Participant flow	numbers randomly assigned, received intended treatment & analysed for primary outcome	Y	Y	Y	Y	Y	Y	Y
	losses & exclusions after randomisation, with reasons	Y	Y	Y	Y	Y	Y	Y
	Dates of recruitment & follow-up	Y	Y	Y	Y	Y	Y	Y
	Why the trial ended or was stopped	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	baseline demographic, clinical characteristics	Y	Y	Y	Y	Y	Y	Y
Numbers analysed	participants included in analysis & whether analysis by original assigned groups	Y	Y	Y	Y	Y	Y	Y
Outcomes and estimation	primary & secondary outcome, results & the estimated effect size & its precision	Y	Y	Y	Y	Y	Y	Y
	binary outcomes, presentation of both absolute & relative effect sizes is recommended	Y	Y	Y	Y	Y	N	Y
Ancillary analyses	Results of other analyses performed, subgroup, adjusted analyses, distinguishing pre-specified from exploratory	Y	Y	Y	Y	Y	Y	Y
Harms	important harms or unintended effects in each group	N	N	N	Y	Y	N	N
Discussion								
Limitations	Trial limitations, sources of potential bias, imprecision, &, multiplicity of analyses	Y	Y	Y	Y	Y	Y	Y
Generalisability	Generalisability of the trial findings	Y	Y	Y	Y	Y	N	Y
Interpretation	Interpretation consistent with results, balancing benefits & harms, & considering relevant evidence	Y	Y	Y	Y	Y	N	Y
Other information								
Registration	Registration number and name of trial registry	N	N	N	N	N	N	N
Protocol	full trial protocol can be accessed, if available	N	N	N	N	N	N	N
Funding	funding and other support, role of funders	Y	Y	Y	Y	Y	Y	Y

Y = Reported N = Not Reported N/A = Not Applicable

Table 12 Assessment of Risk of Bias in included studies

Random sequence generation*	Allocation concealment*	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Manadhar: 2004						
LOW: Page 971: Matched 42 clusters, 21 pairs topographic stratification, ethnic group distributions, & population densities. List of random numbers used to select 12 pairs.	LOW: Page 971: Randomly allocated one cluster per pair to intervention or control on basis of coin toss.	HIGH: Page 972: Due to nature of intervention trial allocation not masked.	HIGH: Page 972: Analysis of primary & secondary outcomes not done until before data monitoring committee meeting at 30 months, not stated if assessors blinded.	LOW: Page 975, figure 3: Loss to follow up 5.4% and 5.0% in intervention &control. breakdown in figure 3	LOW: Page 975: All outcomes reported. Table 3,4	LOW: Page 976: Small baseline difference in poverty and literacy favouring intervention. Authors do not consider these could account for differences in mortality.
More: 2012						
LOW: Page 3: "In transparent process, social workers external to trial drew lots to select 48 clusters in blocks of eight per ward".	LOW: Page 3: same process used to allocate four clusters per block to intervention and control. "chose this method because of emphasis on participation and demystification of research."	HIGH: Page 3: nature of intervention precluded allocation concealment.	HIGH: Page 4: Analysts blind to allocation. Page 7: local residents birth and death identifiers were aware of intervention in community, but focused on their task and did not dwell on comparative nature of trial.	UNCLEAR: Page 5 figure 2: Achieved interviews for 84% and 83% births in intervention and control. Some disparity across arms between interviews follow up of stillbirths and neonatal deaths.	LOW: Page 7,9: All outcomes reported	LOW: Page 4: Baseline difference in age, Islam faith, poverty index, neonatal mortality. Unadjusted are primary analysis but adjusted analyses given.
Azad: 2010						

LOW: Page 1194: Clusters “randomly allocated to intervention or control stratified by district in presence of project staff and external individuals. Cluster names written on pieces of paper, folded and placed in a bottle.”	LOW: Page 1194: For each district first three cluster names drawn from bottle allocated to women’s group intervention and the remaining to control. project manager drew papers from bottle. allocation sequence decided upon by project team before drawing papers.	HIGH: Page 1195: “Neither study investigators nor participants masked to group allocation.”	HIGH: Page 1195: No specific details given for those analysing data	LOW: Page 1198: Interviews completed 84% and 82% births in intervention and control. Main reason across groups for failure to interview was maternal migration	LOW: Page 1199: All outcomes reported table 2,3	HIGH: Page 1194: Control clusters included three areas with substantially worse health & socioeconomic indicators than rest of study area. researchers did not know this difference before recruitment and allocation of clusters therefore not excluded before allocation. Adjusted analyses undertaken but primary analyses all
Tripathy: 2010						

LOW:Page 1183: external observer drew folded papers with numbers corresponding to clusters. done separately for each district.	LOW: Page 1183, figure 2: first clusters drawn from basket allocated to intervention group, rest to control. undertaken in presence of external observers.	HIGH: Page 1183: “Because of nature of intervention, neither intervention team nor participants were masked to assignment during trial.”	HIGH: Page 1191: “no incentives or disincentives for under or over reporting deaths and births and several processes put in place to detect error”	LOW: Page 1187, figure 6: Loss to follow up <1% and 2% in intervention and control.	LOW: Page 1187: All outcomes reported table 2,3	LOW: Page 1187: baseline differences show greater poverty and disadvantage in intervention clusters. Adjusted analyses given, do not influence findings.
Colburn: 2013						

LOW: Page 6: “Clusters allocated to each, both or no intervention with random number sequence. Randomisation stratified by interventions and district, numbers of intervention and control in each district balanced.”	LOW: Page 6: ensure concealment of intervention allocation, identification numbers assigned for each cluster and random number generated for each. numbers sorted in ascending order, and new 'order' variable generated. sequence used to allocate each of intervention groups. sequence concealed until interventions assigned. One researcher generated allocation sequence and assigned clusters to groups in presence of two researchers.	HIGH: Page 6: Neither participants nor those administering interventions blinded to group assignment.	HIGH: Page 6: analysis plan was pre-specified before final analysis carried out.	HIGH: Page 10: 29% loss to follow up. Authors suggest birth rates in study matched expected from crude birth rate within 3%, and in-migration probably broadly matched out-migration, many pregnancies recorded by key informants as ‘lost to follow-up’ may have been recorded as pregnancies by mistake, true loss-to-follow-up probably much lower. Little difference in loss-to-follow-up between arms. maternal deaths verified, 299/2087 (14.3%) stillbirths and neonatal deaths unverified.	LOW: Page 10: All outcomes reported tables 2-6	LOW: Page 13: No data on individual level covariates. Small cluster variations found, adjustments made no difference to unadjusted models.
Lewycka: 2013						

LOW: Page 8: Random number sequence generated	LOW: Page 8: Clusters allocated randomly. Two researchers allocated clusters using random number sequence.	HIGH: Page 8: nature of interventions masking of allocation impossible at participant level.	HIGH: Page 8: Masking at level of analysis and trial monitors. Data collected independently, implementation no results fed back to inform intervention.	LOW: Figure 4: Participants loss to follow up accounted for.	LOW: Page 17: All outcomes reported tables 3-6	UNCLEAR: Page 17: Some small baseline difference. Limitations section in discussion difficult to follow
Fottrell: 2013						
LOW: Page 2: Same randomisation sequence in Azad 2010	LOW: Page 2: Same allocation concealment in Azad 2010	HIGH: Page 3: Neither study investigators nor participants masked to group allocation.	HIGH: No details given for analysts.	LOW: Page 5: 99% of interviews completed, interviews not completed due to maternal migration	LOW: Table 2: All outcomes reported	LOW: No other bias

CHAPTER 5: MATERNAL EMERGENCY TRANSPORT IN LOW AND MIDDLE INCOME COUNTRIES: A SYSTEMATIC REVIEW AND THEMATIC SYNTHESIS OF QUALITATIVE STUDIES

ABSTRACT

Background: Most maternal deaths are preventable with emergency obstetric care, therefore ensuring access to healthcare services is essential. A core component of access to care is emergency transport. Despite the acknowledged link between availability and accessibility of transport and health, there is little focused information on emergency transport of pregnant women.

Methods: Systematic review and thematic synthesis of qualitative studies on transport for emergency obstetric care. MEDLINE, EMBASE, BNI, Cochrane library, CINAHL, African Index Medicus, ASSIA, QUALIDATA, the Reproductive Health Library, and the Science Citation Index were searched (inception-April 2012) without language restriction. Studies using qualitative methodology (focus groups and interviews) were included.

Results: Searches identified 29 relevant articles. Eight major themes were identified: time for transport, transport options, geography, local support, autonomy, culture, finance, and ergonomics. Key issues were availability and speed of transport, terrain (mountainous, flooded or eroded), meteorological (rain or heat), support (family, community and professional), dependence on others for decision-making, cultural issues (preference for traditional health worker, embarrassment and beliefs), cost, lack of comfortable and safe positioning during transport.

Conclusions: Individual themes should be appreciated within local context to provide illumination on local barriers and facilitators. Some potential solutions include motorcycle ambulance programme or collaboration with local minibus taxi services, community education and empowerment (raising awareness with women, partners,

birth attendants and leaders), subsidies, insurance schemes and vehicle and road maintenance.

Impact of review: Published in International Journal of Gynecology and Obstetrics, informed ongoing transport project in Pakistan

Citation of published work on which this chapter is based:

Amie Wilson, Sarah Hillman, Mikey Rosato, John Skelton, Anthony Costello, Julia Hussein, Christine MacArthur, Arri Coomarasamy: A systematic review and thematic synthesis of qualitative studies on maternal emergency transport in low-middle income countries. **International Journal of Gynecology and Obstetrics**. 2013:122: pp192–201

5.1 BACKGROUND

Transport and health are inextricably linked, with transport services relating to numerous aspects of healthcare, not just moving patients to a place of care. Transport systems are needed to ensure attendance of healthcare providers and adequate medical supplies including equipment, drugs and blood for transfusion services. Numerous reports have suggested mobility and transport as key requirements and determinants for health (138-142). Within the UK, the National Health Service acknowledges the positive impacts that an effective and affordable transport system can have on health outcomes (143), particularly in emergency cases.

In many low income countries it is estimated that less than one percent of the population has access to conventional emergency transport, such as an ambulance (144). Motorised vehicle ownership is rare in low income countries, with the vehicle to person ratio as low as 30:100,000 people. Such shortage of vehicles means that very

few people have access to transport for work, social or health purposes, even though transport systems were recognised as a fundamental human need over three decades ago (145). For many, access to transport services is not within easy reach; in Ethiopia, approximately half of all rural households had to travel distances over 15km to access public transport (141). Even if vehicles were available in many low income countries, road systems are insufficient (146), and often unsafe (147).

Most births in low and middle income countries occur outside of health facilities (138), and as most obstetric complications are unpredictable, access to emergency care in a timely manner is essential to reduce preventable deaths. Transport has a critical role in achieving MDGs 4 (reducing child mortality), 5a (reducing the maternal mortality) and 5b (achieving universal access to reproductive health care)(148). The majority of research on transport and health is concentrated on high income countries, and relates to safety (140, 149), or the associated health risks with specific modes of travel (e.g. flying and deep vein thrombosis (139). The research conducted in low and middle income countries often relates to pollution or the spread of communicable diseases such as HIV (139). There is little focused and rigorously evaluated research on emergency transport of pregnant women (139, 141, 149-151). Many reports that explore the role of transport on maternal health do not take into account the cultural, geographical and financial barriers to effective, efficient and acceptable transport. There is also limited synthesis and insight on emergency transport of pregnant women (139, 141, 149, 150).

In this systematic review, we examine the qualitative literature on maternal emergency transport to explore people's experiences of using transport, the options available to them and the barriers and facilitators encountered. We focussed on qualitative studies to elicit insights on how transport systems work and what might be done to improve the

acceptability and availability of different transport modalities, to improve policy and programme interventions relating to transport.

5.2 METHODS

Data sources and searches

Databases were systematically searched for qualitative studies on emergency transport in low and middle income countries. MEDLINE, EMBASE, BNI, Cochrane library, CINAHL, African Index Medicus, ASSIA, QUALIDATA, the Reproductive Health Library, and the Science Citation Index (inception – April 2012) were searched without language restriction. Hand searching complemented electronic searches. The search terms were 'ambulance', 'motorbike AND ambulance', 'bicycle AND ambulance', emergency AND referral', 'emergency AND access', 'emergency AND transport', and 'ambulance AND emergency'. These terms were selected iteratively through scoping searches (76). Qualitative filters were used to refine the search ('focus group', 'qualitative', 'observational methods', 'interview', and 'narrative'). Studies were included if they contained qualitative data alone or if they had both qualitative and quantitative data.

Study selection and data extraction

Studies presenting primary data and utilising qualitative data collection methods (interviews and focus groups) were included if they reported the processes and experiences of emergency transportation to a place of emergency care in low and middle income countries. Studies that had no information on emergency transport, no qualitative data and no primary data were excluded. Studies from countries not classified by the World Bank as low or middle income were excluded (152). Titles and abstracts were scrutinised by the author plus another reviewer (AW and SH) and full manuscripts of studies meeting the inclusion criteria were acquired; disagreements

were resolved by discussion with a third reviewer (AC). Some studies which did not address maternal transport exclusively, but had relevant qualitative information were included.

Comprehensiveness of reporting:

Independent assessment of the reporting criteria was performed by the author plus another reviewer (AW and SH), using the COREQ framework of the consolidated criteria for reporting qualitative research. This framework aims to assess the trustworthiness and transparency of studies within their settings, by focusing on the research team and reflexivity, study design, and data analysis and reporting. (72)

Synthesis of findings:

Information was extracted on study characteristics, study quality and outcome data. Thematic synthesis (76) was used for analysis through examination and translation of common elements across the studies that explored transport in emergency obstetric care. Quotes from respondents and relevant texts in all studies were analysed by the author plus another reviewer (AW and SH). Both authors read and re-read texts. The data were then labelled to develop a code (75). Initial codes closely reflected the quotes from the manuscript. Codes were continuously refined and altered as more quotes were added. Codes then lead to the development of themes and a thematic framework was developed. The thematic framework was agreed between the author and another reviewer (AW and SH). Having applied the thematic framework to individual manuscripts, in order to build up a picture of the data as a whole and to consider the range of each theme, the data was charted. Charts were developed using themes against individual manuscripts. This method sought to develop an analytical framework, ensuring that the themes built up were cross-checked with other data within and then between studies, so that the validity of emerging explanations was tested and improved. This framework is shown in Figure 22.

5.3 RESULTS

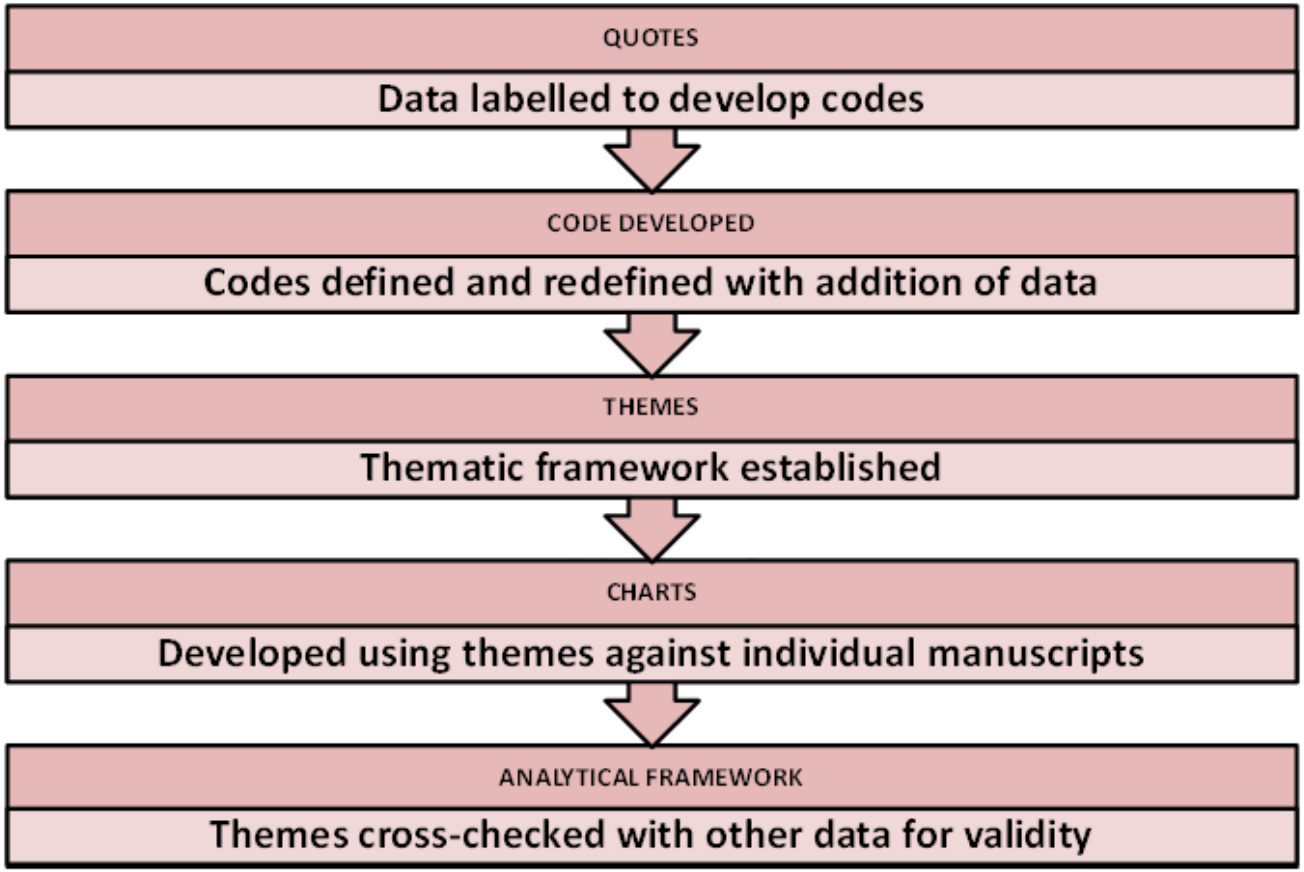
The literature search and study selection process is given in Figure 14. Twenty nine qualitative studies providing information on transport for emergency healthcare in low and middle income countries were included in this review. Study characteristics are included in Table 12, including participants, sample size, study setting, methodology and analytical process used, and the main themes explored in the study.

Study characteristics

All studies were set in developing countries. Five studies focused on the perspectives of transport officials or stake holders (149, 153-156), five studies on transport providers or operators (141, 144, 157-159) and two studies also focused on transport users (159, 160). Two studies focused on the perspectives of stake holders from the health sector (149, 154) and eleven studies focused on the perspectives of healthcare workers (161) (144, 155, 156, 159, 162-167). Six studies focused on the perspective of women who had experienced pregnancy complications (136, 141, 144, 168-170), and eleven on the family members of the pregnant women (14, 137, 156, 160, 161, 167-169, 171-173). Some studies gave multiple perspectives. Seven studies specifically addressed issues relating to transportation of pregnant women (136, 141, 149, 160, 165, 169, 174), whereas nine studies looked at emergency transport within wider issues relating to healthcare access (154, 156-159, 162, 163, 166, 170).

Fifteen studies collected data through the use of focus groups (136, 144, 149, 154-157, 159, 160, 163, 164, 166, 169, 174, 175) and twelve studies collected data through interviews (14, 137, 153, 158, 162, 165, 167, 168, 170-173).

Figure 22 Data analysis framework used in the review



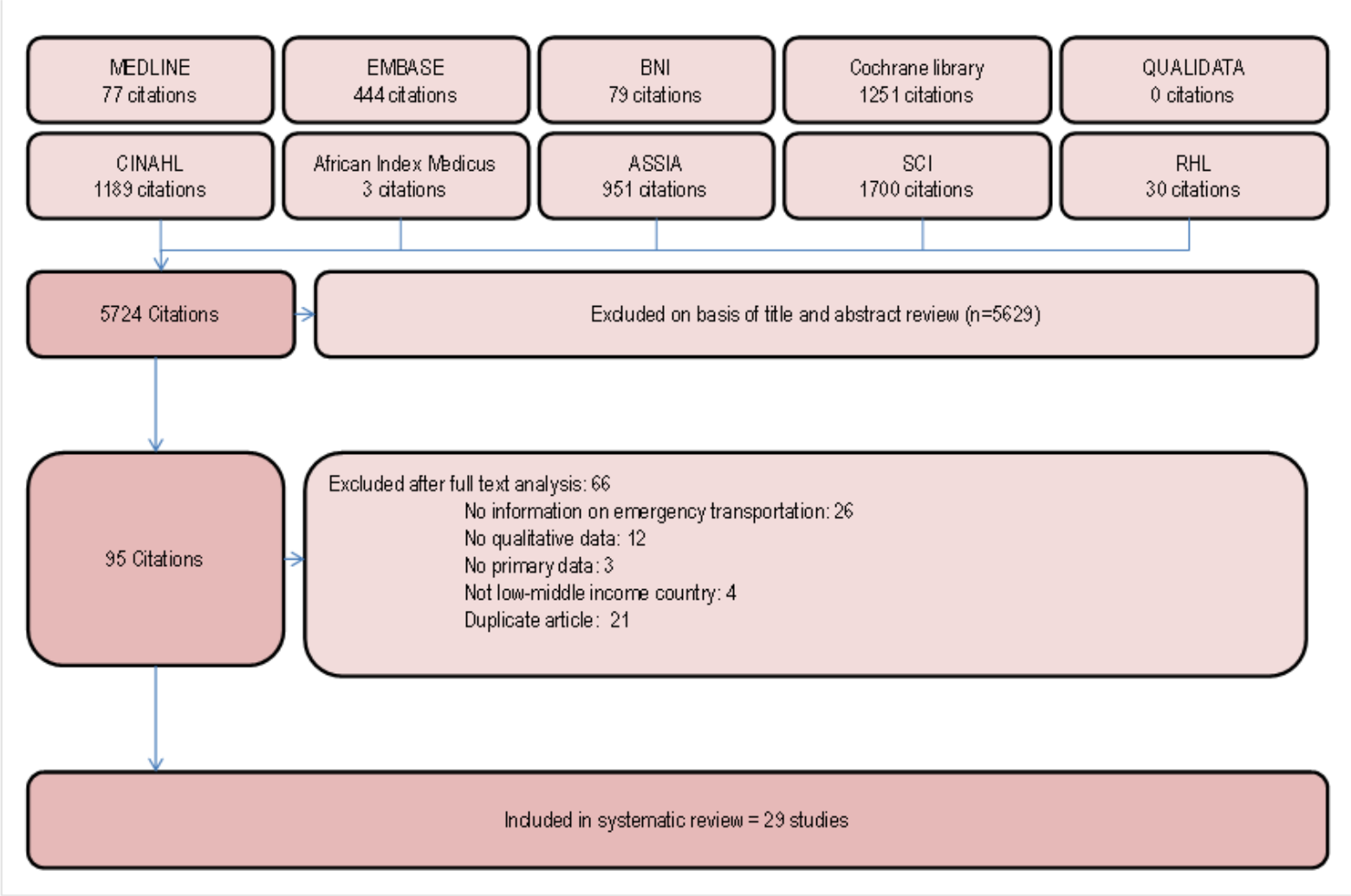


Figure 23 Study selection process and literature included within the review

Table 13 Study characteristics of studies included in the review

Study Setting	Perspective Participants	Focus of paper Themes	Data collection Response	Method* Analysis*
Benegusenga (149)	Stake holders of health & transport sectors. people at health centres	Ingobyi transportation	FGD. Int	PA
Rwanda	97 in Focus groups	TOGEF	NR	NR
Berhanu (141)	Medical personnel, patients, transport operators/users.	Safe transport for high risk patients	Qs. Int	MM
Ethiopia	NR	TOSGFE	NR	NR
Brentlinger (161)	Health workers, heads of households, village & council members, community leaders	Utilisation of pregnancy related service	Survey. Int	MM
Mexico	1227 women	TGCF	20 houses not int	NR
Cham (14)	Family members, persons present at death	Socio-cultural & health service factors associated with maternal death	Int	VA
Gambia	NR	TOSGFEA	10 cases NR	GT
D'ambruoso (171)	Relatives of dead women	Causes of maternal death & Socio cultural factors.	Int	VA
Burkina Faso, Indonesia	174 Relatives	TOACFE	NR	TA
D'ambruoso (172)	Final caregivers	Access to healthcare in obstetric emergencies	Int	VA
Indonesia	Families of 104 deceased women	TGFE	NR	TA
Hasan (157)	Community members, transport operators, doctors, nurses.	Relationship between mobility & access to health in remote areas	FGD. PA	NR
Bangladesh	300 households, 104 participants	TOGFE	NR	NR
Kawuwa (153)	Community, governmental or, female leaders, teachers, transport unions.	Maternal mortality Factors. Barriers to treatment of obstetric issues.	Int	NR
Nigeria	30 interviewees	SFG	NR	NR
Lori (168)	Women with severe morbidity/near-miss, family/carers of dead	Circumstances surrounding maternal mortality & severe morbidity	Int	Descriptive
Liberia	148 cases	TOF	NR	DA
Lungu (169)	Elders, chiefs, childbearing women/partners	Bicycle ambulances for referral of pregnant women	FGD. Int	MM
Malawi	10 villages.30 Focus groups. 92 Interviews	ACF	NR	Iterative
Magnanya	Stakeholders in the transport and health	Linkages between mobility & health	FGD	Exploratory

(154)	sector			
Kenya	389 respondents	TOSGFE	NR	PHA
Mashiri (162)	Homecare practitioner, leaders, community members, health officials	Influence of mobility and access on rural healthcare	Int. Qs. FGD	MM
South Africa	36 Interviews. 3 Focus groups	TOSGCFE	NR	NR
Mlay (136)	Women with obstetric emergencies or of reproductive age and men	Emergency transport needs of rural pregnant women	FGD. Int. Qs	MM
Tanzania	250 Interviews. 24 Focus groups	TOSGACFE	7/10 attended	TA
Muleta (155)	Health professional, road authority officials	Factors of healthcare facility access, development of obstetric fistula	FGD. Int	Case control
Ethiopia	170 participants	TOSGAFE	NR	LR
Nyamandi (144)	Childbearing women, village heads or health workers, parents, leaders, uhuru riders	Impact of the community ambulance among the community	FGD. Int. CS	MM
Zimbabwe	120 Interviews. 10 Focus groups	TOSGCFE	NR	NR
Oyesola (164)	Community members, nurses, doctors, management personnel	Attitudes, perceptions and practices to health care institutions.	FGD. Int	NR
Nigeria	NR	OSGA	NR	NR
Peterson (175)	Neighbourhood caretakers.	Referral of severely ill children to hospital	FGD	MM
Uganda	18 Focus groups	TOAF	77% after 2/52	DA
BEN (159)	transport users, healthcare providers, transport providers, local authorities	Relationship between access to health and access to transport	FGD. Int	MM
Namibia	118 transport users, 43 health providers, 23 transport providers 16 local authority members	TOSACFE	NR	NR
Maine (163)	Health providers.	Barriers of health-care facilities when obstetric problems arise	FGD	FGD
Nigeria, Ghana, Sierra Leone	184 Focus groups	TOSGACFE	NR	TA
Price (170)	childbearing women	Women's perceptions of barriers to EOC services, quality of care.	Int	Key Informant
Nepal	NR	TOGSC	NR	AF
Razzak (158)	Administrators of ambulance service and inpatients	Prehospital system, mode of transport used, barriers to ambulances	Int	Int
Pakistan	92 patients, 7 ambulance administrators	TOGAF	1 refused	EpiInfo

Samai (174)	community members	Mode of referrals and transportation	FGD	Preparatory
Sierra Leone	NR	TGF	NR	NR
Schmid (165)	Community members, leaders, healthcare providers/workers and traditional healers	Emergency transportation plans for urgent obstetric care.	Int	MM
Tanzania	110 Interviews	GA	NR	NR
Shehu (166)	community members, healthcare workers	Transportation problems, causes of poor use of health services	FGD.CS	MM
Nigeria	NR	TOSAFG	NR	NR
Strestha (156)	Mothers, fathers, grandmothers, health workers, district officials, transport organisations,	Transport barriers for health service access for females/poor people.	FGD.Int.CS	MM
Nepal	93 mothers and 121 health service users	TOSGCFA	NR	DA
Terra deSouza (137)	Mothers/female relatives of dead infants	Factors contributing to neonatal deaths.	Int	VA
Brazil	127 households	OSF	NR	TA
Turan (173)	Fistula patients and family members	Community mobilization and safe motherhood education	Int	Ethnographic
Eritrea	11 new patients, 5 family members, 15 follow up patients	TOSAG	26/102	DA
Urassa (167)	Relatives of dead women, healthcare staff	Operational factors in maternal death	Int	VA
Tanzania	117 maternal deaths	TOF	NR	NR
Whitby (160)	Staff, widows, transport users, women, health assistants, women's reps, fathers, couples	Mobility in maternal health	FGD.Int.CS.PA	MM
Indonesia	18 Focus group (15 participants each), 112 Interviews. 18 villages each (approx 20 participants)	TOGACFE	NR	NR

Key		E	Ergonomics	NR	Not reported
*	as reported by the authors	TA	Thematic analysis	T	Time for transport
Int	Interviews	GT	Grounded Theory	O	Transport options
MM	mixed methods	DA	Descriptive analysis	S	Local Support

Qs	Questionnaires	LR	Logistic Regression	G	Geography
CS	case study	PHA	Phenomenological analysis	A	Autonomy
VA	Verbal autopsy	AF	Analytical Framework	C	Culture
FGD	Focus group discussion	PA	Participatory approach	F	Finance

Comprehensiveness of reporting of included studies

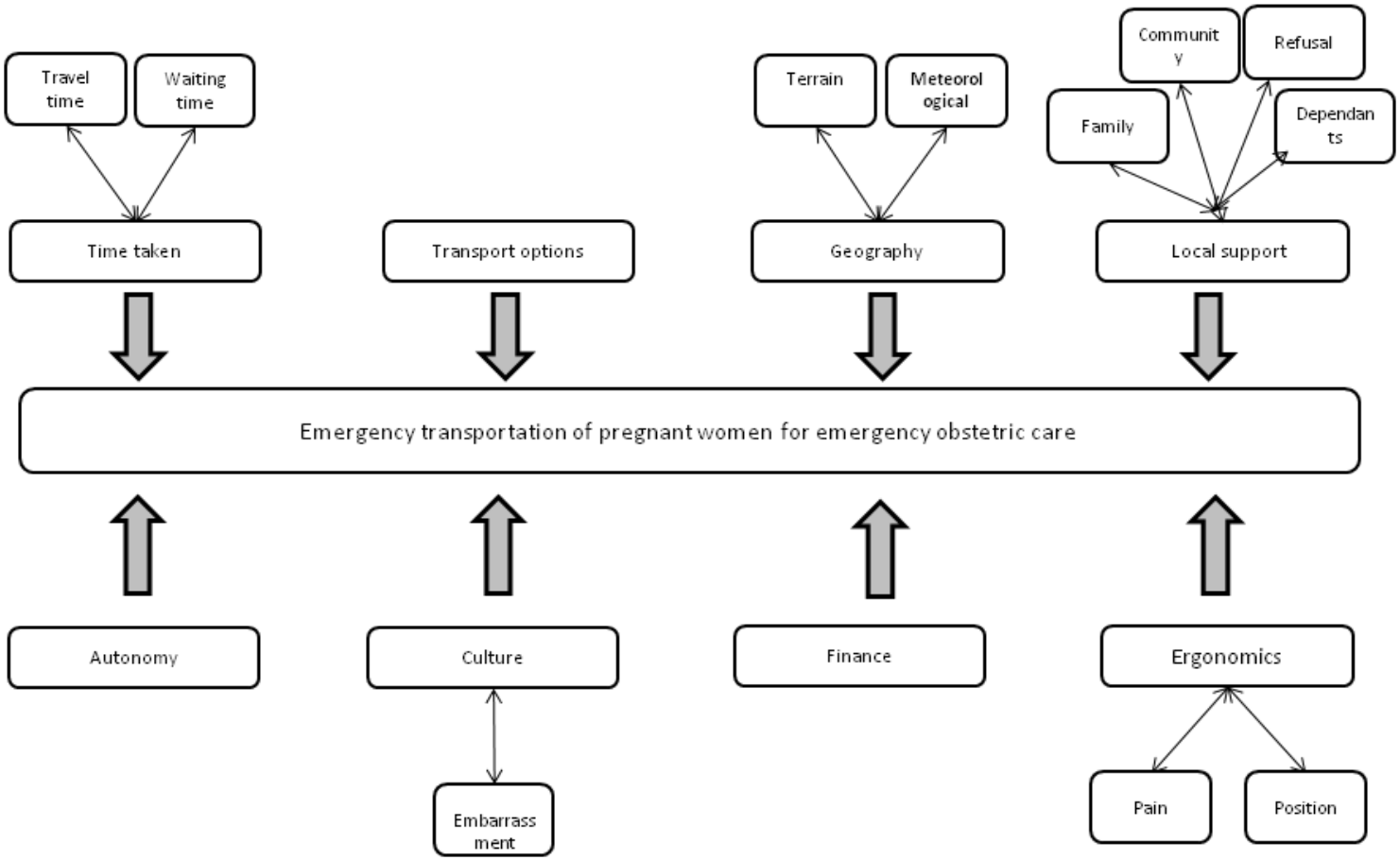
The comprehensiveness of reporting according to the COREQ checklist, varied across the studies (Table 14). Characteristics of the research team were reported in less than 40% of the papers (11/29) and the interviewers' relationship with the participants was reported in just 21% (6/29). The theoretical framework used was reported in 24% (7/29), although the sampling of participants was better described in 83% (24/29). Over half of the studies (62%, 18/29) provided an adequate description of the sample. The research setting was described in 55% (16/29) and the details of the interview guide were given in 45% (13/29). Derivation of the themes was reported in 66% (19/29). All studies (100%) showed consistency in data findings and reporting, and 86% (25/29) demonstrated clarity in reporting and presenting the major themes evolving from the study.

Synthesis

Many forms of motorised and non-motorised transport were used to access emergency obstetric care in low and middle income countries. Non-motorised transport modes included carrying, animal transport, bicycle, and walking. Motorised transport included cars, motorcycles, public and commercial transport, ambulances and jeeps. Various forms of motorised and non-motorised water transport were also used for emergency transport. The framework used is shown below

Eight major themes were identified Figure 24 . These were: time for transport, transport options, geography, local support, autonomy, culture, finance and ergonomics. Key quotes illustrating these themes, drawn from the studies, are provided in Table 14. Table 14 contains quotes that are grouped according to the final themes that developed.

Figure 24 Themes and sub-themes indentified in maternal emergency transport



Time for transport

This theme involves the time spent waiting for transport and the time spent travelling (speed of transport and distance covered). Eight studies reported travel and waiting time (14, 136, 144, 159, 160, 171, 172, 175).

Travel time: Various travel times and speeds of emergency transport were reported in the literature, ranging from 10 minutes to one full day to reach a health facility. Twelve studies reported the journey as being between two to six hours (136, 155-157, 160, 161, 166-168, 171, 173, 174) and six studies reported the time travelled as being in excess of six hours (136, 155, 156, 160, 166, 174).

"People must walk an hour and a half to get to the asphalt road"(160);

Long transport time was associated with mortality by the authors in three studies (156, 161, 167), and a timely transfer in one study demonstrated a favourable maternal outcome, whereas the majority emphasised the link between a lengthy journey and maternal death. One study reported an increase in mortality by 9% for every thirty minutes of vehicular travel. (176)

"My life was saved as the Uhuru served me when I had complications at my last delivery. I was transported from the clinic to the hospital just in time and at a very low price"(144);*

"We took her to the health centre in the village... She was examined by a nurse who later transferred her to another health centre (44km away). There she spent the night, the following morning she was transferred to the hospital (36km away), on our way we had to cross the river at two different crossing points. Immediately after we reached the hospital she died"(14).

*Motorcycle ambulance

Waiting times: Participants in seven studies commented on the amount of time they had spent searching for, or waiting for transport to arrive; (14, 136, 144, 159, 160, 166,

175) a wait of up to two days was reported in two studies.(136, 166) Maternal and neonatal deaths were reported while waiting to travel by public transport. (177)

"I waited for transport [local public bus] for two days because the bus, the only one that comes to our village was out of order."(136);

"Patients get exhausted and even die whilst waiting for an ambulance"(159)

Transport options

Nine studies reported difficulties in finding transport, (136, 144, 155, 156, 160, 164, 171-173) and participants from two studies described the complete lack of transportation (14, 171).

"We looked for transport in the village throughout the night but could not get one"(14);

"Men carried me on their shoulders to a bus stop at Erri Central (about 14 km from Kokmay) where I boarded a local bus to Babait Hospital. There was not any other option."(136)

Availability of transport options, or the lack of transport options, appeared to vary according to geographical location, especially within remote rural areas and economic situations, which can be dependent on distribution of public sector spending (178). Full occupancy of vehicles preventing transport of the patient were reported in four studies (14, 136, 162, 163).

"We took her to the main road to look for transport. We were there up to 12 midnight but couldn't get transport. All vehicles that came were full"(14)

Geography

This theme describes the geographical (terrain) and meteorological aspects related to transport of emergency obstetric patients. Five studies reported that weather conditions or state of roads affected emergency transport (136, 160, 162, 172, 173).

Terrain: Two studies reported poor road conditions, due to mountainous, flooded or eroded terrain (136, 160), although this was not in reference to a specific mode of transport.

"The road is too rough going up the hills and down the valleys"(136)

"A lot of roads have holes"(160).

Terrain is suggested to directly affect the ability of women reaching emergency care.(153) However, some forms of transport such as the Uhuru (144) or eRanger (179) (motorcycle ambulance), were effective because they were particularly compatible with the local terrain.

"Uhuru is the answer to rural transport irrespective of terrain"(144)

Meteorological: Heavy rains are cited in four studies as affecting emergency transport.(136, 160, 162, 172) These studies showed that inaccessible roads during the wet season can cause delays to journeys and unreliable operation of public transport services.

"I was very uncomfortable travelling for 7 hours on a full bus, the roads were very slippery because of the heavy rains which made it worse"(136)

Two studies suggested that the efficiency of different methods of transport varied with seasonal changes (156, 160). These studies showed that public transport was more reliable in the dry season although temperatures at this time of year impacted negatively on the journey experience.

Local support

The theme of local support includes the different sources of support and lack of support for pregnant women to access and use emergency transport. Participants from eight studies commented on the amount, or lack of support they received from the following sources; (136, 137, 144, 154, 160, 162, 171, 172)

Family: Three studies showed that family support, particularly a husband's support, is necessary to access emergency transport.(155, 166, 175) However, two studies showed that arrangements for childbirth, including emergency care and transport, are the sole responsibility of women. (136, 165) Only one study reported that women had received support from their husbands.(136) The lack of support and women feeling alone when needing emergency transport was highlighted in three studies. (136, 171, 172)

"When you are in danger you are just left alone at home with your young children. What can you do, you cannot go to seek help and leave the children alone."(136)

Community: Four studies described community support or involvement in emergency transport; this varied from physical labour when carrying a patient on a stretcher, to providing means of transport, such as bicycles or cars, or financial contributions.(136, 154, 160, 162)

"In emergency situations, we cannot rely on hospitals and clinics....we have to depend on community members with a car or a taxi to help us"(162)

Dependents: In two studies women voiced the constraints they faced when seeking emergency transport while also looking after young children (136, 137).

"*Transportation was difficult, and I also have four other young children"(137)*

Refusal: Owners or drivers of vehicles refuse to provide emergency transport, it is suggested that this was because they were concerned about soilage in the case of haemorrhage (166) or the legal implications if a woman died whilst in transit (163).

Autonomy

This theme includes personal, financial, educational or family autonomy and can be facilitated or removed by family, community and other decision makers. A distinction

can be made between support and autonomy: for instance, a woman's partner can be supportive without affording her autonomy. The financial dependence of women on their husbands and families compromises their autonomy in accessing and using emergency care (136). Two studies expanded on this, finding that women were economically dependent on men, and had restricted or no independent finances to access and use emergency transport, unless designated by their husbands (160, 163).

"They [husbands] do not give a cent for transport"(136)

Three studies suggested that women relied on others for decision making with regards to emergency transport (136, 155, 163). Research found that women forgo emergency transport due to the domestic constraints or limitations placed on them by their husbands (162).

Culture

Various socio-cultural aspects associated with emergency transport were evident throughout the literature. Six studies discussed how existing cultural beliefs or social practices affected emergency transport of pregnant women. (14, 136, 160, 163, 169, 171) One study discussed how emergency transport was not kept readily available as this was considered bad luck (170), whereas another study reported how pregnant women were deterred from using the bicycle ambulance, believing that publicising the onset of labour had the potential to summon evil spirits (169).

"Here if people see you going to the hospital for a delivery, they can bewitch you."(169).

Embarrassment: One study showed that users of emergency transport found the experience embarrassing and shameful particularly when they were bleeding heavily (136). This might be particularly distressing for women from regions where menstruation and bleeding are associated with pollution taboos. (170).

"I cannot explain how bad it was, bleeding whilst riding a bicycle up hills and down valleys" (136)

Social exclusion and difference in caste within cultural groups was cited as a barrier to emergency transport services. However one study found that all social classes within a specific region were able to use the 'Uhuru' without any discrimination (144).

Finance

The theme of finance involves the capacity or inability to pay for emergency transport, due to poverty or excessive transportation fees. Two studies highlighted that users felt they were financially exploited when in need of emergency transport (155, 156). The high cost of emergency transport was reported by respondents in five studies (136, 158, 160, 162, 171). The costs escalated during the evening, the rainy season, where vehicle availability was limited, and where military road blocks were present (161).

"The transport in our village is only lorry and very difficult for poor people to rent because it is very expensive" (160)

"The ambulance was going to be very expensive which is why I was obliged to bring her by bicycle" (171)

Motorcycle ambulance was found to be affordable in one study, in which 100% of respondents felt they could afford the 'Uhuru' (motorcycle ambulance) despite only 20% being in formal employment (144).

"My life was saved as the Uhuru served me when I had complications at my last delivery. I was transported from the clinic to the hospital just in time and at a very low price"(144).

"All the villages are far from the main road and there is a problem to get transportation and this creates a good opportunity for heavy truck drivers to make a fortune from these poor women"(155);

Transport costs to health institutions are often higher than most people can afford (154). For example, only 12% of participants in one study reported that there was an affordable vehicle available to hire (144).

Ergonomics

This theme encompasses the ergonomics of the transport, the journey experience and the comfort of the transport. Four studies commented on aspects relating to transport ergonomics (136, 155, 160, 171).

Pain: Two studies reported that users experienced pain when using emergency transport, particularly bicycles (136, 155, 163). In one of these studies 80% of respondents reported experiencing a painful journey, however the type of vehicle used was not reported (163).

"One can use a bicycle to take a pregnant woman to a hospital, but you can see the pain she is going through when you go through the rough roads"(136);

"A car [ambulance] would be great help because you will not experience the horrible bumps as you go to the district hospital"(136).

Position: The acknowledged optimal position for transfer of an obstetric patient is horizontal, with a left lateral tilt. Transport users are reported as feeling incapable of adopting the position required for emergency transport on a motorcycle (172). Benegusenga et al reported that 66% of respondents who had lost their child believed that their position during transit may have been responsible (149).

5.4 DISCUSSION

Findings

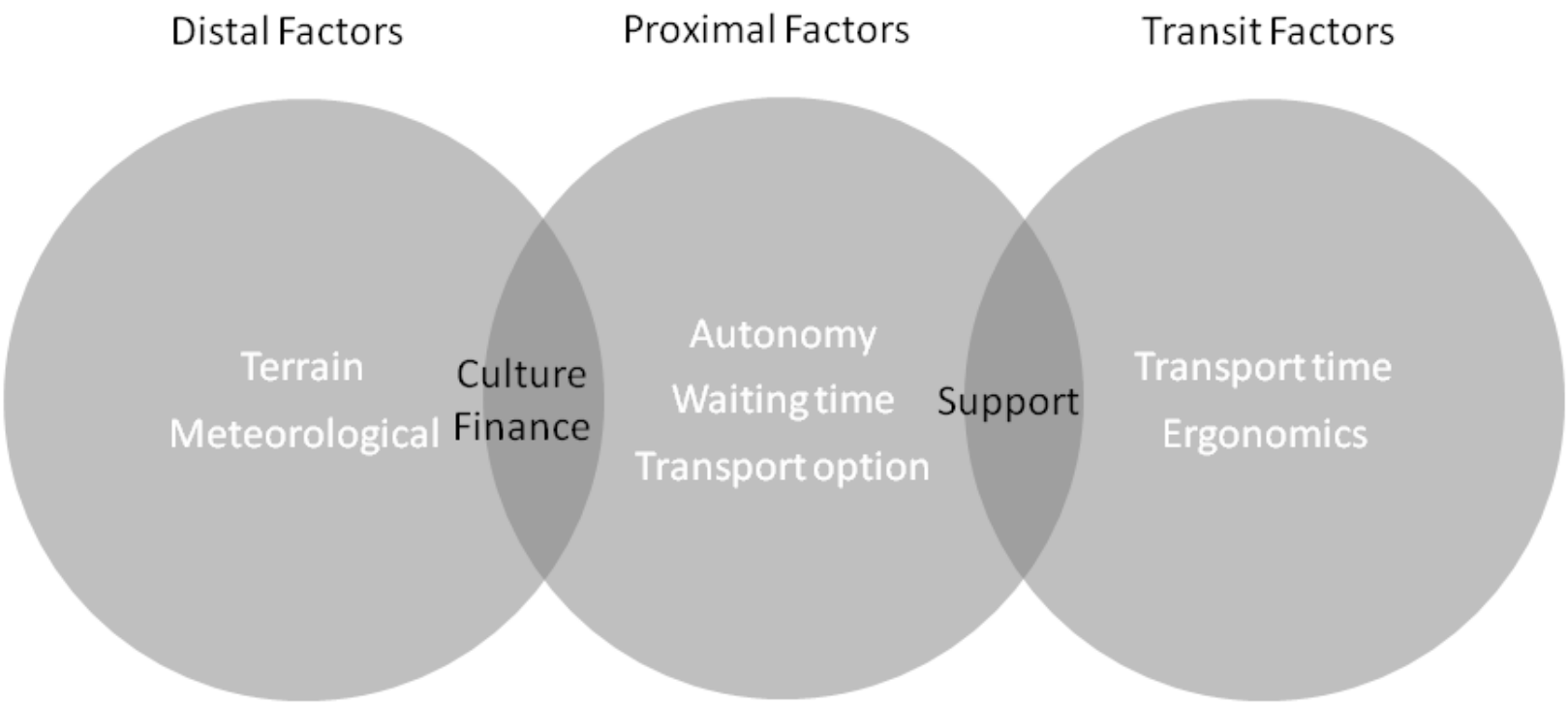
Eight themes emerged from this synthesis of primary studies. The data showed the breadth and depth of the issue of emergency transport for pregnant women, and the

many interlinked physical, psychological, financial, social and cultural facets. It is apparent that the assumption that increasing transport will simultaneously increase accessibility of healthcare, and thus reduce maternal mortality, is not necessarily correct unless attention is paid to key proximal and distal factors (Figure 26).

There is a scarcity of well designed and conducted research on emergency transport of pregnant women in low and middle income countries, and little conclusive evidence on the effectiveness of such transportation (180). A literature review (181) examining auxiliary technologies related to transport and communication for obstetric emergencies highlighted the most significant issue was the short time interval available for action, limiting options for obstetric referrals. It also concluded through 'cumulative experience' that motorised transport is likely to be the most acceptable and effective transport option. Comprehensive reports (182) have focused on the 'second delay', the delay in reaching care, rather than focusing on transport alone. Such reports explore the conceptual understanding of the 'second delay', and review infrastructure, finances and communications in emergency obstetric care, as well as suggesting steps to tackle the 'second delay'. Such reports often lack the perspectives of transport users themselves, or provided limited information on their views.

This systematic review and meta-synthesis of qualitative research will enrich current knowledge on emergency transport of pregnant women. The intention of this review was to provide an overview of emergency transport and a fuller insight into the barriers and facilitators associated with emergency transport, drawing on the perspectives of transport users themselves. The review was not intended to be generalisable to every low and middle income country, instead individual themes, facilitators and barriers could be appreciated within local contexts.

Figure 25 Determinants of emergency transport



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Overcoming barriers and suggested facilitators

Several means of emergency transportation in low to middle income countries were identified within the review although the results highlight that the suitability of emergency transport can vary between geographic locations and across seasons and cultures. Within this context the optimal means of emergency transport for obstetric patients would need to be capable of travelling at a reasonable speed, with immediate arrival to the woman in need and ensure a timely transport.

Reducing time for transport: More than 60% of people in low income countries live more than 8km from their nearest health care facility (183), and maternal mortality is estimated to increase by a rate of 2% with every 10% increase in distance travelled to reach a place of care (183). There is therefore a need for an efficient and effective emergency transport service, to ensure women receive timely life-saving obstetric care. One study reduced the time for transport by placing motorcycle ambulances in the community (144), whereas another provided clear guidelines for emergency transport to prioritise the use of the vehicles, although details of these were not provided in the manuscript (184).

Improving transport options: Transport options can be improved if a suitable, reliable, affordable service is available for pregnant women. For instance, an ongoing programme that has facilitated transport of labouring women in Pakistan involves a partnership with the local minibus taxi service; the taxi drivers provide an emergency service, including out-of-hours, for a fixed fee which is reimbursed from community and charitable sources (185).

Overcoming geographical barriers: A number of studies have recommended ways of overcoming geographical barriers by road (149). Exploration of local topographical challenges before investment in a specific emergency transport type (186), and

collaborating with local services suited to local terrain, such as minibus taxi services, can facilitate effective transport (185).

Improving local support: Community education and awareness raising programmes have been shown to increase support and assistance for pregnant women requiring emergency transport (166). For example drivers of commercial vehicles were reluctant to transport pregnant women, and often charged exorbitant fees. Following community mobilisation schemes and training, transport users gave a much more positive response, and transport providers were more amenable in providing transportation (166). Furthermore community education may address the cultural or social beliefs resulting in a lack of support, or the lack of realisation and awareness of the need for emergency transport (14). Women's groups could potentially be used to overcome the physical barrier caused by dependants when space constraints are present, for example on public buses (120).

Enhancing autonomy: Women's groups, particularly participatory action groups, can play a key role in empowerment and education of women and wider community (120). The restricted independence some women face may pose an obstacle for emergency transport. This may apply to a lack of financial independence, or a dependence on other family member for decision making (166). Community awareness raising and advocacy in support for safe motherhood may contribute to the success of emergency transportation projects (165, 179). It is suggested that transport is effective if the scheme is owned and accepted by the local community (187), although communication, advocacy and stable leadership are necessary to facilitate autonomy in emergency transport.(186)

Addressing culture: Social exclusion and difference in caste within cultural groups was cited as a barrier to emergency transport services, however one study (144) found that

all social classes within a specific region were able to use the 'Uhuru' without any discrimination (144). Shehu recommended that pollution taboos (166) could be challenged by educating transport operators. Community education and awareness raising also have the potential to influence cultural beliefs.

Addressing finances: Money is not an absolute barrier, as relatives are sometimes able to collate necessary funds (163). Four studies supported this finding, showing that people often sold livestock and other resources, or organised loans to raise funds for emergency transport (155, 159, 171, 175). Access to emergency transport was facilitated by subsidies from the local community (e.g. financial or resource) (136) or insurance schemes (e.g. poverty certificates) and charities and non-governmental organisations. Transport schemes organised and ran by the local community such as the Ingobyi scheme (locally made stretcher) can reduce financial barriers, and facilitate emergency transport. The scheme requires small, affordable financial contributions from members of the community which desire to be members of the scheme. Contributions ensure the maintenance of the vehicle and correct management of its use, so it is available and free to use in emergency situations (149).

Addressing ergonomics: Achieving a safe and comfortable position is a key barrier in emergency transportation of obstetric patients. Nyamandi et al reported that respondents described the Uhuru (motorcycle ambulance) as a safe, effective emergency form of transport, particularly as the trailer could be adapted to suit the position of the passenger (144).

5.5 CONCLUSION

To achieve a suitable, efficient, effective, reliable, acceptable and affordable means of transport, a number of key recommendations can be made. Clear guidance should be

given to prioritise the use of the vehicle for emergency transport (184).If vehicles can be isolated for emergency use only this can be beneficial. There should be consistency in the availability of affordable transport options, suitable for use by pregnant women, allowing them to be transported in the optimal left lateral position. The vehicle of choice should be compatible with local economy. For example if the transport is being funded by the government or health ministry, the quality and type of vehicle may differ from the transport that is being funded by the community itself.

Transport type should be compatible with local terrain. It is also beneficial if the transport is accepted and appreciated by local customs and cultures, this is to minimise potential obstructions to use by community members and peers. Literature within this review has suggested that this is particularly important, not only with transport type but the cultural perspective of seeking and receiving maternity care.

Drivers and communities should be educated in the importance of emergency obstetric transport to remove potential barriers. A project that has been shown to have greater effect once the community are involved is the Havelian project. Through education of local stakeholders, and promotion by religious leaders, the project experienced greater success and was utilised by more women (185). Similar effects have been demonstrated in the many eRanger projects globally (179).

Table 14 Quotes used in data analysis from the studies included in the review grouped according to themes

Time for transportation
Travel time
"It took a long time, because we walked slowly" (171)"People must walk an hour and a half to get to the asphalt road"(160) "I took my husband's bike and rode very fast"(136) "My life was saved as the Uhuru served me when I had complications at my last delivery. I was transported from the clinic to the hospital just in time and at a very low price"(144) "I was very uncomfortable travelling for 7 hours on a full bus, the roads were very slippery because of the heavy rains which made it worse"(136) "We took her to the health centre in the village... She was examined by a nurse who later transferred her to another health centre (44km away)There she spent the night, the following morning she was transferred to the hospital (36km away), on our way we had to cross the river at two different crossing points. Immediately after we reached the hospital she died"(14)"It was raining heavily, so when they called the midwife it took longer for her to arrive. Because the rain was heavy, she could not be saved by the time the midwife arrived"(172)"We arrived at the means of transport 1 hour after she died"(171) "The journey took two hours"(171) "Walking to Babati is too far, maybe 7 hours." (136)
Waiting time
"I had to wait for the public pus"(136) "We took her to the health centre in the village... She was examined by a nurse who later transferred her to another health centre (44km away) There she spent the night, the following morning she was transferred to the hospital (36km away), on our way we had to cross the river at two different crossing points. Immediately after we reached the hospital she died"(14)"Four vehicles are available to rent every afternoon, if there is an emergency before that, there is no vehicle available, nor is the mobile health unit available, the patient can only wait"(160)"If you do not have the money you have to look for it first. Sometime you may even have to spend a day or two looking for the money for the treatment. If you have coffee then you first sell it before you go"(175). "The following morning we went to the agricultural department to look for transport but their vehicle had already left for trek. It returned around1100am and thereafter it came to transport the patient to the hospital"(14)"I waited for transport [local public bus] for two days because the bus to Babati hospital."(136)"Patients get exhausted and even die whilst waiting for an ambulance"(159)"I have confidence in the uhuru because of its availability, accessibility and affordability"(144)
Transport options
"My husband took me on a bike because there was no other means"(136)"Getting to hire a car is very rare"(136) " The transport in our village is only lorry and very difficult for poor people to rent because it is very expensive" (160)"We planned to evacuate her but our ambulance had a breakdown a week ago"(14)"All the villages are far from the main road and there is a problem to get transportation"(155)"There was no vehicle...there wasn't anyone who could help, it was late at night"(171)"Four vehicles are available to rent every afternoon, if there is an emergency before that, there is no vehicle available, nor is the mobile health unit available, the patient can only wait"(160) "My husband took me on a bike because there was no other alternative"(136) "Men carried me on their shoulders to a bus stop at Erri Central (about 14km from Kokmay) where I boarded a local bus to Babait Hospital. There was not any other option."(136) "There were no cars, it was only people carrying you on their shoulders, two people or four people hold you in a blanket"(173) "We were there [main road]up to 12 midnight but couldn't get transport"(14) "We looked for transport in the village throughout the night but could not get one"(14) "There was no vehicle.... maybe there was transport, but where?....the problem was there was no vehicle, we couldn't move because of that"(171)"I have confidence in the uhuru because of its availability, accessibility and affordability"(144)"I was bringing her to the hospital but after three junctions I had to go back because I couldn't stand her to be transported by motorcycle"(172) "The bus was very full" (136) "I was very uncomfortable travelling for 7 hours on a full bus, the roads were very slippery because

of the heavy rains which made it worse”(136)“It was sunny and hot making it worse for pregnant woman in a full packed bus”(136)“We took her to the main road to look for transport. We were there up to 12 midnight but couldn’t get transport. All vehicles that came were full”(14)
Support
Family
“Husband placed me on a bike and pushed it”(136) “Husband took me on a bike”(136)
Community
“When a person is bitten by a snake and the local healers have failed him, he is put on a bed and between 4 to 6 young men transport him through the hills to Tonga health centre or the mission hospital”(154) “In emergency situations, we cannot rely on hospitals and clinics....we have to depend on community members with a car or a taxi to help us”(162)“What we normally see is, most of the time the sick person or woman in labour is carried on a stretcher by men on their shoulders”(136) “Such fare cannot be afforded individually. The entire village has got to contribute.”(136)“For sick people the payment can come after, most times it is free, sometimes i even help by giving them money”(160) “The community give as much money as they can for transport costs”(160)“We have to depend on community members with a car or taxi to help us”(162)“My husband borrowed a bicycle from our neighbour because there was no any better option”(136) “Thank god my fellow passenger offered me his seat so I could sit down”(136)“In such cases I would prefer to walk with someone”(162)“All social classes of the community were able to access the services of the Uhuru”(144)
Dependants
“When you are in danger you are just left alone at home with your young children. What can you do, you cannot go to seek help and leave the children alone.”(136) “I cannot wait at the district hospital to give birth safely because I cannot leave my children alone”(136) “Transportation was difficult, and I also have four other young children”(137)
Refusal
“Drivers refuse to take sick people”(170)
Geography
Terrain
“Uhuru is the answer to rural transport irrespective of terrain”(144)“This is a practical solution to rural transportation”(144)“The road is very bad”(136) “The road is too rough going up the hills and down the valleys”(136)“A lot of roads have holes”(160) “The road was slippery and the rain was pouring”(136)“The condition of the mobile health unit is not suitable for the geography of the region”(160)
Meteorological
“I was very uncomfortable travelling for 7 hours on a full bus, the roads were very slippery because of the heavy rains which made it worse”(136) “It was raining heavily, so when they called the midwife it took longer for her to arrive. Because the rain was heavy, she could not be saved by the time the midwife arrived”(172)“The road was slippery and the rain was pouring”(136) “In rainy season it is very difficult for vehicles to get through”(160)“But if it is too hot I sometimes feel my sickness coming”(162) “It was sunny and hot making it worse for pregnant woman in a full packed bus”(136) “Vehicles can only operate in the dry season, during the rainy season they cannot get through at all”(160)
Autonomy

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“I Personally decided to go to Babati district hospital because I was feeling dizzy and near the end of my pregnancy”(136) “I decided to go to the district hospital for treatment.”(136) “Men contribute to our sufferings. They go to pubs to drink local brew. Sometimes they do not leave you with even Tsh 100.”(136) “They [husbands] do not give a cent for transport”(136) “I think our women do not seek medical care because they cannot express themselves to the healthcare providers.”(136) “women are not educated; they do not know their expected delivery dates.”(136) “As husbands we have the responsibility of teaching our wives proper Swahili so they don’t feel shy and alone when admitted to a hospital and been attended by a worker from outside Manyata region...this could be one of the reasons women do not prefer giving birth with skilled health workers.”(136)
Culture
“Here if people see you going to the hospital for a delivery, they can bewitch you.”(169) “[Never deliver] outside of the society bush”(163)“Traditionally at the time of pregnancy when you walk outside you should take a plant with you, this cures black magic, some people take a knife too”(160) “There was no disease, it was about magic. If we get diseases due to magic, the doctor cannot see it, so getting treatment is different, she should go to the shaman”(171) “They go to a TBA seeking for help, most of the time we go to get the TBA to assist the delivery at the mothers home”(136) “Such a woman is sent to an experienced woman in the neighbourhood”(136) “Labour and child birth takes place at certain times... these correspond with Muslim praying times”(14)
Embarrassment
“I cannot explain how bad it was, bleeding whilst riding a bicycle up hills and down valleys” (136) “Health services are better but many women are scared to go to hospitals, particularly if it is their 6th pregnancy and above because service providers rebuke them for not using family planning”(136)
Financial
“My life was saved as the Uhuru served me when I had complications at my last delivery. I was transported from the clinic to the hospital just in time and at a very low price”(144) “The transport in our village is only lorry and very difficult for poor people to rent because it is very expensive” (160)“If it’s after the clinics closing time of 1600, then transport becomes more expensive, and we also then have travel much further away”(162) “We were afraid of the money”(171)“Yes we don’t have any money”(171) “If you do not have the money you have to look for it first. Sometime you may even have to spend a day or two looking for the money for the treatment. If you have coffee then you first sell it before you go”(175) “Women stay at home for they are asked to pay a lot of money for transportation”(155)“The cost was expensive”(171) “The ambulance was going to be very expensive which is why I was obliged to bring her by bicycle”(171) “For emergencies we usually rent a vehicle for rp.50,000 it is expensive because the harvest time is only once a year”(160)“I was asked to buy fuel for the ambulance to take my wife. I bought 20 litres of diesel”(14)“This intervention cuts across all social classes, the poor and the rich are equally benefitting”(144)“I have confidence in the uhuru because of its availability, accessibility and affordability”(144) “All the villages are far from the main road and there is a problem to get transportation and this creates a good opportunity for heavy truck drivers to make a fortune from these poor women”(155) “The road made by the VDC is for jackals”(156)
Ergonomics
Pain

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“You feel like the fetus is coming from the stomach”(136) “One can use a bicycle to take a pregnant woman to a hospital, but you can see the pain she is going through when you go through the rough roads”(136) “Particularly women in labour pain, they suffer a lot” (155) “It is very uncomfortable on a bicycle when in labour or in any other pain”(136) “I tried once, but after a very short distance I told them (the men carrying her), it is better I walk. I feel so uncomfortable.”(136) “The road condition and vehicle conditions right now are not comfortable but there is no other choice” (160)“I wish I was in an ambulance, the trip would have been comfortable”(136) “A car [ambulance] would be great help because you will not experience the horrible bumps as you go to the district hospital”(136) “Because in a car you are comfortable”(136)
Position
“She couldn’t even get on a motorcycle”(171)

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Table 15 Quality assessment of included studies using the COREQ criteria

Reporting Criteria	N= (%)	References of studies reporting each criteria
Characteristics of research team		
Interviewers or facilitator identified	11/29 (38%)	(137, 144, 153-155, 158, 162, 165, 168, 171, 172, 175)
Credentials	7/29 (24%)	(137, 153, 162, 165, 168, 171, 172)
Occupation	10/29 (34%)	(136, 140, 144, 153, 165, 167, 168, 171-173)
Sex	8/29 (27%)	(137, 141, 144, 154, 156, 160, 162, 173)
Experience and training	11/29 (38%)	(137, 140, 144, 154, 156, 158, 162, 168, 171, 172, 175)
Relationship with participants		
Relationship established	6/29 (21%)	(144, 162, 163, 170-172)
Participant knowledge of interviewer	3 /29 (10%)	(136, 144, 173)
Interviewer characteristics	6/29 (21%)	(160, 161, 163, 171-173)
Theoretical framework		
Methodological orientation and theory	7/29 (24%)	(14, 149, 154, 157, 161, 168, 172)
Participant selection		
Sampling	24/29 (83%)	(141)(14, 136, 137, 144, 154-163, 165, 167-173, 175)
Method of approach	12/29 (41%)	(136, 144, 158, 159, 161, 163, 165, 167, 168, 171, 172, 175)
Sample size	21/29 (72%)	(136, 137, 144, 149, 153-158, 160-162, 165, 167, 169, 171-173, 175)
Non-participation	6/29 (21%)	(136, 137, 158, 161, 173, 175)
Setting		
Setting of data collection	16/29 (55%)	(14, 136, 137, 141, 144, 149, 153, 154, 158, 159, 164, 171-173, 175) (167)
Presence of non-participants	4/29 (14%)	(144, 157, 171, 172)
Description of sample	18/29 (62%)	(136, 137, 144, 153, 155-163, 167, 168, 171, 173, 175)
Data collection		
Interview guide	13/29 (45%)	(141)(136, 137, 144, 153, 155, 157-159, 161, 162, 170, 171)
Repeat interviews	0/29	
Audio/visual recording	10/29 (34%)	(14, 136, 144, 153, 160, 163, 171-173, 175)
Field notes	4/29 (14%)	(136, 153, 170, 171)
Duration	7/29 (24%)	(136, 144, 153, 160, 163, 168, 171)
Data saturation	1/29 (3%)	(172)
Transcripts returned	0/29	
Data analysis		

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Number of data coders	1/29 (3%)	(149)
Description of the coding tree	1/29 (3%)	(136)
Derivation of themes	19/29 (66%)	(14, 136, 137, 149, 156, 158-160, 162, 163, 167-173, 175)
Software	15/29 (52%)	(136, 137, 144, 149, 155, 156, 159-161, 167, 169, 171-173, 175, 188)
Participant checking	4/29 (14%)	(149, 156, 161, 170)
Reporting		
Quotations presented	18 /29 (62%)	(14, 136, 137, 144, 149, 154-157, 159, 160, 162, 168, 169, 171-173, 175)
Data and findings consistent	29/29(100%)	(14, 136, 137, 141, 144, 149, 153-175)
Clarity of major themes	24/29 (83%)	(14, 136, 137, 141, 144, 149, 153-156, 158-163, 167-169, 171-173, 175)
Clarity of minor themes	12/29 (41%)	(137, 141, 144, 149, 154, 160, 162, 163, 167, 171-173)

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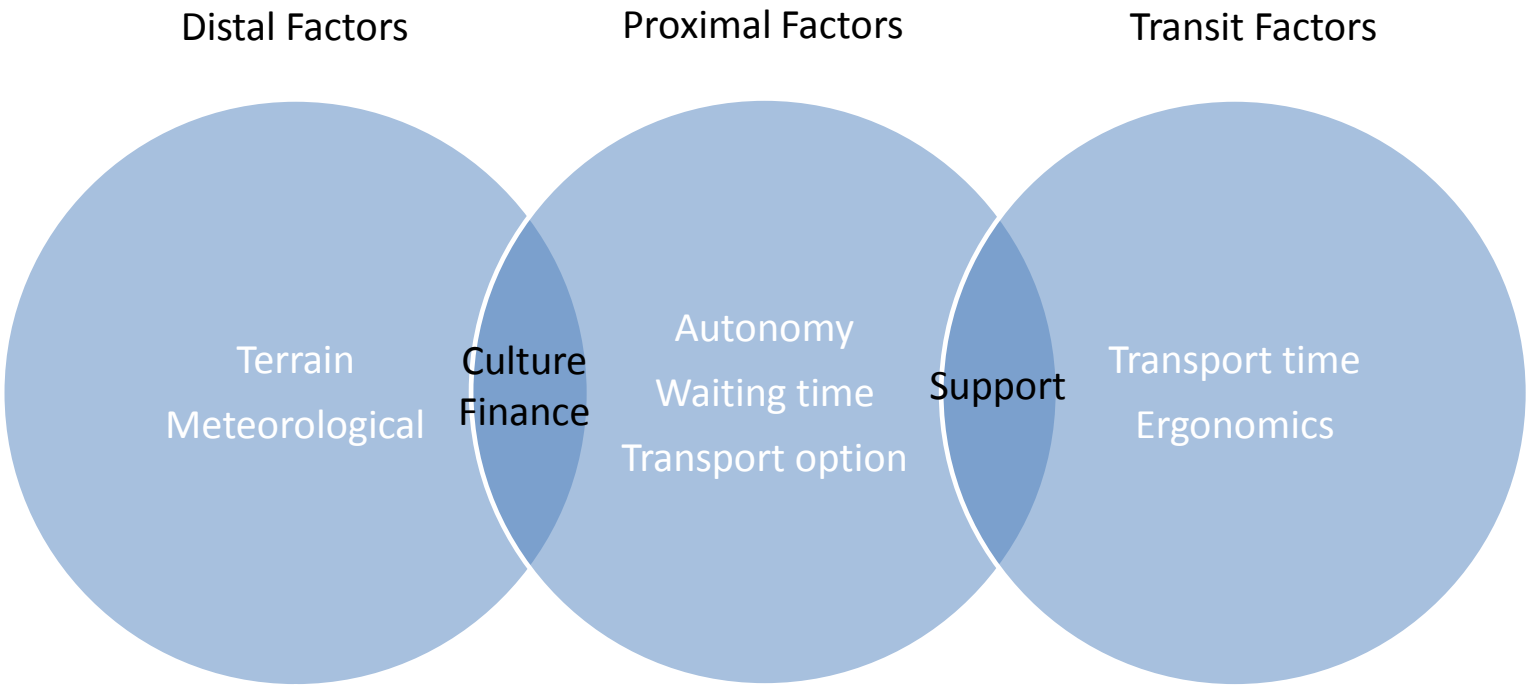

Figure 26 Determinants of emergency transport

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CHAPTER 6: CAN MOTIVATIONAL INTERVIEWS IMPROVE CONTRACEPTIVE COMPLIANCE AND REDUCE UNMET CONTRACEPTIVE NEED: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Reproductive health services provide an important protective function within communities. Enabling family planning can empower women, and effective contraceptive use can directly reduce the incidence of maternal deaths by averting around 230 million potential births every year. Effective family planning also has the potential to reduce poverty and malnutrition, particularly in regions where food security and unemployment is a concern. The use of behavioural and theory based interventions to improve contraceptive compliance and uptake have recently been addressed, however good quality evidence on the effectiveness of motivational interviewing to improve contraceptive practice in developing countries is lacking.

Methods: MEDLINE, EMBASE, AMED, BNI, Cochrane library, CINHAL, LILACS, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index (inception-August 2012) were searched without language restriction. RCTs were selected. In the absence of sufficient data from developing countries, data from developed countries was used and the generalisability discussed. Data was extracted from each study on study characteristics, quality and outcome data. The outcome measures were use of effective contraception and subsequent births.

Results: Eight RCTs were included within the review, with a total of 3424 participants. Seven were from developed countries, one was set in a developing country. Effective contraceptive use between zero up to four months significantly increased with motivational interviews when compared to the control (RR 1.32 95%CI 1.11, 1.56: p=0.002). There was no effect on contraceptive use with motivational interviews

between four up to eight months and eight up to twelve months. There was also a no significant effect on subsequent pregnancies or births.

Conclusion: Motivational interviews increase effective contraceptive use in a population at high risk of unintended pregnancy between zero up to four months. This research complies with current global health research on improving family planning, however there is substantial implication for generalisability of this finding as most of the studies were conducted in developed countries.

Impact of review: This review was used to support the application '*Motivational Interviewing as part of Public Health Midwives consultation to improve contraceptive uptake in northern Sri Lanka: a cluster randomised trial* 'seeking funding from the 'Implementation Research Platform (IRP) call for proposals in Northern Sri Lanka'.

6.1 BACKGROUND

Reproductive health services provide an important protective function within communities (189). Not only does family-planning empower women, effective contraceptive use directly reduces the incidence of maternal deaths by averting around 230 million potential births each year (190). Effective family-planning has the potential to reduce poverty and malnutrition, particularly in regions where food security is a concern (191). It is estimated that 222 million women in developing countries want to delay pregnancy or cease childbearing, but are not actively using contraception (192). Barriers to contraceptive use could be due to supply and demand (192), education around contraceptive use, cultural and social constraints or opposition (192), or the side effects or cost of contraception (193). Consistent and effective contraceptive use is also recognised as problematic, compliance with oral contraception has been demonstrated to be low in some regions (194). Research has demonstrated that 48.5%

of women using oral contraceptives used this method incorrectly, thus resulting in an unintended pregnancy rate of 5.7% (194).

Despite this, modern contraceptive use has improved in many countries, with a global increase from 54% in 1990 to 57% in 2012, however modern contraceptive use in sub-Saharan Africa remains low (192), and improvement has been minimal since 1990, from 23% to 24% in 2012 (192). The unmet need for contraception also remains high (box 1), it is estimated that 53% of women of reproductive age in Africa have an unmet need for modern contraception. Comparatively the level of unmet need in Asia is lower at 21%. Thus progress towards achieving MDG 5b (improving universal access to reproductive health care) is less in sub-Saharan Africa.

The use of behavioural and theory based interventions to improve contraceptive uptake and contraceptive compliance have recently been addressed (195) (196, 197). Prior to this motivational interviews were commonly associated with changing addictive behaviours (198-200), thus are used with alcoholics, drug users or obese patients (201-203). Recently however, they have been used with adolescents (204) and pregnant women (205-207) to invoke changes in 'risky' behaviour (such as unprotected sexual intercourse). Yet good quality evidence on the effectiveness of motivational interviewing to improve contraceptive practice in women of reproductive age in developing countries is lacking, therefore a systematic review was performed to examine the effect on motivational interviews on contraceptive uptake, to address areas where unmet contraceptive need is greatest.

Motivational interviewing

Motivational interviewing is a counselling approach that aims to facilitate and engage the participant's intrinsic motivation to change their behaviour. When compared with non-directive counselling, motivational interviewing is suggested to be more goal-

oriented and more participant-centred, thus aiming to induce behaviour change by encouraging participants to explore and address any ambivalence. Motivational interviewing encourages the participant to think about the changes that could be made, rather than the counsellor offering suggestions. The key concepts of motivational interviews are the participant recognising and accepting the need to make changes in their lives, this approach encourages the participant to consider their readiness to change their behaviour (208, 209). The main goals of motivational interviews are to engage participants, encourage talk of change, and induce motivation to make positive changes. The principles of motivational interviewing are based on autonomy, collaboration, exploration, and evocation. Motivational interviews are often conducted in a one to one setting, with a participant and counsellor contained in a space where the participant is able to talk freely and discuss sensitive or confidential information. The interview should last between 90 and 150 minutes (210)

Box 1: Unmet need of family planning: WHO

The number of women of reproductive age who are married or in a union, who are fecund and sexually active but are not using any method of contraception, and report not wanting any more children or wanting to delay the birth of their next child.

6.2 METHODS

Data sources and searches

Databases were searched for RCTs on motivational interviewing to improve contraceptive use. MEDLINE, EMBASE, AMED, BNI, Cochrane library, CINHAL, BIOMED Central, PsycINFO, LILACS, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index were searched (from database inception to August 2012). Hand searching complemented electronic searches, and reference lists were checked. The search terms were terms were

'motivational interview*, contraception, family planning, maternal, pregnancy'. No language restrictions were applied to the search.

Study selection and data extraction

RCTs were selected, if the study examined the effect of motivational interviewing on contraceptive use. Initially the electronic searches were scrutinised and full manuscripts of appropriate studies were acquired. Final decisions on inclusion or exclusion of manuscripts was made after inspection of these manuscripts by the author and another reviewer (AW and KN). Information was extracted from each article on study characteristics, quality and outcome data by the author and another reviewer (AW, KN). The outcome measures were use of effective contraception and subsequent births, these outcomes were measured at various time points throughout the studies. In the absence of sufficient data from developing countries, data from developed countries was used and the generalisability of the findings discussed.

Methodological quality assessment

The studies were assessed for methodological quality using quality assessment tools appropriate for the study design. Therefore the CONSORT (211) statement was used to evaluate the RCTs against a 25 item checklist for trials design, intervention, randomisation, blinding and analysis. Risk of bias in the studies was assessed using the Cochrane risk of bias tool (130).

Data synthesis

The random effects model was used to pool the risk ratios from individual studies at time points of zero up to four months, four up to eight months, and eight up to twelve months. This model was used to account for variability within the studies, including the intervention, the intervention dose and the method in which the outcomes were measured. Figure 27 is a graphical representation of the time points at which the

outcomes of effective contraceptive use were reported in the studies. Due to the variability in the timing of the follow up assessments, as reported in Figure 27, and the lack of rationale provided by the authors for selection of such time points, time points were pooled into the following categories; zero up to four months, four up to eight months, and eight up to twelve months. If a study reported two time points within the pooled time category, the first reported time point reported by the study author was used within the analysis. Heterogeneity of treatment effects was evaluated using forest plots, χ^2 and I^2tests; the terms low, moderate, and high heterogeneity were assigned to I^2 values of over 25%, 50%, and 75%, respectively. Analyses were done using Revman 5.0 statistical software.

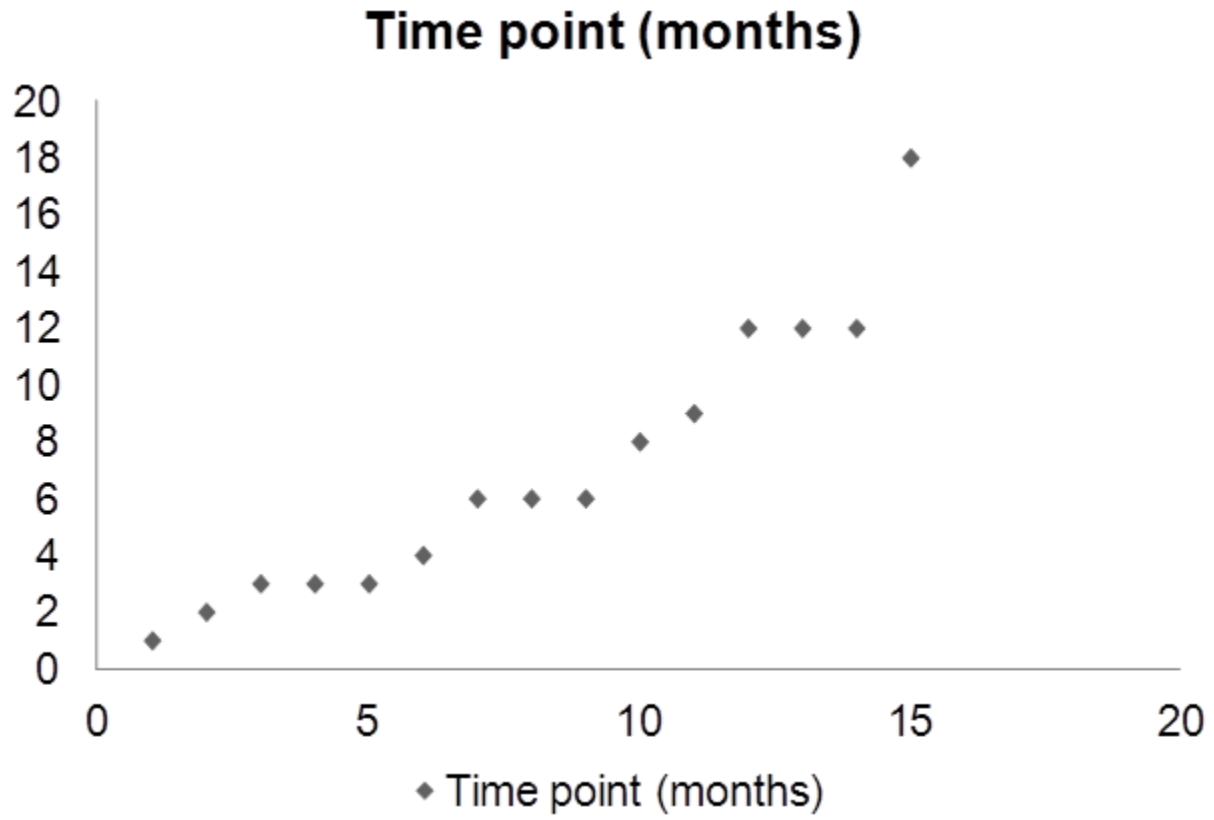

Figure 27 Graphical representation of the time points at which the outcomes of effective contraceptive use were reported in the studies

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6.3 RESULTS

The processes of literature search and selection are given in Figure 18. Eight RCTs with a total of 3424 participants were included in the review.

Study characteristics

The characteristics of the studies included are given in Table 15. Outcome data reported in the studies is shown in Table 16. All included studies, were set in upper or upper-middle income countries and all participants were women of reproductive age, although there was some variation in the population between the studies. One trial by Rendall-Mkosi et al however was set in South Africa (212). The WHO categorise South Africa as a developing country, and although this is an upper-middle income country as per world bank classification, the included participants were from rural districts and of low socio-economic status, thus the findings of this study may be generalisable to other developing countries.

Two studies by Barnet et al and Kirby et al included only women under the age of eighteen, and were described by the authors as adolescents (204, 213). Two other studies by Ingersoll et al and Ceperich et al included only participants aged between 18 and 24 years of age (214, 215). Half of the studies included women participating in high level alcohol consumption ('Risky drinking') (212, 214, 216, 217) as well as ineffective contraceptive use.

There was also clinical heterogeneity between the interventions of the included studies, although all were based on motivational interviews. Four studies offered single sessions, lasting between 60-75 minutes (213-216), including the study by Kirby et al of which offered a further nine follow up phone calls over a period of 12 months (213). One study by Petersen et al offered two sessions including a booster session at two months later (197), but no details on the length of the sessions were reported. Two

studies by Floyd et al and Rendall-Mkosi et al delivered the intervention through five sessions, interviews in both studies being up to 60 minutes in length. The study by Floyd et al conducted the sessions over 14 weeks (217), whereas the sessions were conducted over a period of two months in the other study by Rendall-Mkosi (212). The intervention in the remaining study by Barnet et al consisted of nine sessions (204) that were conducted over a period of two years, sessions were 20 minutes in duration. Baseline rate of effective contraceptive use also varied across the studies, with some studies reporting a complete absence of effective contraceptive at baseline (212, 216, 217), and others, such as Petersen et al, reporting a 59% baseline rate of effective contraceptive (197).

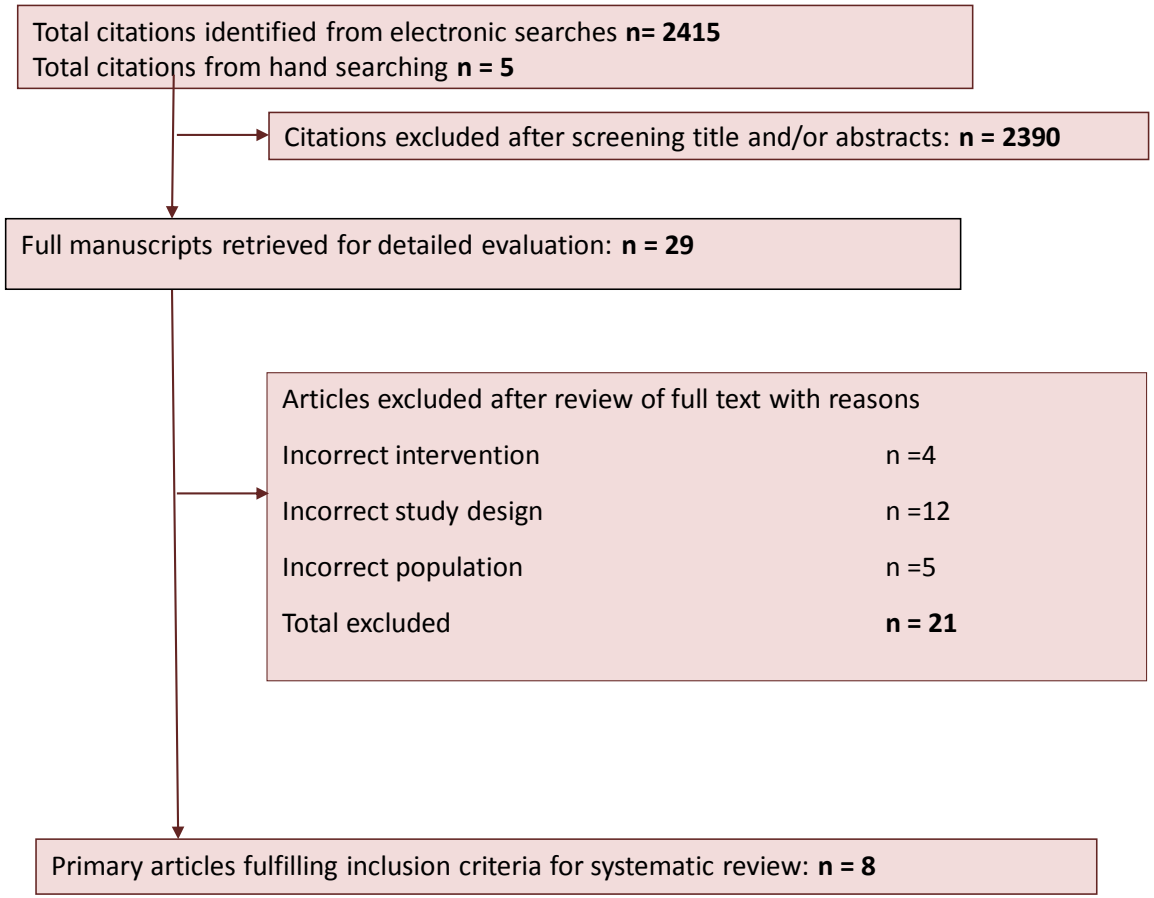

Figure 28 Results of search strategy and identification of publications included in the review

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Table 16 Study characteristics of studies included in the review

Population, Setting	Intervention	Control	Outcome
RCTs: Women of reproductive age in upper-middle income countries			
Ingersoll 2005: USA - DEVELOPED COUNTRY			
University students aged 18-24 risk of alcohol exposed pregnancy from a mid-Atlantic urban university. Sexual intercourse with a man in past 90 days using ineffective contraception, risky drinking levels. DEVELOPED COUNTRY	(n=114) BALANCE package (Birth Control and Alcohol Awareness: Negotiating Choices Effectively) Sessions included 90 day recording timeline follow back data on drinking and contraception, exercises on decisional balance, temptation and confidence charts. No details provided on training of counsellors. No baseline rate of effective contraceptive use but 47% did not use any contraception (inc withdrawal). **Duration: One session lasting 60-75 mins**	(n=114) Informational pamphlet about women's health. No baseline rate of effective contraception 44% did not use contraception (inc withdrawal)	Risk drinking (five or more standard drinks per occasion at least once in past 90 days or eight or more per week), ineffective contraception use (sexual intercourse in last 90 days with ineffective contraceptive use), risk for alcohol exposed pregnancy.
Petersen 2007: USA - DEVELOPED COUNTRY			
Aged 16-44 in 3 primary healthcare facilities in North Carolina, Mar 2003 and Sept 2004, at risk of unintended pregnancy, not pregnant or planning pregnancy within a year, not currently using IUD or partners not sterilised. Approx 60% participants aged 26-44	(n=365) Pregnancy and STD prevention counselling; emphasizes the development of the clients self efficacy. Explore discrepancy between pregnancy intention and contraceptive use, between STD risk and condom use; sharing information with participants; promoting behaviours to reduce risk. Intervention delivered by experienced health educators trained for project. Booster session two months later by phone or face to face, (85% had both sessions). Counselling standardised by providing counsellors with 30-40 hours training on contraceptives, pregnancy and STD prevention counselling, motivational interviewing, clinic operation, study design and implementation, basics of smoking cessation, exercise and nutrition counselling. Quality control measures were used through the study period. Baseline rate 59% effective contraceptive use **Duration: Two sessions (at least one face to face) over three months, no detail on length of session**	(n=372) Session of general health counselling. Baseline rate 58% effective contraceptive use	Change in level of contraceptive use, e.g. from a non-user to low or high-level user. Low level, missed contraceptive pills, used condoms inconsistently, diaphragm, contraceptive patch. High level, oral contraceptive taken every day, consistently used the patch, vaginal ring or condoms.
Floyd 2007: USA - DEVELOPED COUNTRY			
Aged 18-44, at risk of alcohol exposed pregnancy from 6 diverse settings in Florida, Texas, Virginia between Jul	(n=416) Motivational intervention counselling and contraceptive consultation. Sessions involved rapport building, review of current and advice on contraceptive practice and alcohol consumption, use of contraception journal, intercourse and alcohol consumption, self	(n=414) Received information only. Baseline rate	Risky drinking (five or more standard drinks in one day or eight or more drinks in a week), ineffective

2002-Jan 2004. No condition causing infertility, not pregnant or planning pregnancy in next 9 months, sexual vaginal intercourse in last 3 months with fertile man without effective contraception, engaged in risky drinking.	evaluation of behaviour, feedback on journal recordings, review goals and commitment to change. Contraceptive counselling visit involved determining appropriate and suitable methods of counselling. Counselling delivered by 21 trained counsellors (master's level education and above), supervised by project choices efficacy study team and six contraceptive care providers. 98% received at least one session, 63% received all 4 sessions; mean number of visits was 3.2 sessions. Baseline rate 0% effective contraceptive use **Duration: Five sessions over 14 weeks, lasting between 45-60 minutes**	0% effective contraceptive use	contraception (occurrence of vaginal sex when contraception not used or used ineffectively), risk for alcohol exposed pregnancy
Barnet 2009: USA - DEVELOPED COUNTRY			
Pregnant teenagers, aged 12-18 >24 weeks gestation. Excluded if the pregnancy not live birth and withdrawn if infant died in neonatal period. Intervention implemented in post partum period.	(n=167) Initiated 6 weeks postpartum, continuing quarterly to 24 months postpartum. *Nine* sessions were possible, yet >7 sessions classed as adherence. Computer-assisted motivational intervention: CAMI uses software developed for study and programmed with algorithms based on trans-theoretical model. CAMI counsellors conducted a *20-minute* stage matched motivational interviewing session to enhance teen's motivation to use contraception and remain non-pregnant. Half of participants received enhanced home based visit. Intervention ceased if participant became pregnant. Counsellors trained by completing a 2.5 day course on trans-theoretical model, motivational interviewing and CAMI protocol. Counsellor proficiency ascertained by videotaping the sessions. 24% attended > 7 intervention sessions. Details for baseline effective contraceptive use not reported, 23% always used condom **Duration: Nine sessions conducted for a period of up to two years. Sessions were 20 minutes in duration**	(n=68) Usual care, no description provided. Details for baseline effective contraceptive use not reported, 19% always used condom	Repeat births at 24 months and repeat pregnancy outcomes.
Kirby 2010: USA - DEVELOPED COUNTRY			
Reproductive health clinic in San Francisco aged 14-18 2005-2007, not pregnant or trying to become pregnant, had sexual intercourse in last three months, not consistently using a hormonal method of contraception (IUD or contraceptive implant).	(n=402) Motivational interviewing principles and techniques included in phone calls. Staff trained in family planning methods, adolescent risk behaviour and counselling techniques, also received training on content of calls and appropriate conduct. Interviewers trained on motivational interviewing by trained psychologists, and received motivational interviewing guide and training materials designed for intervention. four calls observed before allowed to conduct intervention alone. Counsellors completed 2.7 calls per participant rather than 9 specified in protocol, only 11% received 6 or more phone calls. Details for baseline effective	(n=403) Regular clinic services no regular follow up calls. Details for baseline effective contraceptive use not reported separately for	Measures of contraceptive use (condom and hormonal); frequency, compliance, non-use of contraception. Emergency contraceptive use, STDs, pregnancy, abortion, birth. Correct use of contraceptive method

	contraceptive use not reported separately for intervention and control, 11% used hormonal contraception at baseline. **Duration: One face to face visit followed by nine phone calls over 12 months. Length of phone calls was not reported.**	intervention and control, 11% used hormonal contraception at baseline.	
Ceperich 2011: USA - DEVELOPED COUNTRY			
University students aged 18-24 at risk of alcohol exposed pregnancy from a mid-Atlantic urban university. Not planning pregnancy in next year. sexual intercourse with man in last 90 days used contraception ineffectively and partook in risky drinking.	(n=101) BALANCE package (Birth Control and Alcohol Awareness: Negotiating Choices Effectively) included personalized feedback. Sessions included 90 day recording timeline follow back data on drinking, contraception, exercises on decisional balance, temptation and confidence charts. Counsellors had master's degrees in psychology or social work, received training in motivational interviewing and balance counselling manual. Interviews videotaped for quality control. Motivational interview techniques and principles were practised at least twice a month. No baseline rate of effective contraceptive use provided but 53% did not use any contraceptive means (inc withdrawal). **Duration: One session lasting 60-75 minutes**	(n=106) Informational pamphlet about women's health. No baseline rate of effective contraceptive use provided but 48% did not use contraceptive means (inc withdrawal).	Risk drinking (consuming five or more standard drinks per occasion at least once in past 90 days or eight or more per week), ineffective contraception use (sexual intercourse in the last 90 days with ineffective contraceptive use), risk for alcohol exposed pregnancy, rate of alcohol exposed pregnancy at 4 months
Ingersoll 2012: USA - DEVELOPED COUNTRY			
Aged 18-44 from 2 cities and surrounding areas Virginia, risk of alcohol exposed pregnancy (at least one episode of unprotected vaginal sex with a male partner and drinking alcohol at risky levels during the past 90 days. Without confirmed infertility, English speaking, intending to reside in local community for next 6 months. Excluded women current or intending to get pregnant, opioid dependence without antagonistic treatment, actively suicidal and cognitive problems.	(n=73) Build rapport; provide personalized feedback on drinking, contraception and alcohol exposed pregnancy risk. Information given on alcohol exposed pregnancy and fetal alcohol syndrome. Counsellors encouraged a contraception visit to explore options and referred participants to community women's health resources and offered informational brochures. Counsellors had post graduate degrees and trained in motivational interviews. Weekly supervision of counsellors. Baseline rate 0% effective contraceptive use **Duration: One session lasting 60 minutes**	(n=144) either informational brochure or informational video. Baseline rate 0% effective contraceptive use	Drinks per drinking day, ineffective contraception rate, alcohol exposed pregnancy risk at 3/6 months.
Rendall-Mkosi 2012: South Africa- DEVELOPING COUNTRY			

6 primary care clinics in Western Cape, South Africa aged 18-44, not pregnant, engaged in risky drinking, ineffective or no contraceptive use, not undergone sterilisation or hysterectomy, had vaginal sex in last 3 months, resided in 25 km of main town.	(n=82) Rapport building, session programme, assessing the participants readiness to change and confidence in enacting behaviour change, development of change plan, implementation of the plan, assessing challenges and problem solving. Contraception was integrated throughout. Sessions conducted by locally recruited and trained lay counsellor. Sessions held 2 months in a convenient place and time for participants. Quality control of intervention ensured through regular meetings between trainers and counsellors. 51% participants completed 5 sessions, 12% (10) did not attend any sessions. Baseline rate 0% effective contraceptive use **Duration: Five sessions over two months lasting 60 minutes**	(n=83) Information pamphlet on fetal alcohol syndrome prevention and women's health handbook. Baseline rate 0% effective contraceptive use.	Risk of alcohol exposed pregnancy at 12 months, risky drinking and ineffective contraception at 3 and 12 months, risk of alcohol exposed pregnancy at 3 months (engaged in risky drinking and not using effective contraception at follow-up).

*Table 17 Effective or high level contraceptive use up to four months, between four and eight months and between eight and twelve months (table contains data for only those patients followed up) (*assumptions from data reported in the studies (%))*

Study	Using effective or high level contraception up to four months (%)		Using effective or high level contraception between four to eight months (%)		Using effective or high level contraception between eight to twelve months (%)		Subsequent births or pregnancies at 12-24months n (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Ingersoll	58/94 (61.7)	50/105 (47.6)	NR	NR	NR	NR	NR	NR
Petersen*	233/323 (72)	218/346 (66)	212/331 (63)	215/331 (62)	217/349 (64)	200/334 (60)	35/349 (10)	34/334 (10)
Floyd	152/332 (45.8)	95/333 (28.4)	143/299 (47.7)	100/305 (32.8)	164/291 (56.3)	117/302 (38.7)	NR	NR
Barnet	NR	NR	NR	NR	NR	NR	26/167 (15)	17/68 (25)
Kirby*	NR	NR	257/313 (82)	263/313 (84)	184/231 (80)	187/231 (81)	NR	NR
Ceperich	68/101 (67.3)	59/106 (55.7)	NR	NR	NR	NR	NR	NR
Ingersoll	26/57 (45.8)	46/117 (40)	24/45 (55.3)	49/105 (46.6)	NR	NR	NR	NR
Rendall-Mkosi	20/56 (35.7)	7/61 (11.5)	NR	NR	26/61 (42.6)	16/64 (25)	NR	NR

Study quality

The eight studies achieved scores between 16 and 30 on the CONSORT (218) statement checklist, with most studies reporting adequately on background, objectives, limitations, generalisability and interpretation (Table 17). When assessed for risk of bias most studies scored low risk of bias in random selection, incomplete outcome data and selective reporting, with an unclear risk of bias in blinding of participants, outcome assessors and allocation concealment. All studies apart from one, scored high risk of bias in other sources of bias due to the method in which data was collected (Table 18).

Effective contraceptive use between zero to four months

Six studies (197, 212, 214-217) reported on effective contraceptive use between zero to four months. Meta-analysis showed a significant increase in effective contraceptive use with motivational interviews when compared to the control (RR 1.32 95%CI 1.11,1.56: p=0.002:Figure 29). There was moderate heterogeneity in the analysis (I^2= 67%: p=0.010).

Effective contraceptive use between four and eight months

Four studies (197, 213, 216, 217) reported on effective contraceptive use between four and eight months. Meta-analysis showed no significant difference in effective contraceptive use with motivational interviews when compared to the control (RR 1.10, 95%CI 0.93, 1.32: p=0.27: Figure 30).There was high heterogeneity in the analysis (I^2= 83%, p=0.0004).

Effective contraceptive use between eight and twelve months

Four studies (197, 212, 213, 217) reported on effective contraceptive use between eight and twelve months. Meta-analysis showed no significant difference in effective contraceptive use with motivational interviews when compared to the control (RR 1.18, 95%CI 0.96, 1.46: p=0.12: Figure 31). Heterogeneity was high (I^2= 86%: p=<0.0001).

Motivational interviews to reduce subsequent pregnancies or births at 12-24 months

Two studies (197, 204) reported on the reduction of subsequent pregnancies at 24 months. No significant effect was shown on the incidence of subsequent pregnancies with motivational interviews (RR 0.80 95%CI 0.51, 1.26. p= 0.34: I^2=39%, p=0.20: Figure 32).

Study	MI Events	MI Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
Ceperich 2011	68	101	59	106	1.21 [0.97, 1.50]
Floyd 2007	152	332	95	333	1.60 [1.31, 1.97]
Ingersoll 2005	58	94	50	105	1.30 [1.00, 1.67]
Ingersoll 2012	26	57	47	117	1.14 [0.79, 1.63]
Petersen 2007	233	323	218	346	1.14 [1.03, 1.27]
Rendall-Mkosi 2012	20	56	7	61	3.11 [1.43, 6.79]
Total (95% CI)		**963**		**1068**	**1.32 [1.11, 1.56]**
Total events	557		476		

Heterogeneity: Tau² = 0.03; Chi² = 15.15, df = 5 (P = 0.010); I² = 67%

Test for overall effect: Z = 3.17 (P = 0.002)

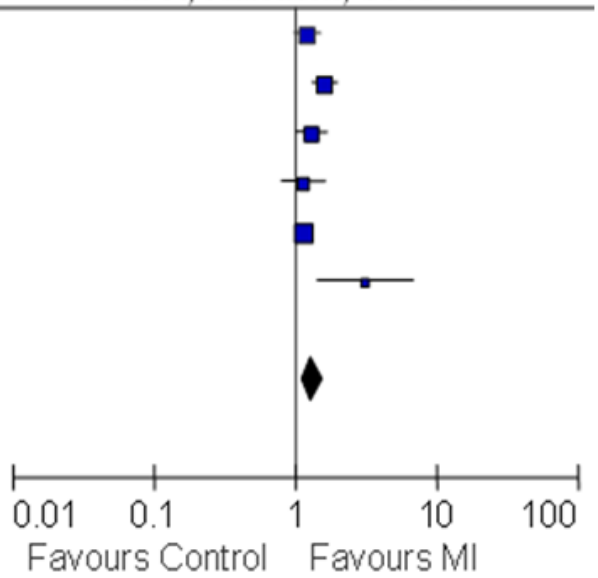

Figure 29 Effective contraceptive use between zero to four months with participants that have participated in motivations interviews and participants that have received standard care

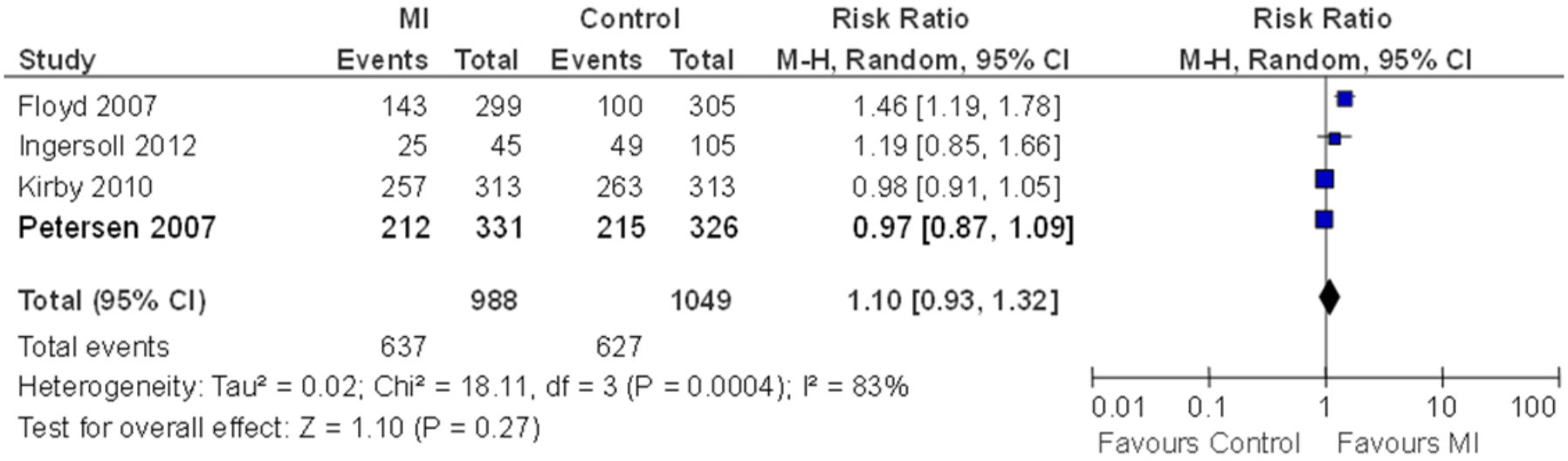

Figure 30 Effective contraceptive use between four and eight months with participants that have participated in motivations interviews and participants that have received standard care

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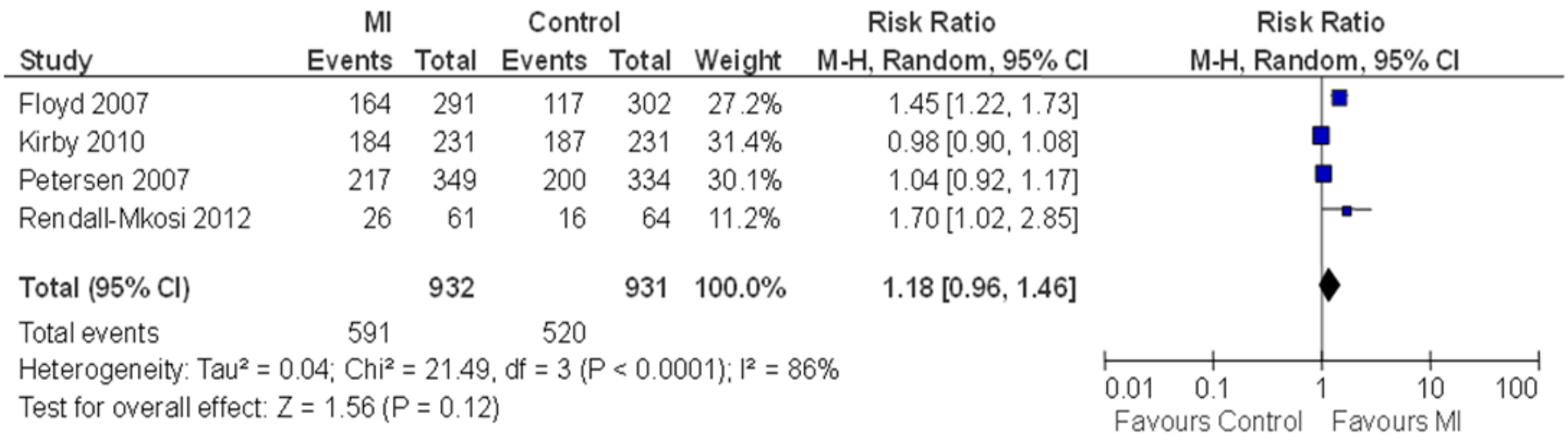

Figure 31 Effective contraceptive use between eight and twelve months with participants that have participated in motivations interviews and participants that have received standard care

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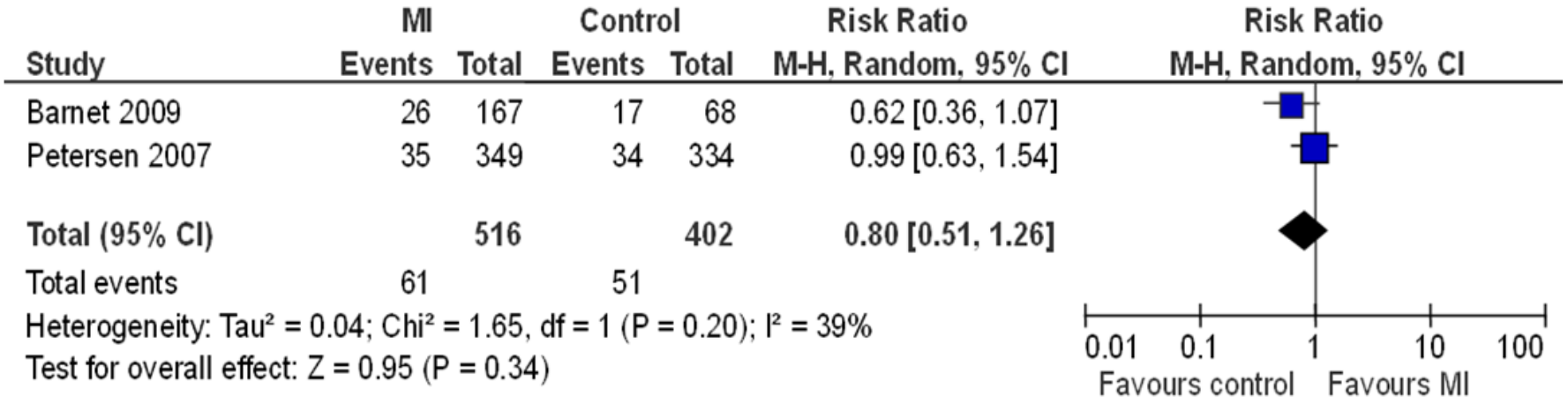

Figure 32 Subsequent pregnancies or births at 12-24 months Motivational interviews with participants that have participated in motivations interviews and participants that have received standard care

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6.4 DISCUSSION

Main Findings

Motivational interviews have a significant effect on the improvement of effective contraceptive use between zero to four months in a population at high risk of unintended pregnancy, but no effect at other time points. No significant difference was seen in subsequent pregnancies or births at 12-24 months (RR 0.80 95%CI 0.51, 1.26). There was moderate to high statistical heterogeneity in all three analyses, as well as clinical heterogeneity between the interventions within the trials. It is possible that the heterogeneity in the analysis in Figure 29 and Figure 31 may be due to the difference in the population in one study by Rendall-Mkosi et al (212), as the largest effect was seen in favour of the intervention. The study by Rendall-Mkosi et al included women of a similar age range (18-44) at risk of alcohol exposed pregnancy, however unlike the other studies, it was reported that the women within this study were predominantly poor, often part-paid with alcohol for working within the agricultural sector, experienced poor living conditions and had a low level of education. One further study by Floyd et al (217) showed a larger effect when compared to other studies. It is possible that the heterogeneity in Figure 30, and the larger effect in both the studies by Rendall-Mkosi et al and Floyd et al (212, 217) may be due to the educational difference in the population. Only a third of the population in the study by Floyd et al had college education and most participants were recruited from women jails or alcohol treatment centres. All of the other studies included in the review recruited university students only. Compliance in the studies by Rendall-Mkosi et al and Floyd et al was low (51% (212) and 63% (217) yet they had the greatest effect. Rather than the interviews having a motivational effect, in populations with low education levels there will be a greater scope for providing new information which may be all that was needed in some cases to change behaviour.

Moreover, one could suggest that the significant improvement in the first reported time point (between zero up to four months), compared to subsequent time points (four up to eight months and eight up to twelve months) could be due to the participants forgetting the message of the intervention. The study by Petersen et al that provided booster sessions at 2 months post intervention (197) showed improved contraceptive usage when compared to other reported time points in the study.

Strengths and Limitations

Although not a methodological limitation, the main limitation of this review for this thesis is that all of the RCTs included in the review were conducted in upper-middle income countries, which has obvious implications for generalisability of the review findings to low-middle countries, where resources may be limited. The cost and intensity of the intervention (as demonstrated in the table of characteristics) may not be suitable or sustainable for developing countries, therefore the generalisability of the results to low income setting must be debated. The study by Rendall Mkosi et al however, was set in a developing country (South Africa), and included participants of low socioeconomic status from a rural setting. Given that this trial alone showed the largest effect size compared to all other trials, it could be suggested that motivational interviews are likely to be effective within a developing country setting, however this could be due to the information transmitted and the educational component of the intervention, rather than a motivated conscious change in the participant's behaviour. Nevertheless, sustainability of this intervention, due to the high cost and intensity, may impede the implementation of this intervention outside of the research context. Furthermore the culture and lifestyle of the population studied may differ from that of women in some developing countries. For example sexual promiscuity, sexual relationships before marriage, and alcohol consumption may not be as widely practiced within some developing countries, as it is in the countries studied. It is therefore possible that this type of intervention may only have the demonstrated effect on some population.

Methodological limitations of the review include the heterogeneity in the intervention, the delivery of the intervention, and the intervention concentration. Additional limitations in the analysis could be the pooling of the time points reported, and including estimations of outcome for two studies (197, 213) within the analysis. Due to the variability in the actual reported time points across the eight studies, there was insufficient data in each category to provide meaningful analysis. Therefore the time points reported in the studies were plotted on a graph (Figure 27) to observe if a cluster effect was present around time specific time points. As this was not observed the time points were pooled in categories (zero up to four, four up to eight, eight up to twelve).

There is possible risk of reporting bias in the primary data, as the majority of the studies relied on self reporting of contraceptive use, and episodes of risky behaviour in relation to unsafe sexual activity. There may also be bias in the outcome data reported by the participants, as outcomes may have underreported, this was therefore assessed to have a high risk of bias within 'other bias.' There were also some discrepancies in the data that we attempted to resolve by contacting authors, however due to the methods of statistical analysis used in the primary analysis, exact numbers for the control and intervention arm could not be provided, only estimates were given (213), thus a further limitation within our analyses.

Existing evidence

Motivational interviews have been examined previously in a Cochrane Review that tested theory based interventions that aimed to promote or inform contraceptive use (196), however it included studies with a wide variety of types of interventions, including home-based mentoring, pamphlets, computer-delivered interventions, general health counselling, group youth and parent programs, educational tools as well as motivational interviews. Four trials (197, 213, 214, 217) primarily examined the effect

of motivational interviewing on alcohol exposed pregnancy (214, 217), the prevention of pregnancy and sexually transmitted infections (197), and improvement in contraceptive use (213). No key patterns were identified with theory type, intervention, or target population, therefore it is suggested that more thorough use of single theories would help inform the field about what is effective.

Motivational interviewing training for general practitioners (219) has also been explored in a systematic review, different aspects of motivational interviewing training for GPs were evaluated. The review included studies of interventions that addressed alcohol counselling for pregnant women, as well as counselling for abuse, smoking, medication adherence, diabetes, lifestyle, exercise and diet. The review concluded that motivational interviewing can improve client communication and counselling concerning lifestyle related issues, however the methodological and clinical heterogeneity of the studies within the review means that the results should be interpreted with caution.

Policy and practice implications

The importance of addressing maternal and child in developing countries has been identified (190, 220), and attempts have been made to prioritise maternal health needs through promoting and supporting essential services, and developing guidelines (221) (222). However, there is a scarcity of data on the effectiveness of these programs. It is apparent from this review that good quality evidence on the effectiveness of contraceptive counselling based on motivational interview techniques is lacking (195). Previous research has demonstrated varying levels of success on contraceptive uptake and unintended pregnancy, however the clinical heterogeneity across the studies, both within the interventions and the populations, causes difficulty with drawing firm inferences between the intervention and the effect. Although there is high cost and intensity associated with this interview, the delivery method (i.e. one to one contact with a health worker) evades any possible cultural, social or religious ‘taboos’ associated

with contraception, as healthcare providers are in a unique position to discuss and explore contraceptive practices (194, 195, 223), and issues that may be culturally sensitive and not openly discussed, thus permitting generalisability to other regions. Moreover, the only study set in a developing country showed the greatest effect on effective contraceptive use with motivational interviews, albeit classed as a middle to high income country.

Unanswered questions and future research

Overall there appears to be a lack of evidence on the effect of motivational interviewing to improve contraceptive use and compliance on women of reproductive age in developing countries, with only a single study being set in a developing country. Thus an RCT would provide good quality evidence on the effect of motivational interviewing on contraceptive practice in post conflict areas where contraceptive need is unmet. This review was used to support the application '*Motivational Interviewing as part of Public Health Midwives consultation to improve contraceptive uptake in northern Sri Lanka: a cluster randomised trial* 'seeking funding from the 'Implementation Research Platform (IRP) call for proposals in Northern Sri Lanka'.

6.5 CONCLUSION

It is apparent from our review that motivational interviews significantly increase effective contraceptive use in a population at high risk of unintended pregnancy from developed countries, between zero up to four months after the intervention has been delivered. Furthermore, the only study that was set in a developing country showed the largest effect on effective contraceptive use with motivational interviews, even with poor compliance in the intervention group. As the WHO is working to promote contraception by producing evidence-based guidelines on service delivery of contraceptive methods, and adapt, implement and improve delivery methods to meet

the needs of individuals, this research complies with current global health research on improving family planning.

Table 18 Quality assessment: CONSORT statement reporting checklist

Item	Checklist item	Ingersoll	Floyd	Ceperich	Kirby	Petersen	Barnet	Ingersoll	Rendall-Mkosi
Title and abstract									
	Identification as RCT in title	N	Y	N	N	Y	Y	N	Y
	Structured summary of trial design, methods, results, conclusions	N	Y	N	Y	Y	Y	Y	Y
Introduction									
Background and objectives	Scientific background, explanation of rationale	Y	Y	Y	Y	Y	Y	Y	Y
	Specific objectives or hypotheses	Y	Y	Y	Y	Y	Y	Y	Y
Methods									
Trial design	Description of trial design including allocation ratio	N	Y	N	N	N	N	Y	N
	Important changes to methods after commencement	N	N	N	N	N	N	N	Y
Participants	Eligibility criteria for participants	Y	Y	Y	Y	Y	Y	Y	Y
	Settings and locations where data were collected	N	Y	N	N	Y	N	N	N
Interventions	interventions with sufficient details to allow replication, how/ when administered	Y	Y	Y	Y	Y	Y	Y	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when assessed	Y	Y	Y	Y	Y	Y	Y	Y
	Any changes to trial outcomes after trial commenced	N	N	N	N	N	N	N	N

Sample size	How sample size determined	N	Y	N	Y	Y	N	N	Y
	applicable, explanation of interim analyses and stopping guidelines	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Randomisation:									
Sequence generation	Method to generate random allocation sequence	Y	Y	Y	Y	Y	Y	Y	Y
	randomisation; details of restriction	N	Y	N	Y	Y	Y	Y	Y
Allocation concealment mechanism	Mechanism to implement random allocation sequence describing steps taken to conceal the sequence until interventions assigned	N	Y	N	N	Y	N	Y	Y
Implementation	Who generated random allocation sequence, enrolled participants, and assigned participants to interventions	Y	N	Y	N	N	N	Y	Y
Blinding	who was blinded after assignment to interventions	N	Y	N	Y	N	N	Y	Y
	If relevant, description of similarity of interventions	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	Y	Y	Y	Y	Y	Y	Y	Y
	Methods for additional analyses, subgroup analyses, adjusted analyses	Y	Y	Y	Y	Y	Y	Y	Y
Results									
Participant flow	numbers of participants randomly assigned, received intended treatment, and analysed for primary outcome	Y	Y	Y	Y	Y	Y	Y	Y
	losses and exclusions after randomisation, together with	Y	Y	Y	N	N	Y	Y	Y

	reasons								
Recruitment	Dates defining the recruitment and follow-up	N	Y	N	Y	Y	Y	Y	Y
	Why trial ended or stopped	N	N	N	N	N	N	N	N
Baseline data	baseline demographic and clinical characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Numbers analysed	number of participants included in analysis and whether analysis by original assigned groups	Y	Y	Y	N	Y	Y	Y	Y
Outcomes and estimation	primary and secondary outcome, results and estimated effect size and precision	Y	Y	Y	N	N	Y	Y	Y
	For binary outcomes, presentation of both absolute and relative effect sizes	N	Y	Y	N	Y	N	Y	Y
Ancillary analyses	Results of any other analyses performed, subgroup analyses, adjusted analyses, distinguishing pre-specified from exploratory	N	Y	Y	N	N	Y	Y	Y
Harms	important harms or unintended effects	Y	N	Y	N	N	N	N	N
Discussion									
Limitations	Trial limitations, addressing sources of potential bias, imprecision, and, multiplicity of analyses	Y	Y	Y	Y	Y	Y	Y	Y
Generalisability	Generalisability of the trial findings	Y	Y	Y	N	Y	Y	Y	N
Interpretation	Interpretation consistent with results, balancing benefits, harms, considering other relevant evidence	Y	Y	Y	N	Y	N	Y	Y
Other information									
Registration	Registration number, trial registry	N	Y	N	N	N	N	Y	N

Protocol	full trial protocol can be accessed	N	Y	N	N	N	N	N	N
Funding	Sources of funding and support	Y	Y	Y	Y	Y	Y	Y	Y

√ = Reported X = Not Reported

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Table 19 Risk of Bias in Included Studies: RCTs

Ingersoll 2005						
LOW: Page 175: counsellor opened a randomisation envelope	UNCLEAR: No details provided on allocation concealment other than randomisation envelopes used	UNCLEAR: No details provided on blinding of participants and personnel	UNCLEAR: No details provided on blinding of outcome assessment	LOW: Page 177: Data provided for follow up rates, those lost to follow up. Rates similar within the intervention and control	LOW: Page 178: All outcomes reported on	HIGH: Page 179: outcome data is self-reported there is potential for under reporting of risky behaviour
Floyd 2007						
LOW	LOW	HIGH	LOW	LOW	LOW	HIGH
Page 3: Random allocation was controlled by a data coordinating centre. A randomisation program developed to generate unique identifiers to randomly assign each ID to either intervention or control.	Page 3: Each unique study ID was then printed on opaque envelope, a card inside envelope indicated group status to which study participant receiving ID number was assigned. Envelopes sealed, boxed in numeric order, drawn in numeric order.	Page 3: It was not possible to blind study participants or those administering intervention to group assignment	Page 3: study sites blind to ID number's group status until envelopes opened. Staff blinded to group assignment conducted follow up interviews	Page 4: Large amount loss to follow up but ITT analysis completed and similar numbers loss to follow up in each arm	Page 7: All outcomes reported on	Page 5: Difference in number of sexual partners between control and intervention arm (although not statistically significant) Page 8: As outcome data is self-reported there is potential for under reporting of risky behaviour
Petersen 2007						

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LOW: Page 22: Random numbers table to generate group assignment in permuted block sizes of 100.	LOW: Page 22: Placed sealed envelopes with the assignments at each site. Enveloped opened after participants were screened.	UNCLEAR: No details provided on blinding of participants and personnel	UNCLEAR: No details provided on blinding of outcome assessment	UNCLEAR: Page 24: Limited information given on participants lost to follow up	LOW: Page 25: All outcomes reported	HIGH: Page 25: numerical numerators and denominators not provided for outcome measures, percentages given Page 26: outcome data is self-reported there is potential for under reporting of risky behaviour
Barnet 2009						
LOW: Page 437: Computer generated randomisation	LOW: Page 437: Randomisation applied to consecutively consenting teens using permuted blocks of 6	UNCLEAR: No details provided on blinding of participants and personnel	UNCLEAR: No details provided on blinding of outcome assessment	LOW: Page 439: Data provided for follow up rates, those lost to follow up. Rates similar within intervention and control arms	LOW: Page 442:All outcomes reported	LOW: Page 437: Intentionally more participants in intervention than control and not balanced on key variables but a multivariate analysis was performed to control for this.
Kirby 2010						

LOW: Page 252: Random number generator.	UNCLEAR: No details provided on allocation concealment	UNCLEAR: No details provided on blinding of participants and personnel	LOW: Page 253: Interviewers were blinded to study group assignments until final follow up as had to ask intervention group additional questions	LOW: Page 254: Data provided for follow up rates, those lost to follow up. Rates similar within the intervention and control. Numerators not given only percentages.	LOW: Page 254 : All outcomes reported	HIGH: Page 257: outcome data is self-reported there is potential for under reporting of risky behaviour Page 257: self-selection bias is possible as only included women willing to receive phone calls, however < 10% declined as were unwilling to take calls, therefore unlikely bias affected results.
Ceperich 2011						
LOW: Page 385: Randomisation envelope	UNCLEAR: No details provided on allocation concealment	UNCLEAR: No details provided on blinding of participants and personnel	UNCLEAR: No details provided on blinding of outcome assessment	LOW: Page 385: Data provided for follow up rates, lost to follow up. Rates similar within intervention and control	LOW: Page 387 table 2, 3 figures 2, 3. All outcomes reported	HIGH: outcome data is self-reported there is potential for under reporting of risky behaviour
Ingersoll 2012						

UNCLEAR: Page 2: Random assignment but not other details provided	UNCLEAR: No details provided on allocation concealment	UNCLEAR: No details provided on blinding of participants and personnel	LOW: Page 3: Research assistant conducting assessments masked to assignment	UNCLEAR: Page 5: Data provided for follow up rates, those lost to follow up. Rates differ within intervention and control arms, no reasons provided for loss to follow up or differences	LOW: Page 7 : All outcomes reported	HIGH: outcome data is self-reported there is potential for under reporting of risky behaviour
Rendall-Mkosi 2012						
LOW: Page 5: Computerised individual randomisation	LOW: Page 5: Sealed envelope	UNCLEAR: No details provided on blinding of participants and personnel	HIGH: Page 5: Blinding fieldworkers to group allocation of participants was difficult in small rural community setting, fieldworkers did not perform counselling only gave questionnaires.	LOW: Figure 1: Data provided for follow up rates, and those lost to follow up. Rates similar within intervention and control arms	LOW: Page 9 table 2 : All outcomes reported	HIGH: Page 11: outcome data is self-reported there is potential for under reporting of risky behaviour

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TASK SHIFTING INTERVENTIONS

CHAPTER 7: A COMPARISON OF CLINICAL OFFICERS WITH MEDICAL DOCTORS ONOUTCOMES OF CAESAREAN SECTION IN THE DEVELOPING WORLD: META-ANALYSIS OF CONTROLLED STUDIES

ABSTRACT

Background: Many low to middle income countries have a shortage of trained medical doctors. Clinical officers were temporarily posted to alleviate the shortage of medical doctors in some low to middle income countries, however since then they have become a more permanent strategy. There is uncertainty about the effectiveness and safety of clinical officers performing caesarean sections. This systematic review examines the effectiveness and safety of clinical officers (healthcare providers trained to perform tasks usually undertaken by doctors) carrying out caesarean section in developing countries compared with doctors.

Methods: Systematic review with meta-analysis was performed. Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, BioMed Central, the Reproductive Health Library, and the Science Citation Index (inception-2010) were searched without language restriction. Controlled studies were selected and information was extracted from each selected article on study characteristics, quality, and outcome data. Risk of bias was assessed using the Newcastle Ottawa Scale.

Results: Six non-randomised controlled studies (16 018 women) evaluated the effectiveness of clinical officers carrying out caesarean section. Meta-analysis found no significant differences between the clinical officers and doctors for maternal death (odds ratio 1.46, 95% confidence interval 0.78 to 2.75; p=0.24) or for perinatal death (OR 1.31, 95%CI 0.87 to 1.95; p=0.19). The results were heterogeneous, with some studies reporting a higher incidence of both outcomes with clinical officers. Clinical officers were associated with a higher incidence of wound infection (OR 1.58,

95%CI 1.01 to 2.47; p=0.05) and wound dehiscence (OR 1.89, 95%CI 1.21 to 2.95; p=0.005). Two studies accounted for confounding factors.

Conclusion: Clinical officers and doctors did not differ significantly in key outcomes for caesarean section, but the conclusions are tentative owing to the nonrandomised nature of the studies. The increase in wound infection and dehiscence may highlight a particular training need for clinical officers.

Impact of review: Published in BMJ, informed WHO recommendations on task-sharing: OPTIMIZEMNH

Citation of paper published from this work on which this chapter is based

Amie Wilson, David Lissauer, Shakila Thangaratinam, Khalid S Khan, Christine MacArthur, Arri Coomarasamy. A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world: meta-analysis of controlled studies. BMJ 2011;342:d2600

7.1 BACKGROUND

There is a global deficit of qualified medical personnel, especially specialist medical practitioners, for example obstetricians and gynaecologists. Many low to middle income countries have a shortage of trained medical doctors. Rural areas are predominantly affected, as doctors largely congregate in urbanised regions as they are easier to travel to, or the facilities posses a great supply or quality of resources (224). A variety of reasons have been linked to the depletion in medical and clinical workforce, including the migration of trained staff due to brain drain. Brain drain is when skilled professionals, namely healthcare professionals leave their country of training or origin to work in a more resource rich setting. This is often due to aspirations for career progression where there is a lack of opportunity, the frustration with lack of resources, both human and clinical impeding medical care, and the desire for improve personal income. Figure 33 demonstrates the factors that have been associated with brain drain

in the literature (224-227). Fear of exposure to blood-borne infections, or sickness or death due to Human Immunodeficiency Virus are also contributing factors.

Clinical officers were initially temporarily posted to alleviate the shortage of medical doctors in some low to middle income countries (135, 226, 228). However, they have now become a more permanent strategy, operating in many countries. Clinical officers are described today as the 'backbone' of healthcare in several settings across the globe (228). Clinical officers are not medical doctors, they have a separate training programme, but their roles include many medical and surgical tasks that are usually performed by doctors, such as anaesthesia, diagnosis and treatment of medical conditions, and prescribing. The perceived benefits of using clinical officers compared to doctors are the reduced training and employment costs, as well as enhanced retention within the local health systems (226, 227, 229).

The scope of practice of a clinical officer within obstetrics is often determined by the country in which they practice (225). In nineteen out of forty seven Sub-Saharan African countries, clinical officers are authorised to provide obstetric care, yet in only five countries are they permitted to perform caesarean sections and other emergency obstetric surgery (228). Given that caesarean section is the most common major surgical procedure in Sub-Sahara Africa (230), and must be delivered in a timely fashion to save a mothers and babies life (231), clinical officers could potentially play an important role in increasing accessibility and availability of emergency obstetric care, particularly caesarean section, and thus ultimately reduce maternal mortality. However, currently there is uncertainty about the role of clinical officers (224), their training, effectiveness and their safety.

Yet given the central role that clinical officers could potentially have in increasing the obstetric care provision, we have systematically reviewed and meta-analysed the effectiveness and safety of clinical officers in caesarean section surgery.

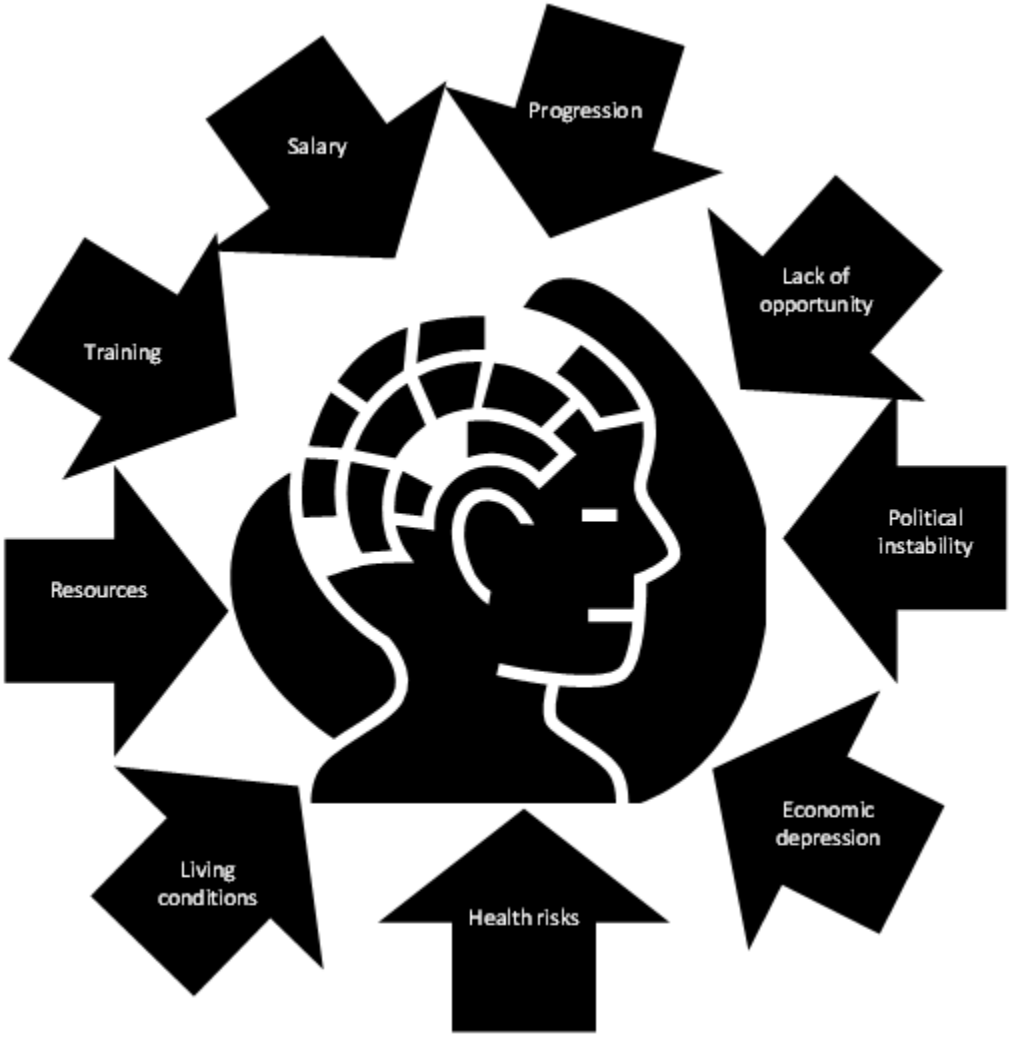

Figure 33 Factors Associated with Brain drain in the literature (224-227)

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7.2 METHODS

Data sources and searches

Databases were searched for relevant literature on clinical officers within obstetrics in developing countries, with particular attention to maternal and perinatal mortality rates, and adverse maternal outcomes. The databases that were searched were MEDLINE, EMBASE, Cochrane, CINHAL, BIOMED Central, the Reproductive Health Library, and the Science Citation Index (from database inception to August 2010). Hand searching complemented the electronic searches performed, and reference lists were checked. Search terms were 'clinical officer', 'medical officer', 'assistant medical officer', 'medex', and 'non physician clinicians'. Pregnancy specific terms were not included within the search terms to increase the sensitivity of the search, to ensure all studies with relevant data were identified. No language restrictions were applied to the search.

Study selection and data extraction

As there was an absence of randomised evidence comparing caesarean section outcomes of clinical officers and medical doctors, controlled studies comparing clinical officers and medically trained doctors for caesarean section in the developing world setting were selected, if they reported on any clinically relevant maternal or perinatal outcomes. Firstly the electronic searches were scrutinised and full manuscripts of relevant studies were obtained. A final decision on inclusion or exclusion of manuscripts was made after examination of these manuscripts by the author and another reviewer (AW and DL), a third reviewer was involved if there were discrepancies in the decision for inclusion. Information was extracted from each selected article on study characteristics, study quality and outcome data. Descriptive studies were also examined to explore the role of the clinical officer further.

Methodological quality assessment

The selected studies were assessed for adequacy of reporting using the Strobe checklist (69). The STROBE statement is a checklist of 22 items considered essential for sound reporting of observational studies. The items included relate to the article's title and abstract, the introduction, the methods, the results of the study and the discussion section. Other information such as funding is also featured. The checklist differs slightly for reporting case-control studies, cohort studies and cross sectional studies. Studies were also assessed for risk of bias using the Newcastle Ottawa Scale (71). The controlled studies were evaluated for representativeness of the cohorts, selection of the cohorts, ascertainment of the intervention and the outcome, comparability of the cohorts, as well as the length and adequacy of follow-up. The risk of bias was regarded as low if a study obtained four stars for selection, two stars for comparability and three stars for ascertainment of exposure (71). Medium risk of bias was suggested to exist in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was deemed to have a high risk of bias.

Data synthesis

Odds ratios from individual studies were pooled using the random effects model to account for the variability in the setting, cadre training and cases included in the studies. Heterogeneity of treatment effects was evaluated using forest plots, chi square and I^2 tests; the terms low, moderate, and high heterogeneity were assigned to I^2 values of over 25%, 50%, and 75% respectively. Where possible, data for adjusted estimates were presented on the forest plot to account for confounding factors. Analyses were performed using Revman 5.0 statistical software.

7.3 RESULTS

Six non-randomised controlled cohort studies, with a total of 16,018 women, were found to be suitable for inclusion in our review (Figure 26). Characteristics of the included studies are shown in (Table 19). There was medium risk of bias in selection, and medium to high risk of bias in comparability and outcome assessment for most studies when assessed on the Newcastle-Ottawa Scale (Table 20).

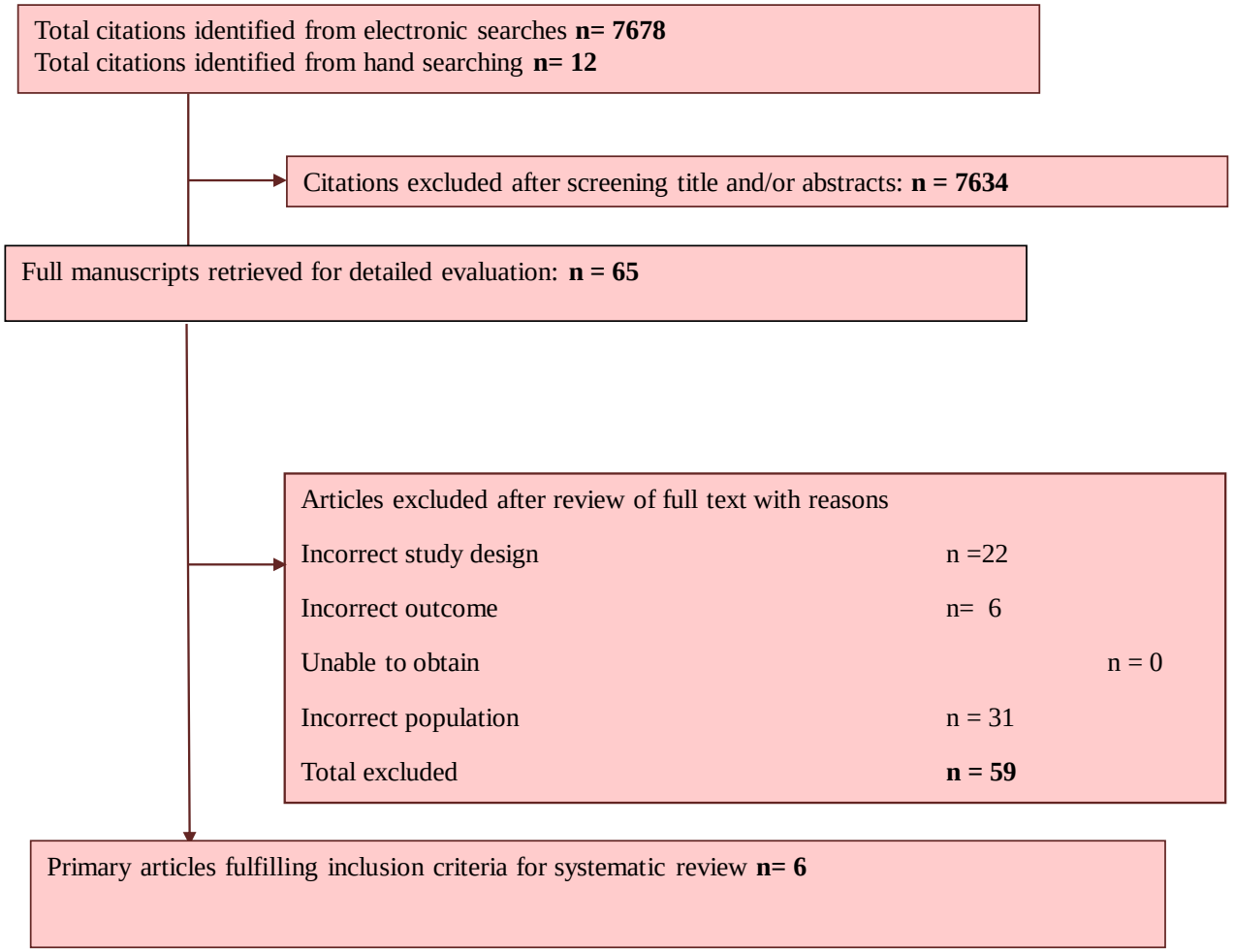

Figure 34 Results of search strategy and identification of publications included

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Maternal Mortality

All six studies compared clinical officers with medical doctors for the outcome of maternal mortality. The meta-analysis showed there was no significant difference between the two groups (OR 1.46, 95% CI 0.78 to 2.75, p=0.24: Figure 27). However, the analysis found significant heterogeneity (p = 0.03) which was quantified to be moderate (I^2 = 60%). One (231) of the two studies (226, 231) that showed an increase in maternal mortality with clinical officers performing caesarean section in the crude analysis, found that the increase was no longer statistically significant when the analysis was adjusted for rural setting, previous caesarean section, haemorrhage, other peri-operative medical complications and the level of training of surgeon (adjusted OR 1.4 95%CI 0.7 to 2.9). The second study (226) that showed an increase in maternal mortality with the clinical officers also adjusted the analysis, but for reported diagnosis and referral status; however the adjusted estimates were not provided. The overall maternal mortality rate in the six studies was high at 1.2%.

Perinatal mortality

Five studies (15,665 women) compared caesarean sections performed by clinical officers and medical doctors for the outcome of perinatal mortality. The meta-analysis showed no significant difference between the groups (OR 1.31, 95% CI 0.87 to 1.95 p=0.19: Figure 27). The analysis found significant heterogeneity (p < 0.01), quantified to be high with an I^2 of 88%. One (231) of the two studies (226, 231) that showed an increase in perinatal mortality with clinical officers in the crude analysis, found that this was no longer statistically significant when adjusted for confounding factors (adjusted OR 1.1 95% CI 0.8 to 1.3). The overall perinatal mortality in the pooled five studies rate was high at 10.7%.

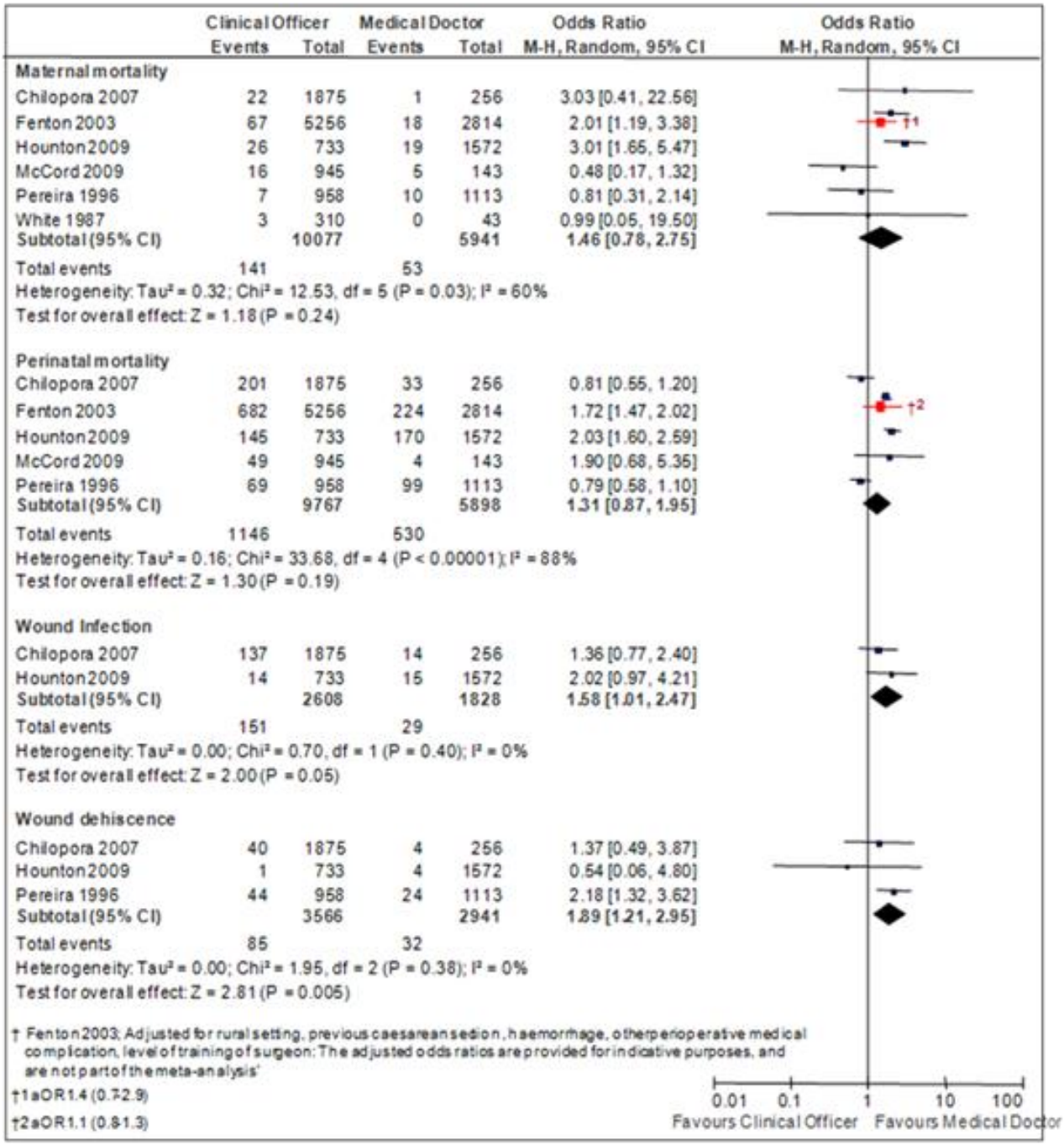

Figure 35 Caesarean section outcomes: comparison of clinical officers with medical doctors

Wound infection

Two studies (226, 232)(4,436 women) compared the rates of wound infection in caesarean sections when performed by clinical officers and medical doctors. The meta-analysis found a significant increase in wound infection when caesarean section was performed by clinical officers when compared with medical doctors (OR 1.58, 95% CI 1.01 to 2.47, p=0.05: Figure 27). There was no significant heterogeneity (p = 0.40, I^2 = 0%).

Wound dehiscence

Three studies (224, 226, 232)(6,507 women) compared the rates of wound dehiscence. The meta-analysis showed a significance increase in wound dehiscence with clinical officers performing caesarean section when compared to medical doctors (OR 1.89, 95% CI 1.21 to 2.95, p=0.005: Figure 27). There was no evidence of significant heterogeneity in the analysis (p=0.38, I^2 = 0%).

Training of clinical officers

All six papers gave training details of clinical officers; training length and specification varied between countries. In Zaire (233) and Burkina Faso (226) nurses attended a 2 year training course to become clinical officers, with an additional 1-2 years of surgical training in Zaire, but no details were reported on experience or length of service. The clinical officer cadre varied in the studies with one study (in Zaire)(233) reporting the cadre to be nurses that were trained to perform obstetric surgery, such as caesarean sections, laparotomies and supracervical hysterectomies (233). The nurses in this study were trained for a minimum of three years at secondary school, followed by a further two years of nurse training, then an additional 1-2 years of surgical training (233), but again no details on experience were reported. In the study set in Mozambique (224), clinical officers were assistant medical officers with three years

surgical training in general surgery, obstetrics, gynaecology, orthopaedics, trauma, intensive care, and neurosurgery (224). No details were reported on experience or length of service. Clinical officers in both studies in Malawi undertook a 3 year health foundation course, with a year as an intern at a hospital or in surgical training (231, 232). One study reported that clinical officers were licensed to practice independently, and performed major emergency and elective surgery. The majority of the clinical officers in this study had over four years surgical experience (232). In the study set in Burkina Faso (226) clinical officers underwent a six month curriculum in emergency surgery to perform operative obstetric care, and registered nurses completed an extra two years additional surgical training. No details on the level of experience were reported. The clinical officers in the study set in Tanzania (234) were assistant medical officers that were authorised to provide clinical services, such as prescriptions and minor surgery. They were also permitted to perform obstetric care and caesarean sections. They were all secondary school graduates with 3 years medical training, plus a further 2 years clinical training, including 3 months in surgery and 3 months in obstetrics.

Description of cases

In the study conducted in Zaire (233) only 12% of patients were operated on by doctors, the remainder operated on by clinical officers. Separate case details were not provided for each cadre. The majority of caesarean section were performed for cephalopelvic disproportion and obstructed labour. This study included participants in two hospitals, however one of the hospitals in this study was without a medical doctor for one year. The nurses in this study performed all of the caesarean sections, however in one of the other units in this study, the resident medical doctor routinely operated on the most complicated and critical cases. The medical doctor in this unit would only

perform the caesarean section when no nurses were available. In the study set in Mozambique (224) clinical officers conducted around half of all caesarean sections, most of which were performed for fetal distress (32.2%). The most common reason for caesarean section in the medical doctor group was also fetal distress (29%). Most emergency operations were performed by clinical officers, and all elective caesarean sections were performed by doctors. In the study in Malawi by Fenton et al (231), a third of caesarean sections were performed by doctors, the remainder performed by clinical officers. No separate details for the surgeons were reported for the indication for caesarean section; again the majority were performed for obstructed labour (63%). In the other study in Malawi by Chilopora et al (232) the majority of caesarean sections were conducted by clinical officers (88%), as before, separate details for both groups were not reported in relation to the indication of the operation. The most common indication was cephalopelvic disproportion or obstructed labour (57.7%). In the study conducted in Burkina Faso (226), the majority of caesarean sections were performed by medical doctors (68%). A higher percentage of these operations were conducted in an urban hospital, only 9% were conducted in a rural hospital. This however was opposite in the clinical officer group, 73% of caesarean sections in this group were performed in a rural hospital. The main indication in both clinical officer and medical doctor groups was obstructed labour (53% and 39% respectively). The women who were referred for complications were not significantly more of less likely to be operated on by medical doctors in relation to clinical officers. In the study by McCord et al that was set in Tanzania (234) 87% of caesarean sections were performed by clinical officers. The most common indication in both cadre groups was the 'absolute maternal indication' which included women who experienced ante-partum haemorrhage, postpartum haemorrhage, malpresentation, eclampsia, ectopic pregnancy, ruptured uterus, sepsis and repair of vesico-vaginal fistula (33.1% and 33.6% respectively).

Table 20 Characteristics of included studies

	Clinical Officer	**Medical Doctor**
White 1987: Zaire		
Cadre details, training	Nurses trained to perform C/S, laparotomies, supracervical hysterectomies: Minimum of 3 yrs at secondary school, 2 yrs nurse training. 1-2yrs additional surgical training	Medically qualified doctor. Not given
Population, Characteristics	Pregnant women needing c/s at 2 rural hospitals or health centres in northwest Zaire. Characteristics not given	As before
Amount, Indication for C/S (%)	310 (88%) No separate details given on surgeon and indication for c/s, only given for Karawa hospital (321 c/s): Cephalopelvic disproportion and obstructed labour 159 (50%). uterine inertia 70 (22%).previous c/s 54 (17%)fetal distress 22(7%) placenta praevia 16(4%)	43(12%) As before
Surgeon allocation, type of operation	One unit was without a MD for 1 yr, nurses performed all c/s. In one unit MD did not routinely perform most complicated operations. In other unit MD operated on most critical cases. MD performed c/s when no nurse available, or training medical students. Operation type not given	As before
Potential confounders	Delay in seeking care, delay in reaching care (transportation), other medical complications No adjustments made.	As before
Outcome	MMR	As before
Pereira 1996: Mozambique		
Cadre details and training	Assistant medical officers (clinical officers with surgical training).3 yrs some surgical experience in general surgery, obstetrics, gynaecology, orthopaedics, trauma, intensive care, neurosurgery.	Trained obstetricians and gynaecologists. Not given
Population, Characteristics	Pregnant women needing c/s at central hospital. c/s rate 16.5% was only hospital performing c/s. Age 25.3yrs, parity 2.2. Shanty town 353 (37%). antenatal care 948 (99%). twin pregnancy 25 (3%)	As before Age 25.5yrs, parity 2.2, shanty town 404(36%), antenatal care 1101 (99%), twin pregnancy 21(2%)
Amount, Indication for C/S (%)	958(46%) Fetal distress. 308 (32.2%) Cephalopelvic disproportion.177 (18.5%) previous c/s 89 (9.3%). placental abruption or praevia 79 (8.2%).impending uterine rupture 72 (7.5%). eclampsia 31 (3.2%). pre-eclampsia 26 (2.7%). no information 176 (18.4%)	1113 (54%) Fetal distress 326 (29%) cephalopelvic disproportion 212 (19%) previous c/s 133 (11.9%) placental abruption or praevia 74 (6.6%) impending uterine rupture 68 (6.1%) eclampsia 40 (3.6%) pre-eclampsia 33 (3%).no information 227 (20.5%)

Surgeon allocation, type of operation	No random allocation for ethical reasons. Some selection occurred when patients allotted to CO or MD. c/s only 682 (71%). c/s+ Subtotal hysterectomy 8 (1%). c/s + total hysterectomy 3 (0.5%). c/s + uterine repair 4 (0.5%). c/s + tubal ligation 257 (26.5%).no info 4 (0.5%)	It is noted that emergencies prevented MD attending complicated c/s. Furthermore medical doctors carried out all elective c/s n=145 (7.0%) c/s only 832 (74.5%). c/s + Subtotal hysterectomy 10 (1%). c/s + total hysterectomy 4 (0.5%) c/s + uterine repair 5 (0.5%). c/s + tubal ligation 256 (23%) no info 6 (0.5%)
Potential confounders	Age, parity, shanty own residence, antenatal care, twin pregnancy. No adjustments made	As before
Outcome	MMR, duration of post operative stay, wound rupture or separation, condition of the newborn	As before
Fenton 2003: Malawi		
Cadre details and training	clinical officer surgeons: 3 year foundation health course, plus 1 year in surgical training	Medically qualified doctor: Not given
Population, Characteristics	Women requiring c/s, after 28 weeks, including surgery for ruptured uterus. 23 district and 2 central hospitals. No separate details given on surgeons for characteristics: District hospital 5236 (65%). urban hospital 2834 (35%)	As before
Amount, Indication for C/S (%)	5256 (65%) No separate details given on surgeon and indication for c/s. Obstructed labour 5110 (63%). fetal distress 885 (11%).ante-partum haemorrhage 384 (5%). pre-eclampsia 268 (3%). haemorrhagic shock 610 (8%). ruptured uterus 333 (4%). other 480 (6%)	2814(35%) As before
Surgeon allocation, type of operation	Not given	Not given
Potential confounders	Previous c/s, pre operative complications, fever, status and training of anaesthetist and surgeon, anaesthesia, blood loss, blood transfusion. Adjusted for confounders	As before
Outcome	MMR, PMR	As before
Chilopora 2007:Malawi		
Cadre details and training	CO: Licensed to practice independently, perform major emergency and elective surgery. Length of surgical experience: 44% >4yrs 24.3% 2-3 yrs 21.4% <1 yr 9.3% 0 0.6% no data 3 Years plus 1 year internship at a hospital	MD: Trained medical doctors. Length of surgical experience: 59% >4yrs: 19.9% 2-3yrs 17.2%<1yr: 3.9% no data: Not given
Population, Characteristics	All women undergoing c/s during study period were included in 38 district hospitals, most were emergency c/s. Groups operated on by CO and MD had no major differences	

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Amount, Indication for C/S (%)	1875(88%) No separate details given on surgeon and indication for c/s: Cephalopelvic disproportion or obstructed labour 1230 (57.7%). previous c/s 452 (21.2%). fetal distress 264(12.3%). impending uterine rupture 87 (4%) antepartum haemorrhage77 (3.6%). cord prolapse 62 (2.9%). failure to progress 60 (2.8%).breech in primigravida 3(2.5%) eclampsia 49 (2.3%)	256(12%)
Surgeon allocation, type of operation	Not given c/s only 1569 (84%). c/s + subtotal hysterectomy 11 (0.5%). c/s + total hysterectomy 7(0.5%) c/s + uterine repair 59 (2.5%). c/s + tubal ligation 224 (12%) not indicated 5 (0.5%)	c/s only 185 (72%). c/s + subtotal hysterectomy 8 (3%). c/s + total hysterectomy 3 (2%) c/s + uterine repair 7(3%) c/s + tubal ligation 53 (20%).not indicated 0 (0%)
Potential confounders	Duration of surgeon's practice, region of hospital, type of operation (if hysterectomy needed also). No adjustments made	As before
Outcome	MMR, infection, wound dehiscence, fever, PMR	As before
Hounton 2009: Burkina Faso		
Cadre details and training	CO: CO working in both rural and urban hospital. 6 month special curriculum CO to perform emergency surgery OR 2 year additional surgical training for registered nurses	Trained MD only based at urban hospitals Obstetricians
Population, Characteristics	2305 pregnant women needing c/s section in 22 public sector urban and rural hospitals Age 25yrs urban hospital 198 (27%) rural hospital 535 (73%)	As above Age 25yrs urban hospital 877 (56%) rural hospital 143 (9%)
Amount, Indication for C/S (%)	733(32%) Obstructed labour 388 (53%) ruptured uterus 81 (11%) eclampsia 15 (2%) haemorrhage 44 (6%) Other 205(28%)	1572(68%) Obstructed labour 398 (39%) ruptured uterus 112 (11%) eclampsia 71 (7%) haemorrhage 51 (5%) other 388 (38%)
Surgeon allocation, type of operation	No details given on selection of operator, retrospective study. However medical doctors were associated with more referred cases, although not statistically significant.	As before
Potential confounders	Place of hospital, maternal age, reported clinical conditions; obstructive labour, ruptured uterus, eclampsia, haemorrhage, referral from other unit, type of anaesthesia. Adjustments made, but adjusted statistics not given.	As before
Outcome	MMR, PMR, haemorrhage, wound infection, wound dehiscence.	As before
McCord 2009: Tanzania		
Cadre details and training	CO: Officially authorised assistant medical officers to provide clinical services; prescriptions, minor surgery. Permitted to perform obstetric care and c/s. Secondary school graduates with 3 years medical training, plus a further 2 years clinical training, including 3 months in surgery and 3 months in obstetrics.	Trained MD:Medical school graduates with >1 year internship

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Population, Characteristics	1088 pregnant women in 14 mission and government hospitals. Not given	As above. Not given
Amount, Indication for C/S (%)	945(87%) Absolute maternal indication (ante-partum haemorrhage, Postpartum haemorrhage, malpresentation, eclampsia, ectopic pregnancy, ruptured uterus, sepsis and repair of vesico-vaginal fistula) 312 (33.1%) major acute problem (no details given) 63 (6.6%) major chronic problem (severe anaemia, symptomatic AIDS, symptomatic malaria) 172 (18.2%). No information 398 (42.1%)	143(13%) Absolute maternal indication (ante-partum haemorrhage, postpartum haemorrhage, malpresentation, eclampsia, ectopic pregnancy, ruptured uterus, sepsis, repair of vesico-vaginal fistula) 48(33.6%).major acute problem (no details given) 14 (9.8%). major chronic problem (severe anaemia, symptomatic AIDS, symptomatic malaria) 22 (15.3%). no information 59 (41.3%)
Surgeon allocation, type of operation	No reason given for choice of operator. However clinical officers were more likely to perform c/s with absolute maternal indicators or clear fetal indicator. CO had more difficulties obtaining blood for transfusion. Not given	No reason given for choice of operator. However MD were less likely to perform c/s for absolute maternal indicators or clear fetal indicator. MD had less difficulties obtaining blood for transfusion. Not given
Potential confounders	Condition on admission, type of operation, indication for operation, blood transfusions. No adjustments made.	As above
Outcome	MMR, PMR	As before

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Table 21 Risk of Bias Assessment in cohort studies: Newcastle Ottawa Scale (Y= reported: N: not reported)

	Selection				Comparability	Outcome		
Article	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome not present at start	Comparability of cohorts on the basis of the design or analysis (2 points available)	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
White 1987	Y	N	Y	Y	N	Y	N	N
Pereira 1996	Y	Y	Y	Y	N	Y	N	N
Fenton 2003	Y	N	Y	Y	YY	Y	N	N
Chilopora 2007	Y	N	Y	Y	N	Y	N	Y
Houton 2009	Y	N	Y	Y	Y	Y	N	N
Mccord 2009	Y	N	Y	Y	N	Y	N	N

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7.4 DISCUSSION

Main findings

The meta-analysis demonstrated no significant difference in maternal or perinatal mortality in caesarean sections performed by clinical officers, compared with medical doctors. However, when the outcomes of wound dehiscence and wound infection were compared, both were found to be significantly more frequent in caesarean sections performed by clinical officers compared with medical doctors.

Strengths and limitations

All of the six studies examined were comparative cohort studies. However, as they were not randomised trials, there is the potential for bias in these studies. There was medium risk of bias in selection, and medium to high risk of bias in comparability and outcome assessment for most studies when assessed on the Newcastle-Ottawa scale. For example, in Pereira et al (224) elective caesarean sections were exclusively carried out by medical doctors, whist emergencies were carried out by both medical doctors and clinical officers. As elective caesarean section is associated with better outcomes when compared with emergency caesarean section (235), this arrangement would have conferred an advantage to medical doctors. Furthermore, clinical officers tend to be located in rural areas (226) where access to life saving facilities such as blood transfusion and high dependency care may not be available. Fenton et al (231) addressed such issues by adjusting for rural setting, previous caesarean section, haemorrhage, other peri-operative medical complications and the level of training of the surgeon. Their initial analysis showed an excess in maternal and perinatal mortality associated with clinical officers. However, when adjusted for the above factors there was no longer a significant difference in these outcomes. This suggests that in this study there may have been more high risk cases in the clinical officer group. It is also plausible that the bias could also be in the other direction. For instance the perceived

severity of the situation may have resulted in a medical doctor performing the caesarean section rather than a clinical officer. This may cause bias in favour of clinical officers. Although most studies reported no differences in patient characteristics or indication for caesarean section, and some studies adjusted for various factors (226, 231), there can still be residual confounding.

There was significant heterogeneity for maternal and perinatal outcomes, which may reflect the diversity of the setting and the population, indications for surgery, surgical approach and training and role of the clinical officers in these studies. Given such clinical heterogeneity, it is unsurprising that statistical heterogeneity was identified in the analyses. Formal exploration of the reasons for statistical heterogeneity by study features was limited due to the small number of studies identified in our review. However, when there was adjustment for confounding factors, the observed heterogeneity was noted to be reduced.

Practice and policy implications

While we acknowledge caution when interpreting the meta-analysis findings due to the non-randomised nature of the included studies, this remains the best current evidence on these outcomes.

There was an increase in wound infection and dehiscence with clinical officers. This was consistent in the two studies that examined these outcomes. We speculate that these outcomes may be associated with surgical technique and a need for enhanced training. Pereira et al (224) highlighted that 97% of caesarean sections were through a vertical abdominal incision, which is known to be associated with increased wound dehiscence and other adverse outcomes when compared with horizontal incisions (235). Thus, there may be substantial scope for improvement in surgical technique. There is evidence that specialist training of clinical officers can improve outcomes.

Fenton (231) measured the incidence of maternal death from anaesthesia, when administered by clinical officers who had received formal training and those that did not. The maternal mortality rate was much higher in those that had not received training (2.4%), when compared to those that had (0.9%). It is also possible that the increase in wound infection and wound dehiscence may be due to the difference in the case mix between the clinical officer and the medical doctor group. For example, the clinical officer cadre conducted more emergency caesarean sections, often associated with increased morbidity compared to elective procedures, but also clinical officers operated in more rural settings, which are often associated with less resources and poorer outcomes.

This review assesses the important and specific role of clinical officers in performing caesarean section, which is an immediate determinant of outcome. However, this must be placed within the wider context of the many distant and intermediate determinants of maternal health and mortality (11) (Figure 36). Part of the value of the clinical officer cadre is that their role can be adapted to suit local needs and conditions. Yet as there are no internationally agreed curricula or scope of practice guidelines (225), the importance of evaluating clinical officers in their specific setting needs to be recognised.

Unanswered questions and future research

Little work has been conducted to assess the role of clinical officers in addressing these wider determinants they can have an important impact on these factors. Therefore the impact of the clinical officers on increasing access to services (228, 236), the clinical officer's role within family planning (225) and within broader preventative health programmes (228, 237) to reduce maternal mortality could be assessed

7.5 CONCLUSION

This meta-analysis suggests that the provision of caesarean section surgery by clinical officers does not result in a significant increase in maternal or perinatal mortality. Enhanced access to emergency obstetric surgery through greater deployment of clinical officers, in countries with poor coverage by medical doctors, can form part of the solution to meet MDGs 4 (reducing child mortality) and 5 (improving maternal health).

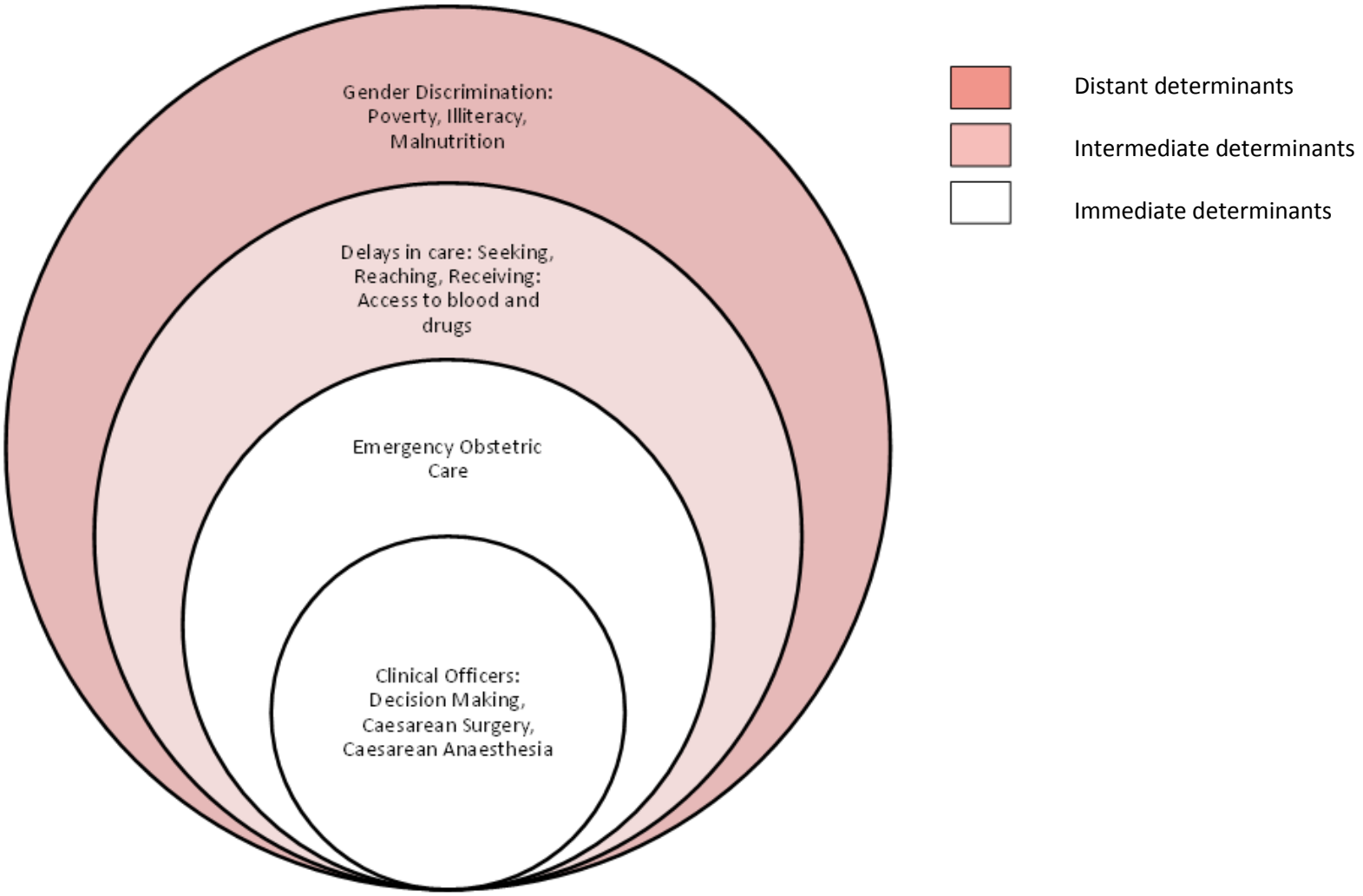

Figure 36 Determinants of maternal mortality (distant, intermediate, immediate)

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CLINICAL INTERVENTIONS

CHAPTER 8: PROPHYLACTIC ANTIBIOTICS FOR UTERINE EVACUATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Infection is a serious potential consequence of surgical treatment of miscarriage and can be associated with mortality and serious morbidity. In areas where abortion services are inadequate or are limited by law, many cases are suggested to be due to physical interference to induce miscarriage. Critical to any method of surgical uterine evacuation, in the case of abortion or miscarriage, are mortality and morbidity, but also the effects on future childbearing. Therefore a systematic review with meta-analysis was performed to assess the effectiveness of prophylaxis antibiotics compared to placebo, for surgical uterine evacuation in cases of miscarriage or abortion.

Methods: Embase, Medline, CENTRAL and PsycINFO bibliographic, African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), Latin American and Caribbean Health Sciences Information (LILACS), Pan America Health Organisation (PAHO) and Western Pacific Region Index Medicus (WPRIM) (from inception to July 2011) were searched without language restrictions. Hand searching complemented electronic searches, and reference lists were checked. Studies of randomised controlled design were selected, with the outcome of infectious morbidity. Relative risks (RR) from the individual studies were pooled for RCTs, using a random effects model.

Results: Twenty one RCTs (n=11,384 women) were identified as suitable for inclusion. Meta-analysis of 18 RCTs showed a reduction in infectious morbidity with prophylactic antibiotics in surgical abortion (RR: 0.59 95%CI 0.47 to 0.73, p<0.001). Three trials were included for miscarriage, meta-analysis was not considered suitable.

Conclusion: Meta-analysis of 18 RCTs showed an average reduction in infectious morbidity in cases of surgical abortion with prophylactic antibiotics by 41%**.** Data on miscarriage was insufficient to draw inferences.

Impact of review: Informed the antibiotics In Miscarriage Surgery trial (AIMS Trial) funded by the MRC, Wellcome and DFID

8.1 BACKGROUND

Miscarriage and abortion affects many women across the globe, with approximately 33 million pregnancies ending in miscarriage (238), and 43.8 million pregnancies ending in abortion every year (239). In areas where abortion services are inadequate or are limited by law, many cases are suggested to be due to physical interference to induce miscarriage (unsafe abortion)(240). In areas where induced abortion is limited by law women may be reluctant to disclose the true nature of the miscarriage for fear of social stigma, legal connotations or treatment denial (241). Cases of unsafe abortion thus may be reported as miscarriage.

An estimated 60 – 70% of women with miscarriage have surgery to remove retained pregnancy tissues from the uterus (242). For many hospitals in low income countries miscarriage surgery is the most common operation performed. Miscarriage surgery accounts for the majority of gynaecology admissions (242) in some hospitals, with some regions performing an average of 160 suction evacuations each month (243).

Infection is a serious potential consequence of surgical abortion and surgical treatment of miscarriage and can be associated with mortality and serious morbidity. In developed countries, where surgical procedures are carried out in sterile conditions, with sterile equipment and where practices are guided by policies, infectious morbidity is often less prevalent. Whereas in developing countries, equipment used for invasive procedures (e.g.

surgical abortion or miscarriage surgery) may be poorly sterilised, patients may be immunocompromised due to malnutrition, HIV, malaria or anaemia, and infection control procedures in the clinical setting may not be in place or adhered to, thus putting the patient at greater risk of infection. Death from unsafe abortion is one the main causes of maternal mortality within low income countries, attributable to approximately 13% of deaths (241). In 2008 it is estimated that 21.2 million unsafe abortions took place within developing regions, compared to 400,000 across the rest of the globe (241).

Critical to any method of surgical uterine evacuation, in the case of abortion or miscarriage, are also the effects on future childbearing (244). Pelvic infection can lead to scarring, increased rates of ectopic pregnancy, and permanently fertility impairment (245). In high income countries, from which most data originates, infection occurs in approximately 6% of women following surgical treatment of miscarriage (246, 247). In a low income setting the infection rate after miscarriage surgery has been reported to be as high as 30% (240). Despite these figures prophylactic antibiotics are not recommended for surgical treatment of miscarriage, unlike surgical abortion: instead if sepsis develops aggressive treatment is advocated to reduce morbidity and mortality (248, 249). The bacteria suggested to be responsible for infectious morbidity in the included studies are gram positive cocci, anaerobes, gram coagulase-negative staphylococci, corynebacterium, lactobacillus (250, 251), Gardnerella vaginalis (252), and Chlamydia trachomatis (253). These bacteria and other associated bacteria along with antibiotics that can be used to treat the infections caused are demonstrated in Figure 38. However choice of antibiotic for a patient with a pelvic infection should be guided by an awareness of the susceptibility patterns of organisms in the setting as well as the organisms frequently involved, as this can vary from setting to setting (254). It is reported in the literature that in animal models there is a higher frequency of female pelvic infection from anaerobic bacteria and gram positive bacteria compared to other bacteria (254).

The latest Cochrane review (255) recognised the lack of available evidence to inform practice guidelines, with a conclusion that there is *" a real and urgent need to find out whether antibiotics should be routinely used in cases of incomplete abortion" (miscarriage),* particularly in low income regions where there is a high prevalence of undisclosed unsafe abortions. There appears to be a lack of clinical guidance both internationally and national on current prophylactic antibiotic policy for miscarriage surgery, but existing guidance on prophylactic antibiotic use in abortion. Figure 37 demonstrates examples of organisations that provide recommendations on prophylactic antibiotic use in miscarriage surgery and surgical abortion. The majority of organisations recommend prophylactic antibiotic use in surgical abortion (249, 256-258), however for miscarriage surgery the majority of organisations recommend administration of antibiotics only if infection occurs (248, 259, 260).

A systematic review and meta-analysis was performed to assess the effect of prophylactic antibiotics on infectious morbidity in surgical uterine evacuation in abortion and miscarriage surgery.

Organisation/ Country	Prophylactic antibiotics for induced abortion surgery	Prophylactic antibiotics for miscarriage surgery
World Health Organisation	✔ Recommend use (249)	✖ Not recommended unless signs of infection (248)
Royal College of Obstetricians and Gynaecologists	✔ Recommend use (258)	? Insufficient evidence to recommend routine antibiotic prophylaxis (260)
Scottish Intercollegiate Guidelines Network	✔ Recommend use (257)	✖ Insufficient evidence to recommend routine antibiotic prophylaxis (257)
American College of Obstetricians and Gynaecologist	✔ Recommend use (261)	✖ Not recommended unless signs of infection (261)
Ugandan Ministry of Health	? No recommendations on prophylactic antibiotics for induced abortion surgery (259)	? No guidelines or consistent practice on prophylactic antibiotics, antibiotics are recommended if signs of infection present (259)
National Abortion Federation	✔ Recommend use (256)	✖ Not recommended (256)

Figure 37 Prophylactic antibiotic recommendations

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	Bacteria reported in trial	Most Effective Antibiotic
Gram-positive bacteria	Lactobacillus	Ampicillin, Amoxicillin/clavulanic acid
	Gram positive cocci	Chloramphenicol , Amikacin , Enrofloxacin , Rifampin, Cephalothin
	Anaerobes Gram coagulase-negative staphylococci, Corynebacterium, Gardnerella vaginalis Chlamydia trachomatis	Amoxicillin/clavulanic acid, Ampicillin, Ceftiofur, Ceftizoxime, Cephalothin, Chloramphenicol, Erythromycin, Penicillin G, Trimethoprim-Sulfonamide

Figure 38 Causative bacteria and effective antibiotics (http://www.dragpharma.cl/pdfs/antibiotic-talbles.pdf)

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8.2 METHODS

Data sources and searches

Embase, Medline, CENTRAL and PsycINFO bibliographic, African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), Latin American and Caribbean Health Sciences Information (LILACS), Pan America Health Organisation (PAHO) and Western Pacific Region Index Medicus (WPRIM) were searched (from inception to July 2011). Hand searching complemented electronic searches, and reference lists were checked. The terms 'abortion', 'miscarriage', 'antibiotics' and 'infection' were used to identify relevant publications. Keywords, word variations and terms associated with these terms were used as part of the search strategy. No language restrictions were applied to the search.

Study selection and data extraction

RCTs were selected. Initially the electronic searches were scrutinised and full manuscripts of relevant studies were acquired. Final decisions on inclusion or exclusion of manuscripts were made after inspection of these manuscripts by the author and another reviewer (AW and RC) and when necessary a second reviewer was involved in decisions (AC). Information was extracted from each article on study characteristics, quality assessment and outcome data by the author and two other reviewers (AW and RC or AC). The outcomes that were focussed on were infectious morbidity.

Methodological quality assessment

The RCTs were assessed for methodological quality using the CONSORT statement (68), assessing for randomisation and sequence generation, baseline comparability, blinding, follow-up, and appropriate statistical analysis (ITT). Risk of bias was also assessed using the Cochrane risk of bias tool (102).

Statistical Analysis

The random effects model was used to pool the risk ratios from individual RCTs. The fixed effects model was not deemed suitable for use as more than a single source of variability existed within the included studies, therefore the random effects model was used to account for the variability within the intervention (i.e. the dose, type and frequency of antibiotics, as well as the patient characteristics). Induced abortion and miscarriage trials were pooled separately. Data from these trials were then pooled separately for participants deemed at low risk and high risk of infectious morbidity. Women deemed at low risk of developing pelvic infection included women without a history of pelvic inflammatory disease, or negative for sexually transmitted infections such as Chlamydia, gonorrhea and syphilis. Whereas women deemed at high risk of developing pelvic infection included women with a history of pelvic inflammatory disease, the presence of Chlamydia, or abnormal vaginal flora. This sub-group analysis was performed in an attempt to make the results transferable to women undergoing similar surgical procedures in areas that may incur greater risk of infectious morbidity (e.g. in cases of unsafe abortion or invasive surgery in developing countries with patients that may be immunosupressed). Heterogeneity of treatment effects was evaluated using forest plots, X^2, and I^2 tests; the terms low, moderate and high heterogeneity were assigned to I^2 values of over 25%, 50%, and 75% respectively. Analyses were performed using the Revman 5.0 statistical software.

8.3 RESULTS

Results of search

The study selection process in provided in Figure 29. Characteristics of the included studies are shown in Table 21 for *Evacuation of the uterus in abortion* and *Evacuation of the uterus in miscarriage*.

Evacuation of the uterus in abortion: Eighteen RCTs were included in this review, with a total of 9328 women (Figure 39). The studies compared the outcome of infectious morbidity in

women who received either prophylactic antibiotics, or control treatment (placebo or no drug), undergoing surgical evacuation for abortion.

Evacuation of the uterus in miscarriage: Three RCTs were included in this review, with a total of 785 women (Figure 39). The studies compared the outcome of infectious morbidity in women who received either prophylactic antibiotics, or control treatment (placebo or no drug), undergoing surgical evacuation of the uterus for miscarriage treatment.

Due to the lack of good quality data on surgical treatment of miscarriage and abortion in developing countries (1/21)(240) the available data on surgical treatment of miscarriage and abortion in developed countries has been focused on, however the outcome has been assessed in terms of high and low risk categories in an attempt to make these results more transferable to women undergoing similar surgical procedures in areas that may incur greater risk of infectious morbidity (e.g. in cases of unsafe abortion or invasive surgery in developing countries).

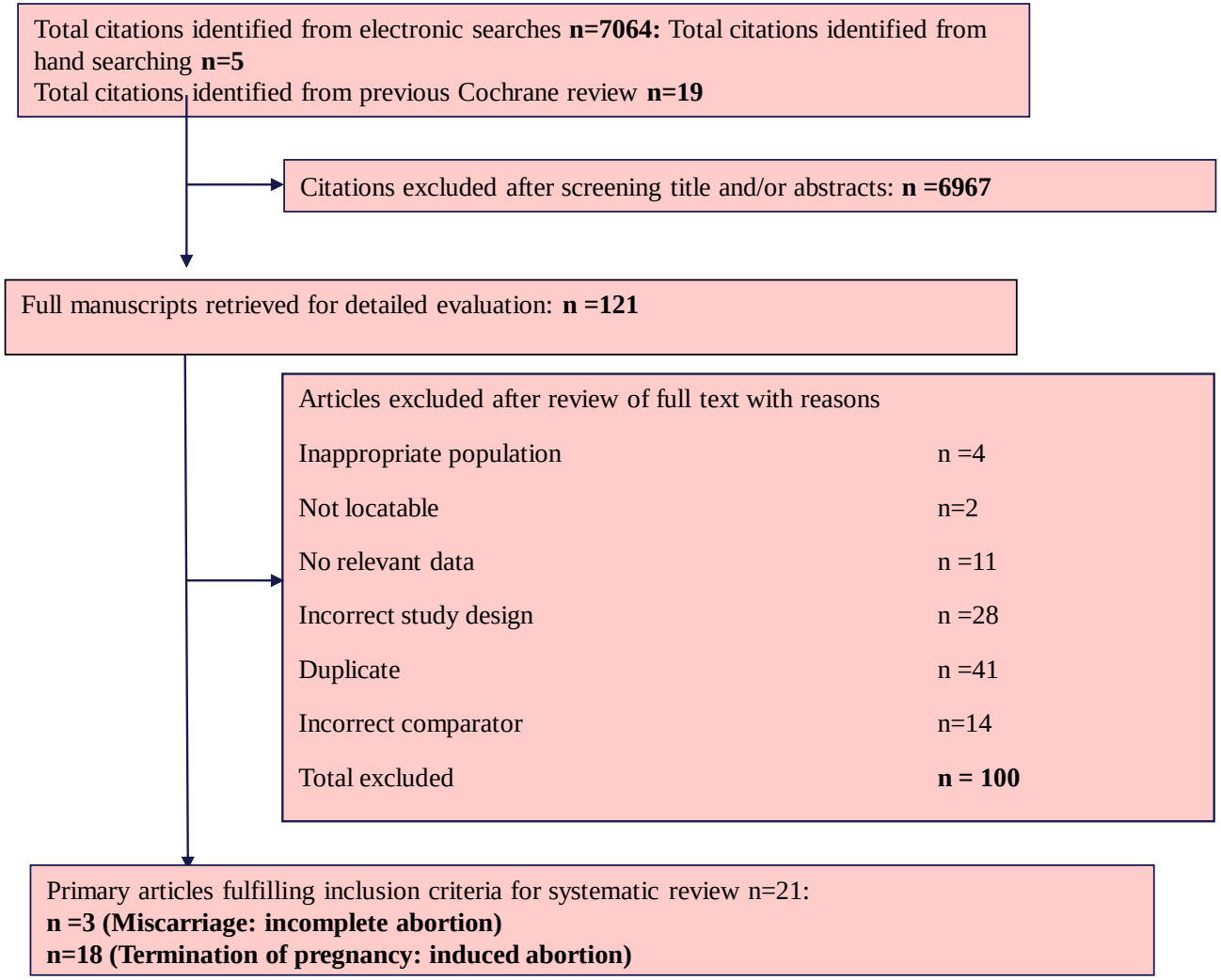

Figure 39 Study selection of included studies in the review

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Study quality

The 21 RCTs varied in quality, a breakdown is provided below:

Evacuation of the uterus in abortion: 16 reported satisfactory baseline comparability, 15 were double blinded, and 11 reported appropriate randomisation. However, only 7 trials reported a sample size calculation and a follow up rate of more than 80%, with only one trial reporting that an intention to treat analysis (ITT) had been conducted (Table 22). Most studies had low risk of bias for blinding of participants and study personnel, incomplete outcome data, selective reporting and other sources of bias. More than half of the studies had unclear risk of bias for random sequence generation, but allocation concealment and blinding of outcome assessors was unclear in most of the studies.

Evacuation of the uterus in miscarriage: Two reported satisfactory baseline comparability, 1 was double blinded, and 3 reported appropriate randomisation. However, only 2 trials reported a sample size calculation and a follow up rate of more than 80%, with only 1 trial reporting that an intention to treat analysis (ITT) has been conducted (Table 22). Most studies had low risk of bias for incomplete outcome data, selective reporting and other sources of bias. All of the studies had low risk of bias for random sequence generation, but allocation concealment and blinding of outcome assessors was unclear in most of the studies.

Outcomes

Evacuation of the uterus in abortion: Meta-analysis of 18 RCTs (9,328 women) showed a significant reduction in infectious morbidity by an average 41% with prophylactic administration of antibiotics in abortion (RR: 0.59 95%CI 0.47 to 0.73, p<0.0001; Figure 30). There was limited but not statictically significant heterogenity in the results (I^2=23%, P=0.18).

Evacuation of the uterus in miscarriage: Three RCTs (785 women) were identified. Given the poor quality of the studies, the clinical heterogeneity in the antibiotic regimen, and the

83% non-compliance in the only study conducted in a low income country (240), a meta-analysis was judged to be inappropriate. All three trials showed no difference in infectious morbidity with prophylactic antibiotics or placebo treatment (Figure 31).

Women at high risk of developing pelvic infection from surgical abortion: Meta-analysis of 13 RCTs showed an average 51 % reduction in infectious morbidity when prophylactic antibiotics are administered to women undergoing surgical abortion deemed at high risk of infectious morbidity. This includes women with a history of pelvic inflamatory disease, the presence of chlamydia, or abnormal vaginal flora (RR 0.49 95% CI 0.34 to 0.71; p=0.0002; Figure 33). There was limited but not significant hetrogenity in the results (I^2 = 24%; p = 0.20).

Women at low risk of developing pelvic infection from surgical abortion: Meta-analysis of 9 RCTs found a significant reduction in infectious morbidity by an average of 58% with propylactic administration of antibiotics to women deemed at low-risk of developing pelvic infection (RR 0.42 95% CI 0.26 to 0.68; p=0.0004; Figure 32). This includes women without a history of pelvic inflamatory disease, or negative for sexually transmitted infections such as chlamydia, gonnorhea and syphillis. There was significant heterogenity within the analysis (I^2 = 52%; p = 0.03).

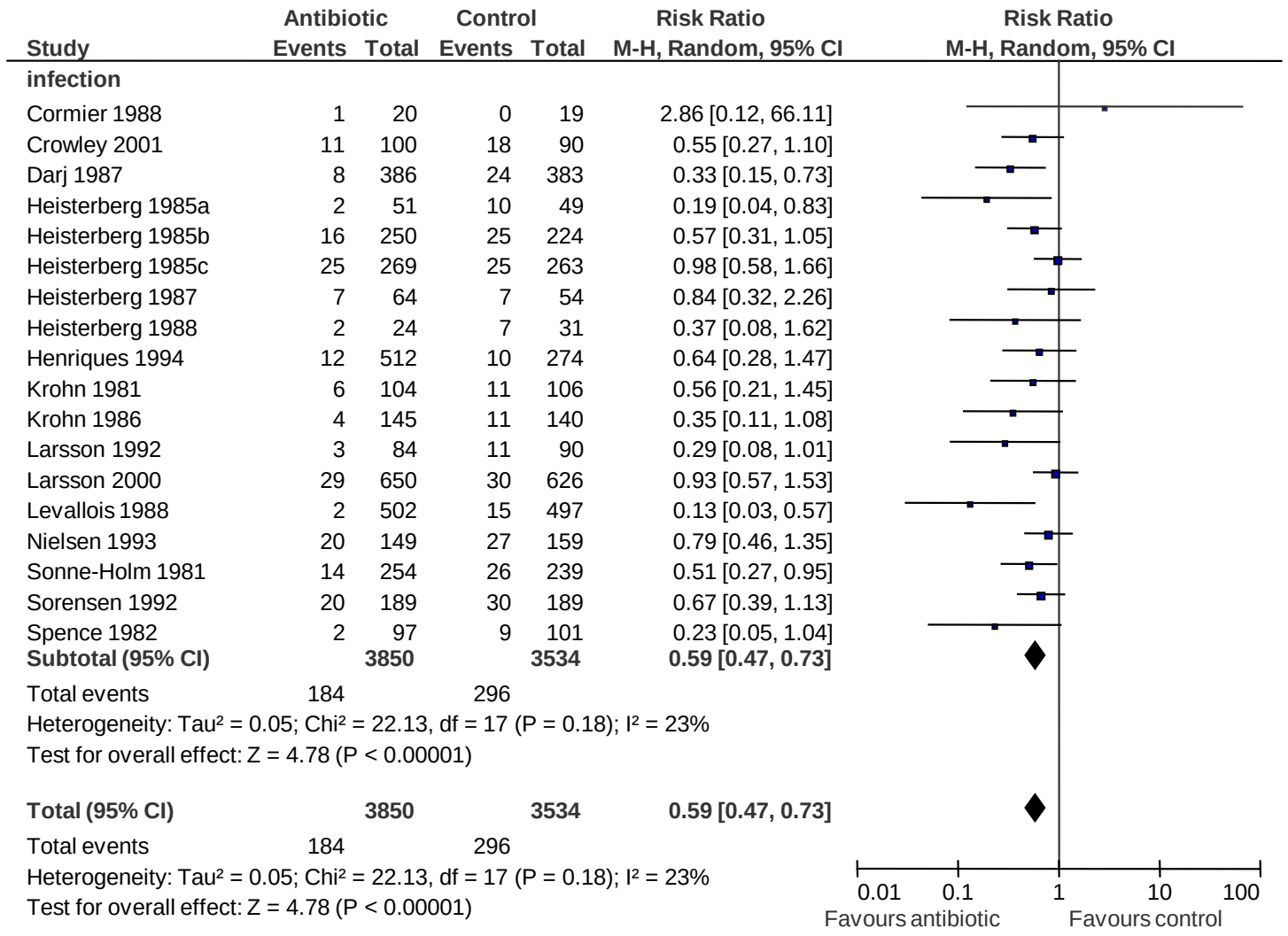

Figure 40 Infective morbidity in antibiotic group and placebo group in surgical abortion

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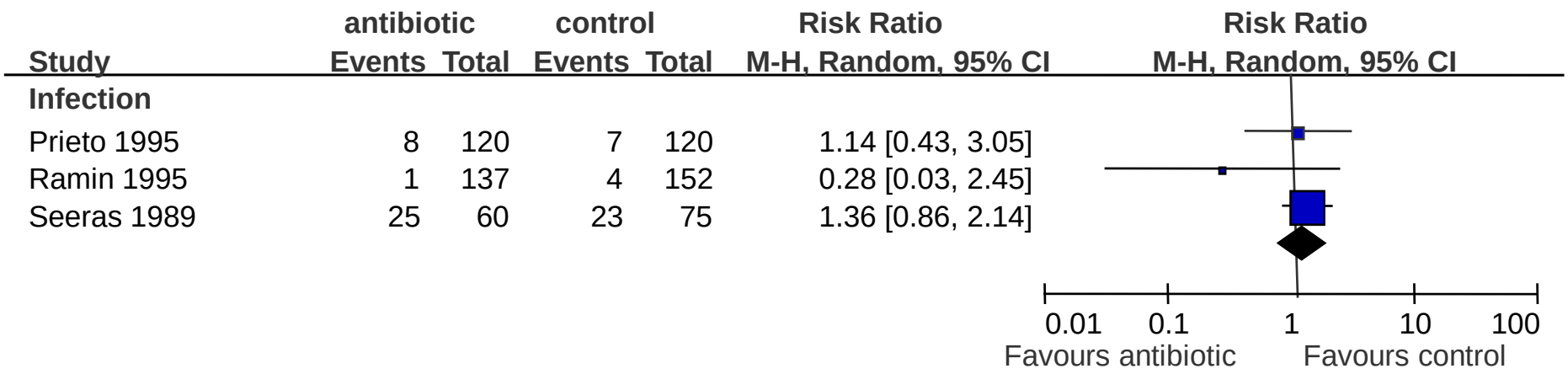

Figure 41 Infective Morbidity in antibiotic group and placebo group in Miscarriage

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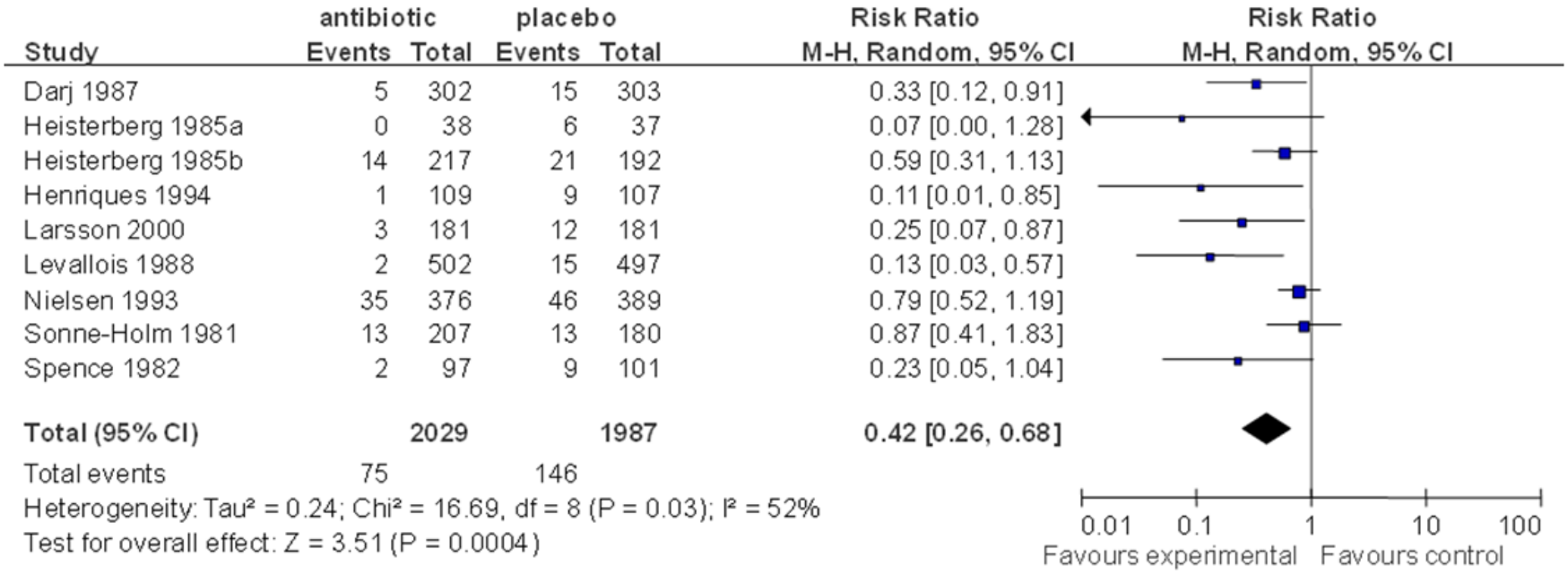

Figure 42 Infective Morbidity in antibiotic group and placebo group in Surgical Abortion of Low Risk Patients

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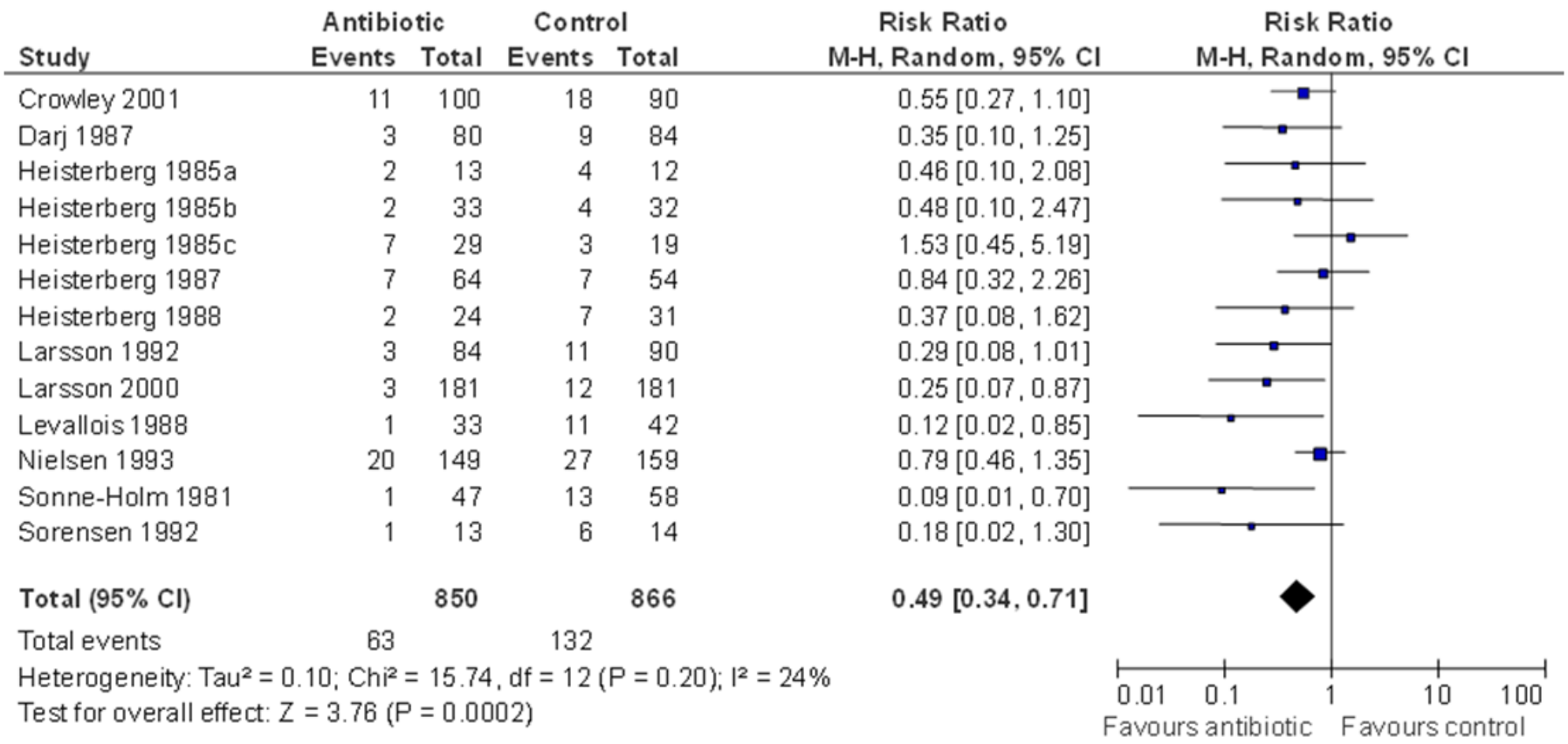

*Figure 43 Infective Morbidity in antibiotic group and placebo group in Surgical Abortion of High Risk Patient*s

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Table 22 Characteristics of included studies within the review

Author Country	Sample size Population	Intervention	Control	Infectious complications Incidence/total events (HR-high risk : LR –low risk)	Risk category
High Income Countries					
Cormier 1988 France	39 Women undergoing surgical abortion	Cefotetan	No prophylaxis	Intervention: 1/20 Control: 0/19	No description
Crowley 2001 UK	273 Women with bacterial vaginosis undergoing induced abortion (surgical abortion)	2g metronidazole suppository (per-operatively)	Identical placebo (per-operatively)	Intervention total 11/100: HR 11/100 Control: total 18/90: HR 18/90	High Risk: all women with bacterial vaganosis
Darj 1987 Sweden	769 Women undergoing induced abortion (surgical abortion)	Four tablets of doxycycline 100mg	Four tablets of placebo	Intervention: total 8/386. LR 5/302. HR 3/80. Control: Total 24/383. LR 15/303. HR 9/84	Low Risk: women with no history of PID. High Risk: women with previous PID
Heisterberg 1985a Denmark	119 Women undergoing elective first trimester abortion (surgical abortion)	Metronidazole	Placebo	Intervention: Total 2/51: LR 0/38: HR 2/13: Control: Total 10/49: LR 6/37.HR 4/12	Low Risk: women with no history of PID. High Risk: women with previous PID
Heisterberg 1985b Denmark	474 Women undergoing first trimester abortion (surgical abortion)	Penicillin/ Pivampicillin	Placebo	Intervention: total 16/250: LR 14/217. HR 2/33 Control: total 25/224. LR 21/192. HR 4/32	Low Risk: women with no bacteraemia. High Risk: women with positive bacteraemia. Unable to separate data of women +/- history of PID
Heisterberg 1985c Denmark	532 Women undergoing first-trimester abortion (surgical abortion)	Lymecycline	Placebo	Intervention: total 25/269: HR 7/29 Control: Total 25/263. HR 3/19	High Risk: Chlamydia positive. Unable to separate data of low risk women, no breakdown provided for women without mycoplasma hominis

Heisterberg 1987 Denmark	135 Women with a history of PID undergoing induced first-trimester abortion (surgical abortion)	Metronidazole	Placebo	Intervention: Total 7/64. HR 7/64. Control: total 7/54 HR 7/54	High Risk: all women with a history of PID
Heisterberg 1988 Denmark	55 Women undergoing first-trimester abortion (surgical abortion)	Lymecycline	Placebo	Intervention: total 2/24. HR 2/24 Control: Total 7/31 HR 7/31	High Risk: all women with a history of PID
Henriques 1994 Denmark	996 Women admitted for legal termination of pregnancy at <12wks gestation (surgical abortion)	Ceftriaxone (both groups)	Standard treatment High risk: preoperative injection of ampicillin and metronidazole, followed by oral doses of metronidazole and pivampicillin 3x daily for 4 days. Low risk: no prophylactic antibiotics were given to women in this group	Intervention: total 12/512. LR 1/109 Control: total 10/274. LR 9/107	Low Risk: no history of PID, negative for Chlamydia. Data for high risk excluded due to different intervention and control treatments, both arms in the high risk category received antibiotics
Krohn 1986 Sweden	305 Women undergoing first-trimester abortion with vacuum aspiration	Sulbactam/ Ampicillin	Placebo	Intervention: 4/145 Control: 11/140	Unable to separate into categories, Chlamydia swabs only taken on over 100 participants
Larsson 1992 Sweden	231 Women undergoing first-trimester legal abortion and fulfilling criteria for bacterial vaginosis (surgical abortion)	Metronidazole	Placebo	Intervention: Total 3/84. HR 3/84 Control: Total 11/90. HR 11/90	High Risk: women with bacterial vaginosis but negative for Chlamydia

Larsson 2000 Sweden	1655 Women attending for surgical abortion prior to 11+4 gestation (surgical abortion)	2% clindamycin cream	Placebo cream	Intervention: total 29/650. HR 3/181 Control: Total 30/626. HR 12/181	High Risk: women with abnormal vaginal flora Unable to extract data for women with normal vaginal flora, no breakdown provided for intervention and control arms
Levallois 1988 Canada	1100 Women seeking induced abortions (surgical abortion)	Doxycycline 100mg	Placebo	Intervention: total 2/502. LR 2/502. HR 1/33 Control: total 15/497. LR 15/497. HR 11/42	Low Risk: women negative for Chlamydia High Risk: women positive for Chlamydia
Nielsen 1993 Denmark	1073 Women with induced first-trimester abortions (surgical abortion)	Ofloxanin	Placebo	Intervention: total 55/525. LR 35/376. HR 20/149 Control: total 73/548. LR 46/389. HR 27/159	Low Risk: women with no history of PID High Risk: women with previous PID
Prieto 1995 USA	345 Women with incomplete abortion (miscarriage)	Doxycycline 100mg IV and suction curettage (experimental gp)	Normal saline and suction curettage (control gp)	Intervention: 8/120 Control: 7/120	Unable to separate into risk categories, no breakdown of data provided for the intervention and control arms for risk categories
Ramin 1995 USA	300 Women with incomplete abortion (miscarriage)	Doxycycline	Placebo	Intervention: total 1/137: HR 0/7 Control: Total 4/152: HR 0/11	High Risk: women positive for Chlamydia, gonorrhoea and syphilis. Unable to extract data for low risk participants as some swab results were inconclusive, or swabs were not performed
Sonne-Holm1981 Denmark	564 Women undergoing induced first-trimester abortions (surgical abortion)	2 million IU of penicillin G intramuscularly (1 ½ hrs before op, then 3 hrs after op) followed by 350mg	Placebo	Intervention: total 14/254: LR 13/207. HR 1/47 Control: total 26/239: LR 13/180. HR 13/58	Low Risk: women with no history of PID High Risk: women with a history of PID

		pivampicillin three times daily for four days			
Sorenson 1992 Denmark	432 Women undergoing induced abortion before 12 weeks gestation (surgical abortion)	Erythromycin	Placebo	Intervention: total 20/189: HR 1/13 Control: Total 30/189:HR 6/14	High Risk: women positive for Chlamydia +/- gonorrhoea . Unable to extract data for women Chlamydia and gonorrhoea negative as breakdown not provided for trial arms
Spence 1982 USA	Women undergoing second trimester intra-amniotic injection abortions (surgical abortion)	2g Sodium cephalothin (IV)	Placebo (IV)	Intervention: Total 2/97: LR 2/97 Control: Total 9/101: LR 9/101	Low: women without any mention of any risk factors; presumed low risk
Low income countries					
Seeras 1989 Zimbabwe	140 women with incomplete abortion (miscarriage)	tetracycline	Control	Intervention: total 25/60: LR 25/60. Control: total 23/75: LR 23/75	Low risk: women without any mention of any risk factors: presumed low risk

Table 23 Quality assessment of included studies: CONSORT checklist (Y = Reported N = Not Reported N/A= Not applicable)

Item	Checklist item	Cormier 1988	Crowley 2001	Darj 1987	Heisterberg 1985a	Hesiterberg 1985b	Heisterberg 1985c	Hesiterberg 1987	Hesiterberg 1988	Henriques 1994
Title and abstract										
	Identification as a RCT in title	N	Y	N	N	Y	Y	N	Y	Y
	Structured summary of trial design, methods, results, conclusions	N	Y	N	Y	Y	Y	Y	Y	Y
Introduction										
Background and objectives	Scientific background and explanation of rationale	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Specific objectives or hypotheses	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods										
Trial design	Description of trial design including allocation ratio	N	N	N	Y	Y	Y	Y	N	N
	Important changes to methods after trial commencement with reasons	N	N	N	N	N	N	N	N	N
Participants	Eligibility criteria for participants	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Settings and locations where data collected	Y	Y	Y	Y	Y	Y	Y	Y	Y

Interventions	interventions for group with sufficient details to allow replication, including how/when actually administered	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how/when they were assessed	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Any changes to trial outcomes after trial commenced, with reasons	N	N	N	N	N	N	N	N	N
Sample size	How sample size determined	N	Y	N	Y	N	N	N	Y	Y
	When applicable, explanation of any interim analyses and stopping guidelines	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Randomisation:										
Sequence generation	Method used to generate random allocation sequence	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Type of randomisation; details of any restriction	Y	Y	Y	Y	N	N	Y	Y	Y
Allocation concealment mechanism	Mechanism used to implement random allocation sequence describing steps taken to conceal sequence until interventions assigned	Y	Y	Y	Y	Y	N	Y	Y	Y
	Who generated random	Y	N	Y	N	N	N	Y	Y	Y

Implementation	allocation sequence, enrolled participants, assigned participants to interventions									
Blinding	If done, who blinded after assignment to interventions and how	Y	Y	Y	Y	N	Y	Y	Y	N
	If relevant, description of similarity of interventions	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Statistical methods	Statistical methods used to compare groups for primary/secondary outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results										
Participant flow	For each group, numbers of participants randomly assigned, received intended treatment, analysed for primary outcome	Y	Y	Y	Y	Y	Y	Y	Y	Y
	For each group, losses and exclusions after randomisation, with reasons	Y	Y	Y	N	N	Y	Y	Y	Y
Recruitment	Dates defining periods of recruitment and follow-up	Y	Y	N	Y	Y	Y	Y	Y	Y
	Why trial ended or was stopped	N	N	N	N	N	N	N	N	N
Baseline data	table showing baseline demographic and	Y	Y	Y	Y	N	Y	Y	Y	Y

	clinical characteristics for each group									
Numbers analysed	For each group, number of participants included in each analysis and whether analysis by original assigned groups	N	Y	N	N	N	N	N	N	N
Outcomes and estimation	For each primary and secondary outcome, results for each group, and estimated effect size and precision	Y	Y	Y	N	N	Y	Y	Y	Y
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N	Y	Y	N	N	N	Y	Y	N
Ancillary analyses	Results of other analyses performed, including subgroup analyses, adjusted analyses, distinguishing pre-specified from exploratory	N	Y	Y	N	N	Y	Y	N	N
Harms	All important harms or unintended effects in each group	Y	N	Y	N	N	N	N	N	N
Discussion										
Limitations	Trial limitations, addressing sources of potential bias, imprecision, if relevant, multiplicity of analyses	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalisability	Generalisability of trial findings	Y	Y	Y	N	Y	Y	Y	N	Y

Interpretation	Interpretation consistent with results, balancing benefits and harms, considering other evidence	Y	Y	Y	N	Y	N	Y	Y	Y
Other information										
Registration	Registration number and name of trial registry	N	Y	N	N	N	N	Y	N	N
Protocol	Where full trial protocol can be accessed, if available	N	N	N	N	N	N	N	N	N
Funding	Sources of funding and other support role of funders	Y	Y	Y	Y	Y	Y	Y	Y	N

Item	Checklist item	Krohn 1981	Krohn 1986	Larsson 1992	Larsson 2000	Levallois 1988	Neilsen 1993	Penney 1998	Prieto 1995	Seeras 1989	Sonne-holm 1981	Sorensen 1992	Spence 1982	Ramin 1995
Title and abstract														
	Identification as a randomised trial in the title	N	Y	N	Y	Y	Y	N	Y	N	N	N	N	N
	Structured summary of trial design, methods, results, conclusions	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Introduction														
Background and objectives	Scientific background and explanation of rationale	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Specific objectives or hypotheses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods														
Trial design	Description of trial design including allocation ratio	N	Y	N	N	N	N	Y	N	N	N	N	Y	Y
	Important changes to methods after trial commencement with reasons	N	N	N	N	N	N	N	N	N	N	N	N	N
Participants	Eligibility criteria for participants	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Settings and locations where	N	Y	N	N	Y	N	N	N	Y	Y	Y	Y	Y

	data collected													
Interventions	interventions for each group with sufficient details to allow replication, including how and when administered	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how/when were assessed	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	changes to trial outcomes after trial commenced, with reasons	N	N	N	N	N	N	N	N	N	N	N	N	N
Sample size	How sample size determined	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N
	When applicable, explanation of any interim analyses and stopping guidelines	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Randomisation:														
Sequence generation	Method used to generate random allocation sequence	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y
	Type of randomisation; details of restriction	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y
Allocation concealment mechanism	Mechanism used to implement random allocation sequence	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y

	describing any steps taken to conceal sequence until interventions assigned													
Implementation	Who generated the random allocation sequence, enrolled participants, and assigned participants to interventions	N	N	Y	N	N	N	Y	Y	Y	Y	Y	N	Y
Blinding	If done, who blinded after assignment to interventions/how	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y
	If relevant, description of similarity of interventions	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N	N	N	Y	N	N	Y	Y	Y	N	N	N	Y
Results														
Participant flow	For each group, numbers of participants who randomly assigned,	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	received intended treatment, and analysed for the primary outcome													
	For each group, losses and exclusions after randomisation, with reasons	N	N	N	Y	N	N	Y	Y	N	N	Y	N	Y
Recruitment	Dates defining periods of recruitment and follow-up	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
	Why trial ended or stopped	N	N	N	N	N	N	N	N	N	N	N	N	N
Baseline data	table showing baseline demographic and clinical characteristics for each group	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Numbers analysed	each group, number of participants included in analysis and whether analysis by original assigned groups	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N
Outcomes and estimation	each primary and secondary outcome, results for each group, the estimated effect size and precision	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	binary outcomes, presentation of both	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y

	absolute and relative effect sizes is recommended													
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N	Y	Y	N	N	Y	Y	Y	N	N	N	N	N
Harms	All important harms or unintended effects in each group	Y	N	Y	N	N	N	N	N	N	N	N	N	N
Discussion														
Limitations	Trial limitations, addressing sources of potential bias, imprecision, if relevant, multiplicity of analyses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalisability	Generalisability of trial findings	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y
Other information														
Registration	Registration number and name	N	Y	N	N	N	N	Y	N	N	N	N	N	N

	of trial registry													
Protocol	Where full trial protocol can be accessed, if available	N	N	N	N	N	N	N	N	N	N	N	N	N
Funding	Sources of funding and other support role of funders	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N

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Table 24 Risk of Bias in RCTs

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cormier 1988						
UNCLEAR: Page 829: Random allocation, no further details provided on random sequence generation	LOW: Page 829: Allocation information carried in sealed envelope	HIGH: Page 829: No control was given to participants	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	LOW: Page 831: Complete data set given for excluded from analysis	LOW: Page 831: All outcomes reported	LOW: Appears to be free from other sources of bias
Crowley 2001						
LOW: Page 397: Random number table	LOW: Page 397: sequentially numbered drug containers of identical appearance	LOW: Page 397: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken as all unaware of allocation	LOW: Page 397: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken as those collecting follow up data unaware of allocation	UNCLEAR: Page 398: Loss to follow up rates given, balanced across arms, no further data or reasons provided for loss to follow up	LOW: Page 399: All outcomes reported: table 2 and 3	HIGH: Page 398: Recruitment slower than expected and study terminated before target sample size reached due to lack of resources.
Darj 1987						
UNCLEAR: Page 755: Random allocation, no further details provided on random sequence generation	UNCLEAR: Page 755: Randomly allocated in blocks of ten to two groups, no further details given	LOW: Page 755: Intervention given in double blind fashion	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	HIGH: Page 756: Complete data set missing for women excluded from analysis, reason given for 3 women.	LOW: Page 756: All outcomes reported table 2 -5	LOW: Appears to be free from other sources of bias

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Heisterberg 1985a						
LOW: Page 371: Random number sequence	LOW: Page 371: Allocated to either metronidozole or placebo groups, each group contained ten patients using random numbers, 5 in each received placebo and 5 metronidozole'	LOW: Page 371: The randomisation was not known to therapist and patients until the trial was concluded	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	LOW: Page 372: Complete data set given for excluded from analysis	LOW: Page 372: All outcomes reported	HIGH: Page 372:Treatment regime su to change according judgement of gynaecologist in charg
Heisterberg 1985b						
UNCLEAR: Page 73: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 73: Randomised allocation stated, no further details provided on allocation concealment	UNCLEAR: No information provided on blinding	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	LOW: Page 74: Data was provided for all patients not included in the analysis	LOW: Page 75: All outcomes reported	HIGH: Page 75: Blood drawn for cultures a few minutes after bacteria were released into blood stream during abortion procedure.
Heisterberg 1985c						
UNCLEAR: Page 72: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 72: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 72: double blinded	UNCLEAR: Page 72: double blinded but no specific information provided on blinding of data outcome assessors or analysts	LOW: Page 73: Data was provided for all patients not included in analysis	LOW: Page 73: All outcomes reported	HIGH: Page 74:Unbalanced non-compliance with treatment (4 placebo, 11 active) due to gastro-intestinal effects, remained in analysis
Heisterberg 1987						

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LOW: Page 15: Random number sequence	UNCLEAR: Page 15: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 15: double blinded	UNCLEAR: Page 15: Classed as double blinded but no specific information provided on blinding of data outcome assessors or analysts	LOW: Page 16: Data was provided for all patients not included in the analysis	LOW: Page 16: All outcomes reported	HIGH: Page 17: Sample size too small to demonstrate significant difference. microorganisms not sensitive to treatment-metronidozole
Heisterberg 1988						
UNCLEAR: Page 241: Randomised allocation stated, no further details on random sequence generation	UNCLEAR: Page 241: Allocation performed in blocks of 10, each block containing 5 regimes of lymecycline and 5 of placebo	LOW: Page 243: Randomisation was not known to patient or staff.	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	UNCLEAR: Page 243: Incomplete data set for those lost to follow up or excluded	LOW: Page 224: All outcomes reported	LOW: Appears to be free from other sources of bias
Henriques 1994						
LOW: Page 611: Computer based randomisation	LOW: Page 611: Allocation information carried in sealed envelope not opened until woman given study number	UNCLEAR: No information provided on blinding	UNCLEAR: No information provided on blinding	UNCLEAR: Page 612: Incomplete data set for lost to follow up or excluded	LOW: Page 612: All outcomes reported	LOW: Appears to be free from other sources of bias
Krohn 1981						
UNCLEAR: Page 101: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 101: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 101: double blinded	UNCLEAR: No information provided on blinding	LOW: Page 26: Data provided for all patients not included in analysis	LOW: Page 102: All outcomes reported	LOW: Appears to be free from other sources of bias
Krohn 1986						

UNCLEAR: Page 576: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 576: Randomised allocation stated, no further details provided on allocation concealment	UNCLEAR: Page 576: Classed as single blinded no information provided on blinding	UNCLEAR: Page 576: Classed as single blinded no information provided on blinding	LOW: Page 577: Data provided for all patients not included in analysis	LOW: Page 576: All outcomes reported	LOW: Page 577: Although only 100 participants has swabs for C.trachomatis, this was not an outcome set out to be measured
Larsson 1992						
UNCLEAR: Page 101: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 101: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 101: Double blinded, placebo and active treatment were identical.	LOW: Page 101: Double blinded, all data fed into computer before code indicating placebo or active treatment broken	LOW: Page 102: Data provided for all patients not included in analysis. Yet unable to examine 8 smears due to contamination or specimen insufficiency.	LOW: Page 101: All outcomes reported	LOW: Appears to be free from other sources of bias
Larsson 2000						

LOW: Page 392: Block randomisation	UNCLEAR: Page 392: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 391: Double blinded, 109 smear randomly reinvestigated without knowledge of result from air dried smears.	LOW: Page 392: All records scrutinised by 2 authors to decide if patient fulfilled diagnosis criteria, was done before code of placebo or active treatment broken and before smear result included in analysis.	LOW: Page 393: Data provided for all patients not included in analysis and lost to follow up. 5 had to be excluded due to contamination or specimen insufficiency.	LOW: Page 394: All outcomes reported	HIGH: Page 395: Selection bias may have occurred if physicians seeing women with obvious BV chose not to enrol them into study, to avoid possible placebo treatment, as was an unexpectedly low incidence of BV
Levallois 1988						
LOW: Page 101: Randomisation was prepared by a micro-professor, equalization each 20 patients.	LOW: Page 101: each of the three capsules was placed in a sealed bag and given on randomly determined schedule to each consecutive woman. Randomisation codes were kept secret until analysis began.	LOW: Page 101: Double blinded, placebos and active alike in appearance and randomisation codes kept secret	LOW: Page 101: Double blinded, performed by trained nurse using pre-coded forms	LOW: Page 103: Data was provided for patients not included in analysis, 0.3% lost to follow up	LOW: Page 103: All outcomes reported	LOW: Appears to be free from other sources of bias
Nielsen 1993						

UNCLEAR: Page 557: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 557: Randomised allocation stated, no further details provided on allocation concealment	LOW: Page 556: double blinded	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	LOW: Page 557: Data was provided for all patients not included in analysis	LOW: Page 557: All outcomes reported	HIGH: Page 558: Most anaerobic bacteria are resistant to ofloxacin, treatment in study was not effective against BV caused by anaerobic bacteria, may explain failure of our regime.
Prieto 1995						
LOW: Page 692: Computer software randomisation	LOW: Page 692: Random block sequence allocation in numbered, opaque, sealed packets prepared independently	HIGH: Page 692: Unblinded yet placebo given	HIGH: Page 692: Unblinded but physicians performing follow up not aware of allocation	HIGH: Page 693: High rates of loss to follow up, identical in both arms, no data for participants	LOW: Page 694: All outcomes reported	LOW: Appears to be free from other sources of bias
Ramin 1995						
LOW: Page 214: Randomised by sealed envelope	UNCLEAR: no details given on allocation concealment	LOW: Page 214: double blinded	UNCLEAR: Page 214: Classed as double blinded but no further information provided on blinding of data outcome assessors or analysts	LOW: Page 215: Data was provided for all patients not included in analysis	LOW: Page 215: All outcomes reported	LOW: Appears to be free from other sources of bias
Seeras 1989						

LOW: Page 607: Randomised by sealed envelope	UNCLEAR: no details on allocation concealment	UNCLEAR: No information provided on blinding	UNCLEAR: No information provided on blinding of data outcome assessors or analysts	LOW: Page 609: Data provided for all patients not included in analysis	LOW: Page 608: All outcomes reported	HIGH: Page 608: poor compliance of treatment (82.6% cases)
Sonne Holm 1981						
UNCLEAR: Page 693: Randomised allocation stated, no further details provided on random sequence generation	UNCLEAR: Page 693: Randomised allocation stated, no further details on allocation concealment	LOW: Page 693: double blinded	UNCLEAR: Page 693: Classed as double blinded no further information provided on blinding of data outcome assessors or analysts	HIGH: Page 694: 7.8% loss to follow up, no details provided for 60% patients lost to follow up	LOW: Page 695: All outcomes reported	LOW: Appears to be free from other sources of bias
Sorensen 1992						
LOW: Page 435: Randomisation in consecutively numbered blocks of tablet boxes	UNCLEAR: Page 435: Randomisation in consecutively numbered blocks of tablet boxes, no further details on allocation concealment	LOW: Page 434: double blinded	LOW: Page 435: clinical and laboratory personnel blinded to treatment allocation. Results of C.trachomatis tests blinded.	LOW: Page 435: All patients followed up by some form (mail, telephone, visit)	LOW: Page 437: All outcomes reported	LOW: Appears to be free from other sources of bias
Spence 1982						

UNCLEAR: Page 503: Randomly assigned, no further details	UNCLEAR: Page 503: Randomly assigned to one of two groups, no further details	LOW: Page 503: group assignment was double blind; pharmacy kept code and prepared all solutions. code not broken until 200 patients studied	LOW: Page 503: group assignment was double blind; the pharmacy kept code and prepared all solutions. code not broken until 200 patients studied	LOW: Page 505: All patients followed up	LOW: Page 505: All outcomes reported	LOW: Appears to be free from other sources of bias

8.4 DISCUSSION

Findings

This meta-analysis has shown a significant reduction in infectious morbidity with the administration of prophylactic antibiotics in women undergoing surgical abortion, accounting for an average of 41% reduction in the given population. When the population was divided into sub groups of risk categories, a reduction of 58 % was noted in women deemed at low risk of pelvic infection, and a reduction of 51% in women deemed at high risk of developing pelvic infection. Various antibiotic regimes were included in the treatments groups of the trials. It is important to note that the most effective treatment may vary according to the setting and local sensitivities. Furthermore the availability of different types of antibiotics may vary in settings with limited resources; therefore it is important to consider other effective and available antibiotics.

Limitations

There is sufficient high quality evidence on prophylactic antibiotic administration in surgical abortion. However the overall evidence on miscarriage consists of a limited number of poor quality studies that are vastly heterogeneous in the antibiotic regimen, as well as outcome, and have low compliance rates with the antibitoics. Therefore no inferences could be drawn on the impact of prophylactic antibiotics on infectious morbidity in surgical treatment of miscarriage.

Existing Research

Surgical abortion: A meta-analysis was conducted by Sawaya et al in 1996 (262), the twelve included trials mainly being conducted in the 1980's, eleven of which feature within our review. Our analysis excluded one trial (Westrom et al (263) included in Sawaya's (262) review due to lack of randomisation. Four more RCTs have been published since this review was conducted over a decade ago (246, 247, 264, 265).

Our review also included six additional RCTs (240, 250, 266-269) some of which were excluded by Sawaya (262) (266) (267) due to lack of blinding. Sawaya et al (262) found a reduction of 42% in infectious morbidity (RR 0.58 95% CI 0.47 to 0.71) with women receiving prophylactic antibiotic therapy during surgical abortion. A further review was conducted by Penney in 1997 discussing the risk factors for post-abortion infective morbidity, however the data on prophylactic antibiotic administration is taken from the Sawaya (262) review and the manuscript contained no new data on infectious morbidity with prophylactic antibiotic administration with abortion.

Miscarriage surgery: Prophylactic antibiotics following surgical miscarriage treatment to reduce sepsis has been identified as an area where there is a crucial need for further research (255). The results of this question have the potential to have considerable implications for maternal health, particularly in low income settings where associated mortality and morbidity from sepsis following surgical treatment for 'miscarriage' or unsafe abortion is substantial. To date there has been little research in this area. A Cochrane review investigated the evidence for antibiotic prophylaxis compared to no prophylaxis following miscarriage (255). This review included only one of the three studies in our review, the two further studies included in our review, but excluded from the Cochrane review were Prieto et al (246), and Ramin et al (247). Prieto et al (246) was excluded due to loss to follow-up exceeding their inclusion criteria, and the reason for the exclusion of Ramin et al (247) was not stated. This review, with a single study (n = 140 women) concluded that there was 'insufficient evidence to evaluate a policy of routine antibiotic prophylaxis to women with incomplete abortion' (miscarriage), and a 'real and urgent need to find out whether antibiotics should be routinely used in cases of incomplete miscarriage'.

Policy and practice implications

Prophylactic administration of antibiotics is recommended for women undergoing surgical evacuation for abortion, where there is an associated risk of developing infections and pelvic inflammatory disease (258, 267), including women who currently have genital tract infections such as N.gonorrhoea, C. Trachomatis, or bacterial vaginosis (258). However the value of prophylactic administration for surgical uterine evacuation without such risk factors is less clear (267); This could apply to cases of unsafe abortion presenting as 'miscarriages,' and antibiotics not administered as per clinical and current WHO guidelines (Figure 34). As there is little reliable evidence available on the administration of prophylactic antibiotics in miscarriage, one could suggest that the findings from the meta-analysis of uterine evacuation in women deemed at low risk of developing pelvic infection could be used to guide practice. The procedure of surgical uterine evacuation in miscarriage and abortions are alike, however the risk of developing pelvic infection may vary depending on setting. Where abortion is permitted by law the procedure is often conducted in a safe and sterile manner, yet in countries where abortion is restricted by law, unsafe abortion may present as a 'miscarriage', and may be initiated in an unsanitary manner with the insertion of unsterile objects into the uterus. Furthermore, infection rates of Chlamydia and gonorrhoea in women presenting with 'miscarriage' are often high and compromised immunity from HIV/AIDS or malnutrition and anaemia may mean that this group of women are at a greater risk of pelvic infection.

Unanswered questions and future research

As there is little reliable evidence available on the role of prophylactic antibiotics in miscarriage a high quality RCT is needed to guide practice on this area, particularly in regions where the risk of developing pelvic infection is high.

8.5 CONCLUSION

There now appears to be sufficient, up to date evidence for the administration of prophylactic antibiotics in abortion, yet there is little reliable evidence available on the administration of prophylactic antibiotics in surgical uterine evacuation for miscarriage. A RCT is needed to guide practice on this area, particularly in low resource settings where the risk of developing pelvic infection may vary from a high resource setting. Prophylactic antibiotics may reduce the burden of death and disease from sepsis following surgical treatment in low income countries. This will directly address MDG5 (reducing maternal mortality), where progress has been uneven and slow, particularly in settings where the aetiology of the miscarriage is unknown.

This review was used in support of an application that was successfully funded by MRD, DfID and Wellcome (£1.6 million) 'Effectiveness of antibiotic prophylaxis during surgical evacuation of the uterus for miscarriage management in low income countries (AIMS): a multinational, randomised, double-blind placebo-controlled trial'

CHAPTER 9: CELL SALVAGE IN CAESAREAN SECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Obstetric haemorrhage is one of the leading causes of maternal death globally. Significant morbidity is also associated with obstetric haemorrhage, particularly in low income countries where there is a shortage of available blood to transfuse for cultural, financial and practical reasons. Thus the need for alternatives to homologous blood transfusion in low income countries is great.

Methods: A systematic review of available evidence was conducted (RCTs, cohort studies, and case series). The databases MEDLINE, EMBASE, AMED, the Cochrane library, CINHAL, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index were searched without language restrictions (from database inception to February 2012). Information was extracted on study characteristics, quality of the included studies and outcome data. Outcomes were pre and post operative haemoglobin, estimated blood loss, amount of autologous blood re-infused, and use of additional homologous blood for transfusion.

Results: Eleven studies were included (1983 women): One RCT, two cohort studies and eight case series. Post-operative haemoglobin dropped by 0.90g/l from the pre-operative haemoglobin in the group that received cell salvage in the RCT, and by 3.70g/l in the group that did not receive cell salvage. In the case series this reduction was 1.78g/l in those that underwent cell salvage. The groups that received cell salvage in the RCT and cohort studies appeared to be transfused more homologous blood than the groups that did not receive cell salvage. However there was no trend in estimated blood loss with additional homologous blood transfused in the case series. There was also no significant difference in serious adverse effects, or length of hospital stay reported with cell salvage within the studies.

Conclusion: It is possible that cell salvage may be beneficial in restoring normal haemoglobin levels for women that have undergone caesarean section, however further primary research of sound quality is needed to draw firm inferences on the use in caesarean section.

9.1 BACKGROUND

Obstetric haemorrhage is one of the leading causes of maternal death globally, with 87% of deaths from haemorrhage occurring in developing regions (270). Significant morbidity is also associated with obstetric haemorrhage. Blood transfusion has been shown to reduce maternal mortality rates and research suggests that a substantial proportion of maternal deaths could be prevented with access to blood transfusion (271). Thus blood transfusion is recognised as one of the essential components of comprehensive emergency obstetric care. However in many low income countries this core component is often not achieved for a variety of reasons.

Research has demonstrated a correlation with maternal mortality and morbidity and the availability of blood transfusion. A complete lack of available blood to transfuse, or a lack of timely blood transfusion are commonly cited problems (271). This could be due to a number of reasons, for example inadequate storage facilities, inadequate transport, cultural barriers or high costs associated with blood donation.

There are however other problems associated with blood transfusion in developing countries. There is the risk of potential bacterial contamination during reinfusion, as the equipment may be re-used for transfusions and poorly sterilised, thus allowing bacteria to enter the central circulation directly and put the patient at risk of septicaemia. There may also be pathogens contained in the blood, HIV, Hepatitis B and C are often more prevalent in developing countries. It is suggested that Africa has some of the highest

prevalence rates of these infections in the world (272). The possibility of acquiring HIV from an HIV contaminated unit of blood is almost 100%. It is suggested that between 5 and 15% of HIV infections have been transmitted by transfusion of infected blood or blood products (273, 274). Although blood donation screening is suggested to have improved globally, comprehensive transfusion policies suited to local context are lacking, and many transfusion-related tests are still not conducted (272). HIV and Hepatitis are not the only blood borne viruses that contaminate donor blood; malaria and syphilis can be transmitted to the blood recipient. There are also serious transfusion related reactions associated with homologous transfusion (e.g. haemolytic reaction); these are often caused by the transfusion of incorrect blood, due to clinical errors in the transfusion process, such as incorrect identification of patients, blood units or labelling errors.

It is possible that cell salvage may be ineffective in some situations. For example if blood collection is delayed due to the time taken to set up the equipment needed, a large amount of blood that could have been salvaged may have already been lost. Blood cannot be salvaged retrospectively. Furthermore the time taken to prepare the blood for re-infusion may mean the patient becomes more hypovolemic and haemodiluted before re-infusion is able to occur, thus resuscitation of the patient is more difficult. Cell salvage alone may also not be sufficient to restore the blood lost; patients may still require transfusion of plasma and platelets.

Cell salvage can reduce the risks associated with homologous blood transfusion which may be particularly useful in areas where the prevalence of blood borne viruses such as HIV are high, or where there are difficulties with cross-matching. Cell salvage may also be a more culturally or religiously acceptable option in groups that decline homologous blood products such as Jehovah's witnesses (275). However both types

of transfusion are not without risk and the risk of blood transfusion against not transfusing blood should always be considered.

Today, intraoperative blood cell salvage is commonly used in cardiac, orthopaedic and vascular surgery. NICE guidance (276) describes intraoperative blood cell salvage as an efficacious technique for blood replacement. In obstetrics however, it has not been routinely adopted because of the theoretical safety concerns associated with pregnancy such as haemolytic disease in future of pregnancies due to alloimmunisation, and amniotic fluid embolism (276). Although the uses of salvaged blood has been endorsed by CEMACH (277), NICE (276) guidance suggests that this procedure must be carried out by multidisciplinary teams that have knowledge and experience of the process of intraoperative blood cell salvage.

Autologous blood collection can occur pre-operatively; this is when blood collection is performed through venepuncture before an operative procedure. Blood cell salvage however is performed intraoperatively, this is where the blood that is shed during an operation is collected and filtered to produce autologous red blood cells for transfusion back to the patient. Re-infusion of collected blood can occur intraoperatively or postoperatively. During caesarean section, blood that is lost can be aspirated from the surgical field and collected in a reservoir where a filter removes debris. The filtered blood is washed and re-suspended for transfusion, during or after the operation. The concept of autologous blood transfusion in obstetrics is documented from 1818 (278), with a much simpler procedure to the one described above. The serous fluid found in the body cavities as a result of trauma, or in ruptured ectopic pregnancies, was re-instated back into the patients veins (279), this will be further discussed in chapter ten. The more advanced procedure that concerns this review was utilised on a large scale in 1962 for operations such as cholecystectomy (280).

A systematic review was performed using the data from all available studies, and the applicability of the findings to low resource setting are discussed.

9.2 METHODS

Data sources and searches

Databases were searched for literature on cell salvage in caesarean section. Although the focus was on developing countries, if no data were available from developing countries, the available data was examined. The applicability of the data to developing countries was then considered and discussed. The population was women who underwent preoperative or intra-operative cell salvage with re-infusion. The databases MEDLINE, EMBASE, LILACS, the Cochrane library, CINHAL, African Index Medicus, the Reproductive Health Library, and the Science Citation Index were searched (from database inception to February 2012). Hand searching complemented electronic searches, and reference lists were checked. The primary search terms were 'cell salvage', 'blood salvage', erythrocyte salvage', 'cell saver', autologous transfusion', 'autotransfusion' AND 'caesarean section' OR 'obstetrics'. No language restrictions were applied to the search.

Study selection and data extraction

The best possible evidence available was included in the review following the hierarchy of evidence, starting from well conducted RCTs and proceeding to expert opinions if necessary. In the absence of sufficient data from RCTs alone for this review, lower levels of evidence available were included, both RCTs, non-randomised cohort studies and case series were selected, as these were the evidence available. Initially the electronic searches were scrutinised and full manuscripts of appropriate studies were acquired. Final decisions on inclusion or exclusion of manuscripts was made after inspection by the author and another reviewer (AW and HH). Information was extracted from each article on the study characteristics and the outcome data.

The quality of the included studies were assessed by the author and another reviewer (AW, HH). The outcome measures were pre operative haemoglobin, post operative haemoglobin, the transfusion of additional homologous blood, the amount of autologous blood re-infused, serious adverse events and length of hospital stay. Where possible data for outcomes of caesarean section only were included in the analysis, other modes of delivery (vaginal and instrumental) and gynaecological or obstetric surgery (laparotomy) were excluded. For cases receiving the intervention we included the outcome data of those that received only autologous blood, individual data was excluded from the study analysis if additional homologous blood was given and thought to influence the outcome measure (i.e. post-operative haemoglobin). Studies that did not provide separate outcome data for autologous and homologous transfusions were excluded, as were studies that collected blood during caesarean section for purposes other than re-infusion.

Methodological quality assessment

The studies were assessed for methodological quality and adequacy of reporting using the tools appropriate for the study design. RCTs were assessed using the CONSORT statement (68). Cohort studies were assessed using the STROBE statement (a checklist for all observational studies) (69), and the MINORS (70) checklist was used to assess the case series. The CONSORT statement assesses trials for adequacy of reporting on randomisation and sequence generation, baseline comparability, blinding and appropriate statistical analysis. The STROBE statement assesses adequacy for reporting on setting, participants, variables, bias, quantitative variables, statistical methods and generalisability in observational studies. The MINORS checklist assesses for reliability, consistency and validity. The items are scored between 0 and 2 for the adequacy of the reporting, with the ideal score being 16 for non-comparative studies and 24 for comparative studies. Where possible studies were assessed for risk of bias

using the appropriate tools (e.g. Cochrane collaborations risk of bias tool (102) and the Newcastle-Ottawa Scale (71).

Data synthesis

The fixed effects model was used to plot and compare the means and standard deviations for pre and post operative haemoglobin (of studies that reported this) in the RCT. As there was only one study in this analysis the fixed effects model was appropriate, as the intervention was the only source of variation. The random effects model was used in the case series analysis to account for the variation across the studies. Revman 5 software was used for the analysis to calculate the mean difference and inverse variance for pre and post haemoglobin. Heterogeneity of treatment effect was assessed using forest plots and χ^2 tests, and determined the magnitude by calculating the I^2 statistic. Other outcomes are reported narratively.

9.3 RESULTS

The processes of literature search and selection are given in Figure 44. Eleven studies were included in the review from the 1439 articles identified from the searches. All of the studies meeting the inclusion criteria of the review were included due to the shortage of available data. The studies included were one RCT (68 participants), two cohort studies (373 participants) and eight case series, totalling 1542 women (Table 24). All of the included studies were conducted in developed countries due to the lack of available data available from developing countries, however the applicability of the findings to developing countries will be discussed.

Study characteristics

The RCT (281) was set in Italy and included 68 women having caesarean section. Both groups had similar patient characteristics. Women in the intervention group received intra-operative cell salvage and re-infusion. The criterion used in the study for re-

infusion of salvaged blood was not reported. Women in the control group did not receive cell salvage and re-infusion. The two cohort studies were set in USA and UK and included 226 (282) women and 147 (283) women having caesarean section. Women that received cell salvage had intra-operate cell salvage and re-infusion in both studies. The other group of women in both cohort studies did not receive cell salvage and re-infusion. Both studies included women at high risk of postpartum haemorrhage or refusal of blood transfusion. Neither of the cohort studies reported criteria for re-infusion of salvaged blood. The case series were set in Tokyo (284), UK (285-287), Australia (288), USA (289), Ireland (290) and Singapore (291). The women in the case series by Ralph et al (286), McDonnell et al (288), Sullivan et al (287) and King et al (285) also underwent intra-operative blood collection and re-infusion. Whereas the women in the case series by Watanabe et al (284), McVay et al (289), O'Dwyer et al (290) and Yeo et al (291) underwent ante-natal blood collection and intra-operative re-infusion.

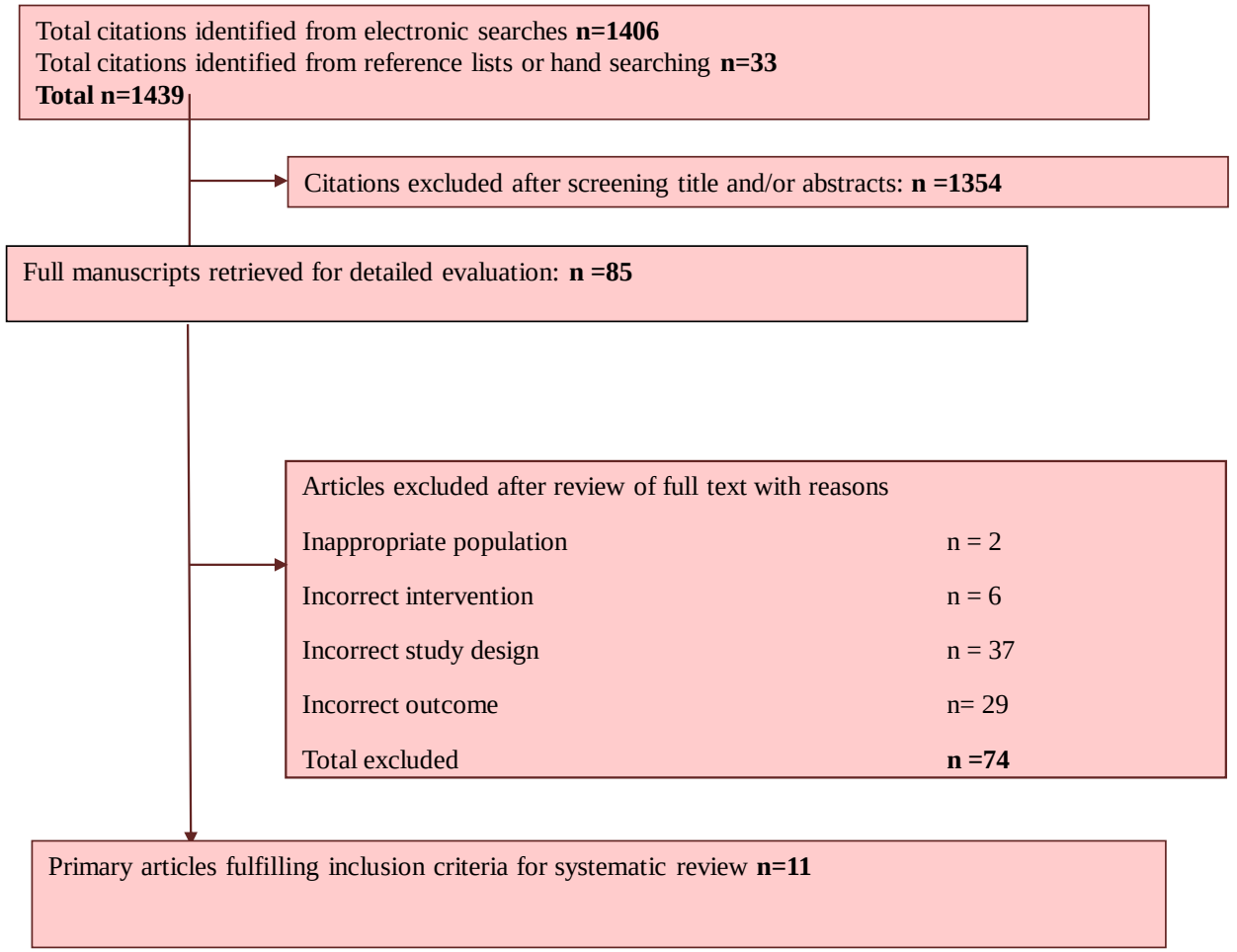

Figure 44 Study selection process in the systematic review of Cell Salvage in Caesarean Section

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When assessed for adequacy of reporting the RCT received a score of 12 out of a possible 22, with details lacking on sequence, allocation, implementation, blinding and recruitment (68). The cohort studies achieved a score of 12 and 14 out of a possible 22 for adequacy of reporting, details were lacking in both studies on data sources, bias, other analysis and funding (69). Case series adequately reported between 50% and 70% (range 8/24-17/24) of items required in the Minors (70) checklist (Table 26). The RCT (281) was assessed as having unclear risk of bias for random sequence generation, allocation concealment and blinding, however there was low risk of bias in outcome data, selective outcomes and other bias. The cohort studies (282, 283) were deemed as having low to medium risk of bias for selection, high risk of bias for comparability, and medium to low risk of bias for outcome assessment (Table 27). Case series were not assessed for risk of bias.

Does re-infusion of salvaged blood improve haemoglobin?

The RCT and seven of the case series reported on pre or post operative haemoglobin, totalling 901 participants (281, 285-291). The RCT (281) demonstrated higher haemoglobin levels for the first four days following the caesarean section, when compared to the control group, even though pre-operative haemoglobin was lower in the intervention arm. The RCT was found to have mean difference of -0.09 (95%CI -1.59 to -0.21: p=<0.001:Figure 45) between the post operative haemoglobin and pre operative haemoglobin following re-infusion of salvaged blood, whereas the control had a mean difference of -3.70g/l (95%CI -4.39 to -3.01: p=<0.001) between the post operative haemoglobin and pre operative haemoglobin. Meta-analysis of the seven case series (285-291) demonstrated a weighted mean difference between the post operative and pre operative haemoglobin of -1.78 (95%CI -2.39 to -1.16: p=<0.0001; Figure 46) following re-infusion of salvaged blood. There was however significant heterogeneity in this analysis (I^2=62%, p=0.03).

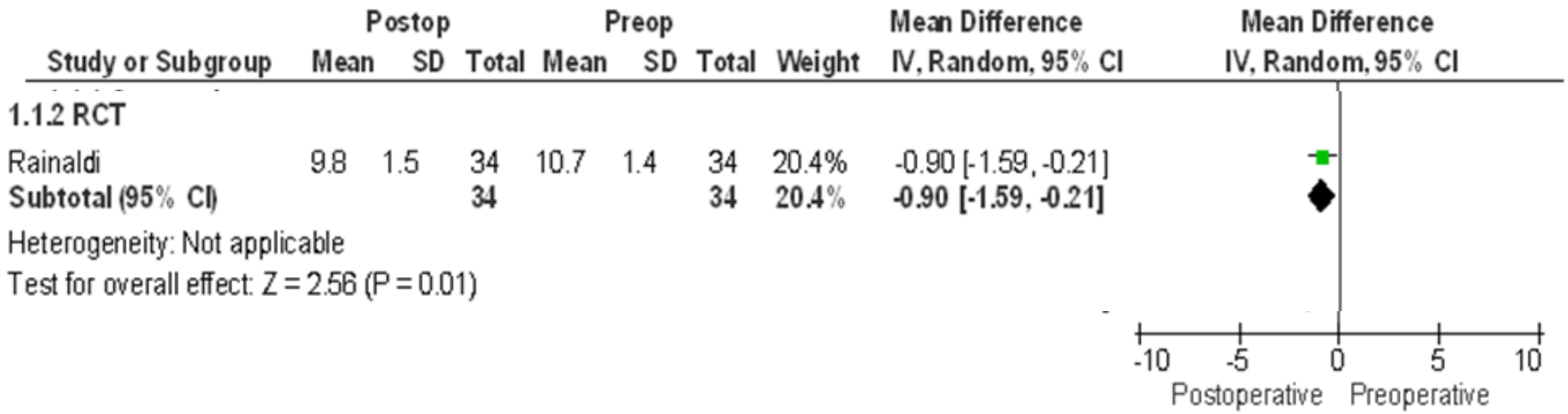

Figure 45 Weighted Mean Difference in Pre and Post operative Haemoglobin in RCT

258

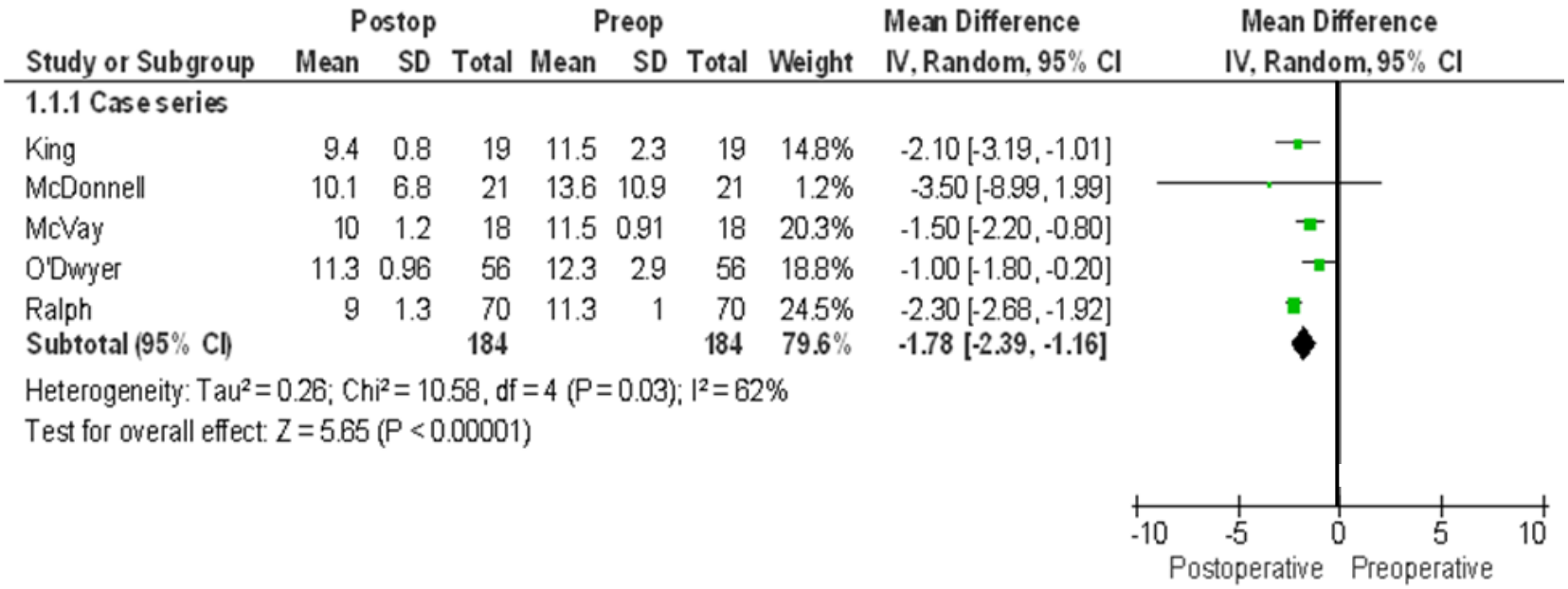

Figure 46 Weighted Mean Difference of pre and post operative haemoglobin in case series

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Does a greater blood loss increase the likelihood of additional homologous transfusion?

The RCT (281) demonstrated a reduced need for additional homologous transfusion in the group that received re-infusion of salvaged blood, when compared to the control group, however no details were provided on estimated blood loss. One cohort study (282) reported a median blood loss of 690ml (range 300-9000ml) and a mean 1,120ml in the group that received cell salvage. In the group that did not receive cell salvage the median blood loss was 800ml (200-4500ml) and the mean blood loss was 1,098mls. The standard deviation was not reported for either group. No further information was reported by Malik et al on estimated blood loss other than this summary statistic for each group in the study. The group that received cell salvage were transfused with more homologous blood (31units) than the group that did not (29 units). This may be due to selection bias, as patients anticipated as having a greater blood loss were included in the cell salvage group. However, given the conflicting data on estimated blood loss that is reported in the summary statistics (e.g. greater mean but lower median in the cell salvage group), albeit incomplete (lacking the standard deviation) it is difficult to draw conclusions on this. Five case series (282, 284, 287-289, 291) (765 participants) reported estimated blood loss and a further five case series (282, 284-286, 289) reported the additional use of homologous blood products.

There was no trend in estimated blood loss with requirements for additional homologous blood in the case series (Figure 37). Case series reporting an average estimated blood loss between 500–1000 mls, classified as minor postpartum haemorrhage, had additional homologous transfusion rates of 5.5% (286) and 56% (289). Case series reporting average blood loss between 1000–2000 ml (moderate postpartum haemorrhage) had additional homologous transfusion rates of 26% (285), 28% (287), and 66% (288). One case series reporting severe post partum

haemorrhage (more than 2000 ml) (284) reported 8.9% of patients requiring additional homologous blood.

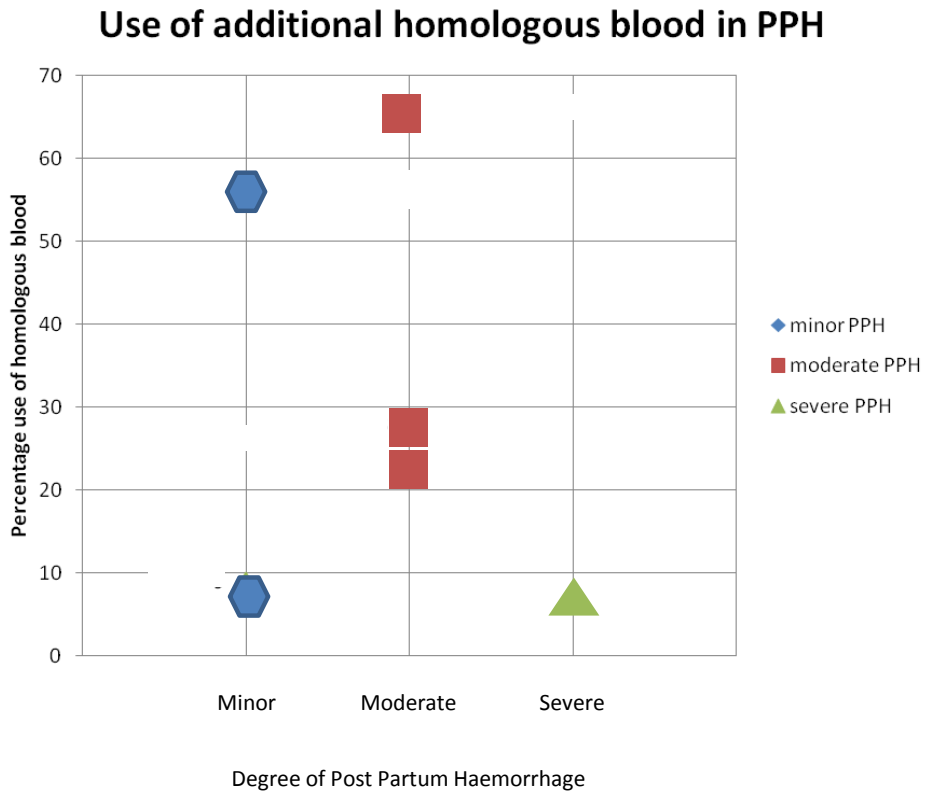

Figure 47 Estimated blood loss use of additional homologous blood

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Is autologous transfusion associated with serious adverse effects?

Two cohort studies and three case series (282-285, 288) reported on this outcome, and no serious adverse effects in the patients that were transfused with autologous blood were reported. This included amniotic fluid embolism (282, 283) acute respiratory distress syndrome (283), rhesus isoimmunisation (282) and thromboembolism (282). The cohort study by Rebarber et al that reported on this outcome, no significant difference was found in infectious complications (283) and disseminated intravascular coagulation (283) between the group that received cell salvage and the group that did not.

Is cell salvage associated with a shorter hospital stay?

Limited data was reported on post operative hospital stay, however a shorter duration of hospital stay was shown with cell salvage when compared to no transfusion in one study by McVay et al (289), but another study found no significant difference between the groups that did and did not have cell salvage (290).

Table 25 Table of study characteristics of included studies in the review

Study Setting	**Population**		**Cases of cell salvage Method used**		**Cases with C/S and reinfusion Criteria for re-infusion**	
RCT	Intervention	Control	Intervention	Control	Intervention	Control
Rainaldi 1998 Italy	34 women with C/S.Mean age: 33.6yrs. Mean weight:73.3kg. Mean height: 161cm	34 women with C/S. Mean age: 31.9yrs. Mean weight: 71.6kg. Mean height: 160cm	34: Intra-operative cell salvage and re-infusion	34: No cell salvage	34 C/S: NR	34: No reinfusion of salvaged blood
Cohort studies			Cell salvage	No cell salvage	Cell salvage	No cell salvage
Rebarber 1998 USA	226 patients with C/S or similar surgical procedures 3 hospitals Jan 1988 – Jul 1997		139: Intra-operative cell salvage and re-infusion	87: No cell salvage	139 C/S: NR	87: No reinfusion of salvaged blood
Malik 2010 UK	147 patients with placenta praevia or Jehovah's witness having C/S Jul 2005 – Aug 2008. Mean age 32yrs. Mean parity 1.46. Mean previous C/S 2.2		77: Intra-operative collection and re-infusion	70: No cell salvage	77 C/S : NR	70: No reinfusion of salvaged blood
Case Series						
Watanabe 2011 Tokyo	314 patients at high risk of excessive blood loss, or difficult to match for transfusion. Mean gestation: 37.8wks 57.6% had C/S, mean age 34.8yrs. Excluded donating: maternal medical complication or fetal growth restriction or abnormalities		56: Antenatal autologous blood transfusion from pre-op patient donation 5 weeks before C/S		56 C/S : Unstable vital signs or low urine output	
Ralph 2011 UK	70 women having C/S. Mean age: 33 yrs 68% Elective C/S. 27% Emergency C/S excluded: category 1, women not read study information		70: Intra-operative autologous collection at C/S, re-infusion 2-6hrs post collection		70 C/S: EBL>1lt and a full bowl of blood was processed. Did not depend on post op Hb	
McDonnell 2010 Australia	51 Patients at high risk of haemorrhage or at risk of refusing donor transfusions Mar 2007 – Jul 2009		21: intra-operative cell salvage and re-infusion		20 C/S (5 autologous reinfusion only): Discussion with obstetrician and anaesthetist, all re-infused if sufficient blood for processing	
McVay 1989 USA	273 3rd trimester pregnancy blood donors between Jan 1987 – June 1988. Delivery data available 209 deliveries.		24: Antenatal pre-operative blood donation (single or multiple donations) up to 3 days before delivery. 7 transfusions in		18 C/S (17 autologous re-infusion only): Re-infused to all patients, even if homologous transfusion not deemed necessary.	

	Cell salvage and re-infusion in 18 C/S, 6 vaginal births. 40% primiparous, 42% over 35 yrs	operating theatre	
O'Dwyer 1993 Ireland	266 Patients having elective c/s, total abdominal hysterectomy and vaginal repair. Mean age 32yrs	Pre-operative blood donation and re-infusion	56 C/S : year 1 patients received routine transfusions without clinical need, year 2 transfusion if actively bleeding/ anaemic
Sullivan 2011 UK	107 patients undergoing cell salvage during C/S Jan 25 2007, Jul 6, 2009.	36: intraoperative cell salvage and re-transfusion	36 C/S:>800mls collected
King 2009 UK	46 patients at high risk of haemorrhage having cell salvage May-Oct 2007	19: Intra-operative collection and re-infusion	19 C/S: Active bleeding, Hb <8g/l, symptomatic anaemia
Yeo 1999 Singapore	20 patients with C/S. Antenatal collection > 36/40 gestation	8: Antenatal autologous blood collection and intraoperative reinfusion	8 C/S : No real indication or excessive blood loss, tendency to transfuse autologous blood

Table 26 Data of outcomes reported in included studies (estimated blood loss, amount of autologous blood reinfused, haemoglobin, additional homologous transfusion, maternal complications)

Study	**EBL***		**Autologous blood re-infused***		**Hb *¥**		**Additional homologous blood (%)**		**Maternal complications**		**Outcome of intervention compared to control (for comparative studies)**
RCT	Int	Con	Int	Con	Int	Con	Int	Con	Int	Con	
Rainaldi 1998	NR	NR	363 (153)	0	Pre: 10.7 Post day 1: 9.8	Pre: 11.7 Post day 1: 8	1/34 (2.9)	8/34 (23.5)	14 previous C/S, 3 placenta praevia,5 fibroids,2 placental detachment	9 previous C/S, 1 placenta praevia,0 fibroids,1 placental detachment	Hb concentrations during 1st 4 days post op higher, pre op Hb lower, need for homologous blood lower, hospital stay shorter in intervention group than control (5.3 vs. 7.3 days p=0.003)
Cohort studies	Cell salv	No cell salv	Cell salv	No cell salv	Cell salv	No cell salv	Cell salv	No cell salv	Cell salv	No cell salv	
Rebarber 1998	NR	NR	H:250(125-4750) G:543(225-1160) Y: 450 (200-11250)	0	NR	NR	NR	NR	median 6 (range3-15) hysterectomy	median 5 (range3-59) hysterectomy	No cases acute RDS, amniotic fluid embolism identified. No significant difference between DIC, infectious morbidity, or post-partum hospitalisation between cell salvage group and no cell salvage group.
Malik 2010	690 (300-9000)	800 (200-4500)	13 units re-infused	0	NR	NR	31 units	29 units	10 fibroids,5 previous massive haemorrhage, 6 multiple C/S, 1 ruptured uterus	NR	Larger EBL, less homologous blood transfused, no adverse outcomes reported in cell salvage group compared to no cell salvage group.
Case series											
Watanbe 2011	2243(1090)		NR		Delivery: 10.8 (1.1)		5/56 (1.6%)		28 placenta praevia, 9 leiomyoma, 12 low lying placenta, 1 previous C/S, 3 previous haemorrhage		
Ralph 2011	900 (400-7000)		324(118-1690)		Pre: 11.3 (1) Post: 9.0 (1.3)		13/70 (56%)		2 ruptured uterus, 1 fibroid, 1 placenta praevia/ Accrete		
McDonnell 2010	1960 (364)		359(242-546)		Pre: 13.6 (10.9) Post: 10.1 (6.8)		14/21 (66%)		5 placenta praevia +/- placenta accrete, most had hysterectomy		

McVay 1989	900(150-2000)	1.2 units (0.56 unit)	Pre: 11.5 (0.91) Post: 10.0 (1.2)	1/18 (5%)	4 placenta praevia, 7 previous C/S, 1 low lying placenta
O'Dwyer 1993	NR	68 units (64.7 unit)	Pre: 12.3 (0.9) Post:11.3 (0.96)	NR	NR
Sullivan 2011	1274	268	Pre: 9.5 Post: 8.9	10 (28%)	All at high risk of haemorrhage (placenta praevia, multiple repeat C/S, ante-partum haemorrhage.
King 2009	120 (500-2000)	300 (200-800)	Pre: 11.55±2.3 Post: 9.4 ± 0.8	5 (26%)	4 placenta praevia, 3 fibroids, 2 multiple C/S, 2 previous haemorrhage
Yeo 1999	390 (250-600)	NR	Pre:12.09 (10.5-13.5)	NR	NR

*****Mean and SD or Median and range (ml) ¥ Post op excludes additional homologous transfusion data. H=Hinsdale, G=Good Samaritan, Y=Yale new haven

Table 27 Quality assessment: Reporting checklist of RCT (Y=Reported; N=Not Reported)

Topic	Consort checklist	
Rainaldi 1998		
Title and abstract		
	Identification as RCT in title	N
	Structured summary of trial design, methods, results, conclusions	N
Introduction		
Background objectives	Scientific background, explanation of rationale	Y
	Specific objectives or hypotheses	Y
Methods		
Trial design	Description of trial design including allocation ratio	Y
	Important changes to methods after trial commencement, reasons	N
Participants	Eligibility criteria for participants	N
	Settings and locations where data collected	N
Interventions	interventions for group with sufficient details to allow replication, including how and when actually administered	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when assessed	Y
	Any changes to trial outcomes after trial commenced, reasons	N
Sample size	How sample size was determined	Y
	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation		
Sequence Generation	Method used to generate random allocation sequence	N
	Type of randomisation; details of restriction	N
Allocation concealment mechanism	Mechanism to implement random allocation sequence, describing any steps taken to conceal the sequence until interventions assigned	N
Implementation	Who generated random allocation sequence, enrolled participants, assigned participants to interventions	N
Blinding	If done, who blinded after assignment to interventions and how	N
	If relevant, description of similarity of interventions	N/A
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	Y
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N
Results		
Participant flow	numbers of participants were randomly assigned, received intended treatment, and analysed for primary outcome	Y
	losses and exclusions after randomisation, with reasons	N
Recruitment	Dates defining periods of recruitment and follow-up	N

	Why trial ended or stopped	N
Baseline data	A table showing baseline demographic and clinical characteristics for each group	Y
Numbers analysed	For each group, number of participants included in each analysis and whether analysis by original assigned groups	N
Outcomes and estimation	primary and secondary outcome, results for group, and estimated effect size and precision	Y
	binary outcomes, presentation of both absolute and relative effect sizes is recommended	Y
Ancillary analyses	Results of other analyses performed, subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N
Harms	All important harms or unintended effects in group	N
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, imprecision, multiplicity of analyses	Y
Generalisability	Generalisability of trial findings	Y
Interpretation	Interpretation consistent with results, balancing benefits and harms, considering other relevant evidence	N
Other information		
Registration	Registration number and name of trial registry	N
Protocol	Where full trial protocol can be accessed, if available	N
Funding	Sources of funding, other support role of funders	N

Table 28 Quality assessment: Reporting checklist for cohort studies

STROBE Checklist	Rebarber 1998	Malik 2010
Title and abstract		
Design	Y	N
Summary	Y	Y
Introduction		
Background	Y	Y
Objectives	N	Y
Methods		
Study design	Y	N
Setting	Y	N
Participants	Y	N
Variables	Y	Y
Data sources	N	N
Bias	N	N
Study size	Y	Y
Quantitative variables	Y	N
Statistical methods	Y	N
Results		
Participants	Y	Y
Descriptive data	N	Y
Outcome data	N	Y
Main results	N	Y
Other analysis	N	N
Discussion		
Key results	Y	N
Limitation	N	Y
Interpretation	Y	Y
Generalisability	Y	Y
Other information		
Funding	N	N

Table 29 Quality assessment: Reporting checklist for case series

Minors checklist								
	McVay 1989	O'Dwyer 1993	Yeo 1999	King 2009	McDonnell 2010	Ralph 2011	Sullivan 2011	Watanabe 2011
Aim	1	2	2	2	1	2	2	2
Inclusion of patients	2	2	2	1	1	2	2	2
Prospective data collection	1	2	2	1	1	2	1	2
Appropriate end points	2	2	2	2	1	2	2	2
Unbiased end point assessment	0	0	0	0	1	1	0	0
Appropriate follow up	1	0	0	0	0	2	2	2
Loss of follow up <5%	1	2	2	2	2	2	2	2
Prospective study size calculation	0	0	0	0	0	0	0	0
Adequate control group	1	-	1	2	1	-	-	1
Contemporary groups	1	-	1	2	0	-	-	1
Baseline equivalence	0	-	0	1	0	-	-	1
Statistical Analysis	2	-	1	2	0	-	-	2

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Table 30 Risk of Bias in RCT (Y= Reported; N= Not Reported)

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
Rainaldi 1998							
UNCLEAR: Page 195: Randomly allocated no further details	UNCLEAR: Page 195: No details provided	UNCLEAR: No details reported	UNCLEAR: No details reported	LOW:Page 197: Data provided for all patients	LOW: Page 197: All outcomes reported	LOW: Appears to be no other sources of bias	
Selection				Comparability		Outcome	
Representativeness	Selection on comparison	Ascertainment of exposure	Demonstration of outcomes	Comparability(2 points available)	Outcome assessment	Follow up length	Adequate follow up
Rebarber 1998							
Y	Y	Y	Y	N	Y	Y	N
Malik 2010							
N	Y	Y	Y	N	Y	Y	Y

9.4 DISCUSSION

Main findings

The systematic review reports the outcomes of pre and post operative haemoglobin, estimated blood loss during the caesarean section, the use of additional of homologous blood transfusion and adverse events in cases of cell salvage in caesarean section. In the RCT post-operative haemoglobin dropped by 0.90g/l from the pre-operative haemoglobin in the group that received cell salvage, whereas the control group post-operative haemoglobin dropped by 3.70g/l from the pre-operative haemoglobin. The post-operative decrease in haemoglobin was 1.78g/l in the case series. The groups that received cell salvage in the cohort studies were transfused more homologous blood than those that did not receive cell salvage, but this may be due to selection bias. However, there was no trend in estimated blood loss with additional homologous blood transfusion in women that received cell salvage in the case series. There was no significant difference in serious adverse effects reported using cell salvage, or length of hospital stay, although there was limited data available on this outcome.

The selection bias that may exist in relation to this finding, may be due to the inclusion of more patients at greater risk of post partum haemorrhage due to various clinical characteristics and risk factors, such as multi-parity, multiple pregnancy, uterine fibroids and previous caesarean section, in the cell salvage group. Therefore the increased likelihood of additional homologous transfusion may not be related to the process of re-infusion of autologous blood, but to the patient and their clinical picture, which may differ from that of the patient in the group that did not receive cell salvage (because these patients were less likely to experience post partum haemorrhage). It is however difficult to draw firm inferences on this as only one cohort study reported estimated blood loss. A higher mean blood loss was reported in the group that received cell salvage (no standard deviation was reported) yet a lower median blood loss.

Study Limitations

There was a complete lack of data originating from developing countries; therefore all of the included studies in the review were from developed countries. Due to the complexities and costs associated with the training and resources required for this procedure, the applicability of this type of cell salvage in a low resource setting would need to be debated.

The type of study design from which the majority of the data originates (case series) is a serious limitation within this review. The methodological quality of most of the studies included in the review was also poor, with the majority lacking control in the study design; In the RCT there was lack of blinding and adequate concealment of treatment allocation. The cohort studies were retrospective and lacked information on the setting, data sources and attempts to address bias. Furthermore the sample size of the studies included were predominantly small, therefore there may be insufficient power to detect rare outcomes such as amniotic fluid embolism and maternal death.

A further limitation of the review was that although the majority of studies within the analysis focus on women undergoing caesarean section, and outcomes have been analysed for caesarean section where possible (288, 289), for one large study (314 patients) it was not possible to exclude the outcomes of women having vaginal or instrumental births from those having caesarean section, thus it is acknowledged that this is likely to incur bias within the results (284).

In addition to this a large proportion of the caesarean sections performed within the studies were elective procedures, therefore one could speculate that haemoglobin would have been checked prior to surgery to identify and correct anaemia before the caesarean section was performed. Furthermore four of the included studies (284, 289-291) performed preoperative blood collection for intra-operative donation, in which women with an Hb below 10.g/l (284) and 11.0g/l (289, 291) were excluded. As no low Haemoglobin values were included within

these groups, selection bias could confer an advantage to this group giving higher haemoglobin levels. Attempts have been made to address this by comparing weighted mean differences rather than comparing the pre and post haemoglobin values.

Estimated blood loss also differed between the group that received cell salvage and the group that did not (only reported in one cohort study), this could be influenced by the inclusion criteria of some studies, as some only recruited patients at risk of increased blood loss (e.g. placenta praevia) in the group that received cell salvage. Yet as conflicting data was provided on this outcome in this study it is difficult to draw inferences. Most studies however included patients at a similar risk of haemorrhage (282, 284, 285, 287, 288) although reasons for re-infusion varied across studies. For example some studies only re-infused salvaged blood when clinically indicated through unstable vital signs (284) or anaemia (285), whereas others re-infused when estimated blood loss was greater than 800ml (287) or one litre (286). Yet some studies re-infused without clinical need if there was sufficient blood salvaged for processing and re-infusion (288, 289) (291)

Existing Research

The reduced need for homologous red cell transfusion has been demonstrated in a Cochrane review (292) in elective adult cardiac and orthopaedic surgery with the use of intra-operative cell salvage. This type of surgery is quite different and due to the additional concerns of amniotic fluid embolism and maternal fetal alloimmunisation in caesarean section, these results cannot be generalised to obstetric patients. To date there is no Cochrane review on the use of cell salvage in caesarean section. There has been one literature review published recently (293) that examined the safety, efficacy, indications and contraindications of cell salvage in obstetrics, however this did not take a systematic approach, the methodology was unclear, and studies were omitted from the review. Two previous literature reviews were published in 2008 (294) and 2009 (295), but since these publications seven more studies have been published on cell salvage in caesarean section.

From the literature, it is apparent that the safety concerns with cell salvage are often perceived as a barrier to use in obstetrics. Issues with training and the complexity of equipment have been raised (296), however the theoretical risk of transfusing salvaged blood that may contain small amounts of amniotic fluid has recently been debated (297).

Practice and policy implications

Cell salvage could possibly be suggested as a safe and effective intervention to increase haemoglobin levels for women undergoing caesarean section. Although this review includes data from poor quality studies that are vulnerable to bias, it suggests that minimal adverse affects are associated with cell salvage in caesarean section. In the absence of good quality data from developing countries, is not possible to suggest policy implication for this procedure. Furthermore, there are serious cost implications with the type of cell salvage explored in this review. A unit of homologous is suggested to cost approximately £120 (although this cost does fluctuate globally with the cost of processing (298), whereas the equipment required for cell salvage, is much more costly. For example the cell salver machine is over £4000, the cost of the collection and infusion kits are £77, plus the running and maintenance costs of the machine (298). Therefore it is unlikely that this intervention is sustainable within a developing country, where limited funds and resources are put into healthcare.

Moreover the practical implications associated with cell salvage should also be taken into consideration. There may be a delay in the patient receiving adequate treatment (i.e. blood transfusion of salvaged blood) due to the time taken to set up the apparatus. This may also result in blood being lost and not being able to be salvaged, as it is not possible to retrospectively salvaged shed blood. In turn this may result in the patient's condition deteriorating. In addition, the time taken to process the blood for reinfusion may result in further deterioration of the patient's condition.

There is also an additional risk associated with the transfusion of salvaged blood is the theoretical risk of coagulopathy reported in the literature, this could occur with the reinfusion of activated clotting factors, as the blood may no longer be coagulable following the process of fibrinolysis, due to a deficiency in fibrinogen and factors V, VII and X (299). The risk of the transfusion being ineffective should therefore be taken into consideration when discussing this service with patients.

Unanswered questions and future research

Primary research of sound quality is needed to draw firm inferences on the safety and effectiveness of cell salvage in caesarean section. A health economics assessment is also needed to assess the feasibility of this intervention in developing countries.

9.5 CONCLUSION

Accounting for the substantially greater blood loss between the groups that received cell salvage and the groups that did not, and the similarities in the pre and post operative haemoglobin, it is speculated that cell salvage may be beneficial in achieving normal haemoglobin levels for women that have undergone caesarean section. The applicability of these findings however, to a low resource setting needs to be questioned due to the training and resource costs associated. Cell salvage using the method in which was included in the studies in this review, may not be a financially sustainable option, it may also not be an economically viable alternative to homologous transfusion, as this is often associated with lower costs. No firm inferences can be drawn from the conclusions of this review on cell salvage in caesarean section in women in developing countries, due to the setting of the studies and the quality of the data. It is acknowledged that the study design of most of the included studies (case series) is vulnerable to bias and confounding. However despite this, this remains the best evidence available on cell salvage in caesarean section to date. Further primary research of sound quality, with health economics is needed to draw firm inferences

on the use of cell salvage in caesarean section, and the feasibility of it in developing countries.

CHAPTER 10: CELL SALVAGE IN ECTOPIC PREGNANCY: A SYSTEMATIC REVIEW

ABSTRACT

Background: Haemorrhage from ruptured ectopic is a major cause of maternal death in many low income countries. Significant morbidity is also associated with massive haemorrhage, particularly in countries where resources are limited or there is a shortage of available blood to transfuse for financial, cultural or practical reasons. Simple cell salvage has been used in many low resource settings as an alternative to homologous blood transfusion.

Methods: A systematic review of available evidence was conducted (RCT, Cohort studies and case series). The databases MEDLINE, EMBASE, AMED, BNI, the Cochrane library, CINHAL, LILACS, African Index Medicus, Web of Science, the Reproductive Health Library, and the Science Citation Index (inception-May 2012) were searched without language restriction. Data were extracted from each study on study characteristics, study quality and outcome data. Outcomes were pre and post operative haemoglobin, additional use of homologous blood transfusion, serious adverse effects and length of hospital stay.

Results: Seventeen papers were included (2220 women), one RCT, two cohort studies and 14 case series. The RCT demonstrated a greater increase in post operative haematocrit in the group that received cell salvage, compared to the control group. The use of additional homologous blood transfusion in addition to transfusion of salvaged blood was reported in half of the group that received cell salvage in the cohort study. Comparatively 4.9% of women that received cell salvage in the case series received additional homologous blood. No significant difference was found in infectious morbidity in the RCT or the cohort study. The majority of the deaths reported in the case series were reported as not associated with the transfusion of salvaged blood.

Conclusion: It is possible that simple cell salvage in ectopic pregnancy could be safe and effective alternative to donor transfusion if culturally unacceptable or unavailable. However

further primary research of sound quality is needed to draw firm inferences on the use of simple cell salvage in ectopic pregnancy.

10.1 BACKGROUND

Haemorrhage from ruptured ectopic pregnancy is a major cause of maternal death, particularly in low income countries where resources are limited or there is a shortage of available blood to transfuse (as discussed previously in chapter eight). Significant morbidity is also associated with haemorrhage from ruptured ectopic pregnancy.

Blood transfusion is one of the essential components of comprehensive emergency obstetric care (270, 300), however many low income countries lack this core component. The availability of blood can directly affect maternal mortality rates, for example in Sub-Saharan Arica where blood donation rates are very low, maternal mortality rates are high (301). As stated before there is a need for alternatives to homologous donor blood transfusion in low income countries, not only for caesarean section but for other obstetric and gynaecological procedures.

The notion of autologous blood transfusion in gynaecology and obstetrics was first acknowledged in 1818 (278), this process involved collecting the blood found in the body's cavities as a result of ruptured ectopic pregnancy and re-infusing it back into the patients veins (279), this process is described below. Today cell salvage is a more advanced procedure in high income countries (previously described in chapter eight), having been used widely for operations such as cholecystectomy since 1962 (280). It is also commonly used in cardiac, orthopaedic and vascular surgery, with NICE guidance (276) describing intra-operative blood cell salvage as an efficacious technique for blood replacement. Yet in low income countries cell salvage remains a more basic technique, and this is the technique that will concern this review. Not only can cell salvage be used in areas that lack homologous

blood transfusion services, it can reduce the risks associated with homologous blood transfusion, for example blood borne infections and transfusion related reactions. This may be particularly significant in areas where the prevalence of HIV and other blood borne infections are high. Cell salvage may also be a more suitable option culturally, for groups such as Jehovah's Witness that may decline homologous blood products (275).

Although intra-operative autologous blood transfusion has a long history in the treatment of haemorrhage from ruptured ectopic pregnancies, and is frequently used in areas where there are limited resources (270), little is known about clinical outcomes of exclusive autotransfusion in ectopic pregnancy (302). A systematic review and meta-analysis was performed using the data from all available studies, and the applicability of the findings to low resource settings are then discussed.

The process of cell salvage

In the case of cell salvage for ruptured ectopic pregnancy, the Tanguieta funnel is the most common method used (270). A perforated funnel is placed in the peritoneal cavity to collect the pooled blood, then a small incision in the peritoneum is performed to avoid blood spillage. The blood is then collected by aspiration or scooped using a sterile galipot or ladle. Clots and debris are filtered out by passing the blood through a gauze filter into a receiving bowl. The blood is then aspirated into a sterile syringe, transferred into an intravenous transfusion set that has been prepared with an anti-coagulant solution. It will then be re-infused back into the patient (303).

Risks associated with transfusion

The risks of blood transfusion relative to those of not transfusing blood should always be considered. The serious risks that can occur with homologous transfusion are less likely in autologous transfusion, as they are often due to the transfusion of incorrect blood, caused by clinical errors in the transfusion process, such as incorrect identification of patients, blood

units or labelling errors. Yet there are still risks associated with homologous transfusion, particularly in low resource settings where the method of autologous transfusion, as described above is used. The equipment may be re-used for transfusions and poorly sterilised, allowing bacteria to directly enter the central circulation, thus putting the patient at risk of septicaemia. An additional theoretical risk noted by Carty et al (304), as associated with the transfusion of salvaged blood is the possibility of coagulopathy: this could occur with the reinfusion of activated clotting factors, as the blood may no longer be coagulable following the process of fibrinolysis, due to a deficiency in fibrinogen and factors V, VII and X (299).

10.2 METHODS

Data sources and searches

Databases were searched for literature on cell salvage in ectopic pregnancy. The focus was on developing countries, however if no data were available from developing countries, the available data was examined, and the applicability to developing countries discussed. The population was women with ectopic pregnancy who underwent cell salvage with re-infusion. MEDLINE, EMBASE, Cochrane library, CINHAL, LILACS, African Index Medicus, the Reproductive Health Library, and the Science Citation Index were searched (from database inception to February 2012). Hand searching complemented electronic searches, and reference lists were checked. The primary search terms were ‘cell salvage’, ‘blood salvage’, ‘cell salver’, ‘erythrocyte salvage’, autologous transfusion’, ‘autotransfusion’, ‘tubal pregnancy’ and ‘ectopic pregnancy’. No language restrictions were applied to the search.

Study selection and data extraction

The best possible evidence available was included in the review following the hierarchy of evidence, starting from well conducted RCTs and proceeding to expert opinions if required. As there was a lack of adequate data from RCTs alone, lower levels of available evidence

were included; RCTs, non-randomised cohort studies and case series were selected, as these were the evidence available. Initially the electronic searches were scrutinised and full manuscripts of appropriate studies were acquired. Final decisions on inclusion or exclusion of manuscripts was made after inspection of these manuscripts by the author and another reviewer (AW and HH). Information was extracted from each article on study characteristics, quality and outcome data by the author and another reviewer (AW, HH). The outcome measures were pre operative and post operative haemoglobin levels, estimated blood loss or haemoperitineum, use of additional homologous blood, duration of post operative hospital stay, and serious adverse events. Individual data was excluded from the study analysis if an additional intervention was given and it was thought to influence the outcome measure, for example if additional homologous blood was given post-operative haemoglobin may be influenced. Therefore the outcome data of participants who received only autologous blood in the cell salvaged group were included in the analysis. Studies that did not provide separate outcome data for autologous and homologous transfusions were excluded, as were studies that collected blood for purposes other than re-infusion.

Methodological quality assessment

The studies were assessed for methodological quality using reporting assessment tools appropriate for the study design. The CONSORT (211) statement was used to assess RCTs, the STROBE (69) statement was used to assess the cohort studies, and the MINORS (70) checklist was used for case series studies. These have been discussed previously in chapter eight. Where possible studies were assessed for risk of bias using the appropriate tools (e.g. Cochrane collaborations risk of bias and the Newcastle Ottawa Scale (71).

Data synthesis

Outcomes are reported narratively, and data from RCTs, cohort studies and case series are reported separately. There was insufficient data to conduct a meaningful meta-analysis, therefore it was not deemed appropriate with the outcome data available.

10.3 RESULTS

The processes of literature search and selection are given in Figure 38. Seventeen studies were suitable for inclusion within the review with a total of 2220 participants that were undergoing surgery for ruptured ectopic pregnancy. This included one RCT (139 women), two cohort studies (176 women) and 14 case series (1905 women). Characteristics of the included studies are shown in Table 28, and the outcome data reported for women undergoing cell salvage for ectopic pregnancy is shown in Table 29. Unlike chapter eight, where all of the included studies originated from developed countries, most studies in this review originate from developing countries. All of the studies meeting the inclusion criteria of the review were included due to the shortage of available data.

Study characteristics

The one RCT by Selo-Ojeme (299) was set in Nigeria and included 139 women with Haemoperitoneum greater than 500mls, or where there was evidence of haemorrhagic shock. Women with sickle cell were excluded, as were those with a leaking chronic ectopic pregnancy. The intervention group (received autologous transfusion) and the control group (received homologous transfusion) had 56 patients in each group. The intervention group received all of the collected intraperitoneal blood through re-infusion. The method that was used to salvage the blood in the intervention group involved making an opening in the top of a fluid bag large enough to allow the pouring of the salvaged blood from the midline subumbilical incision that was made. Artery forceps were used to hold up the edges of the incised parietal peritoneum, to prevent subcutaneous blood from mixing with intraperitoneal blood. A galipot was then used to scoop out the intraperitoneal blood into a sterile bowl, which was then covered with doubled latex gauze to act as a filter. The full bowl was then turned into the infusion container that had already been cleaned with spirit. No anticoagulant was used. The control group women received the total number of units that had been obtained for them (usually through patient relatives). Baseline characteristics were similar for

the intervention and the control group, with the majority of women being nulliparous (89% and 87% respectively), gestational age below ten weeks (87% and 89%) with a history of miscarriage or abortion (75% and 71%), and a history of sub-fertility (20% and 23%). This trial reported pre-operative and post operative haemocrit, wound infection, fever, mortality, haemoperitoneum, hospital stay greater than seven days, surgery duration and transfusion greater than one litre.

The two cohort studies by Duncan et al and Selo-Ojeme et al included 53 patients (305) and 123 patients respectively (306), however in the study by Duncan et al (307), only a small proportion of the patients received autologous transfusion for ruptured ectopic pregnancy (8 patients), there were also no patients that received homologous transfusion alone to compare outcomes with. The other study by Selo-Ojeme et al (299) reported on 33 patients that received autologous transfusion and 85 patients that received homologous transfusion for ruptured ectopic pregnancy. The methods of cell salvage used were similar to the method described above (299). Limited baseline characteristics were reported for patients in both studies, with Duncan et al reporting participants age (range 19-41 median 37) (307) and Selo-Ojeme et al reporting gestational age below 12 weeks gestation (94% and 90.5% in the autologous and homologous groups respectively). The studies reported on the outcomes of mortality, post operative complications, haemoperitoneum, duration of hospital stay, transfusion of additional homologous blood and the volume of blood transfused.

Study quality

When assessed for quality the RCT received a score of 16 out of a possible 22 on the CONSORT (211) statement checklist (Table 34) with details lacking on blinding, implementation, study objectives, statistical methods, recruitment and ancillary analysis. The cohort studies received a score of 11 out of 22 on the STROBE statement, lacking details on study design, study size, statistical methods, descriptive data, other analyses and limitations (Table 35). The case series received a median score of 6 on the MINORS checklist out of a

possible 16 (range 1-9). Most case series reported a clearly specified aim, described the inclusion of consecutive patients, gave unbiased endpoint assessment, appropriate follow up and had a loss of follow up of less than 5%. Most case series did not have a prospective study size calculation, or prospective data collection (Table 36). Risk of bias in the RCT was low for sequence generation, allocation concealment, incomplete outcome data, selective reporting and other bias (Table 37). However there was unclear risk of bias in blinding of participants and outcome assessors. Risk of bias in the cohort studies was assessed as low for selection in one study, and high in another, this was also true for comparability, and outcome assessment (Table 37). Risk of bias was not assessed for case series.

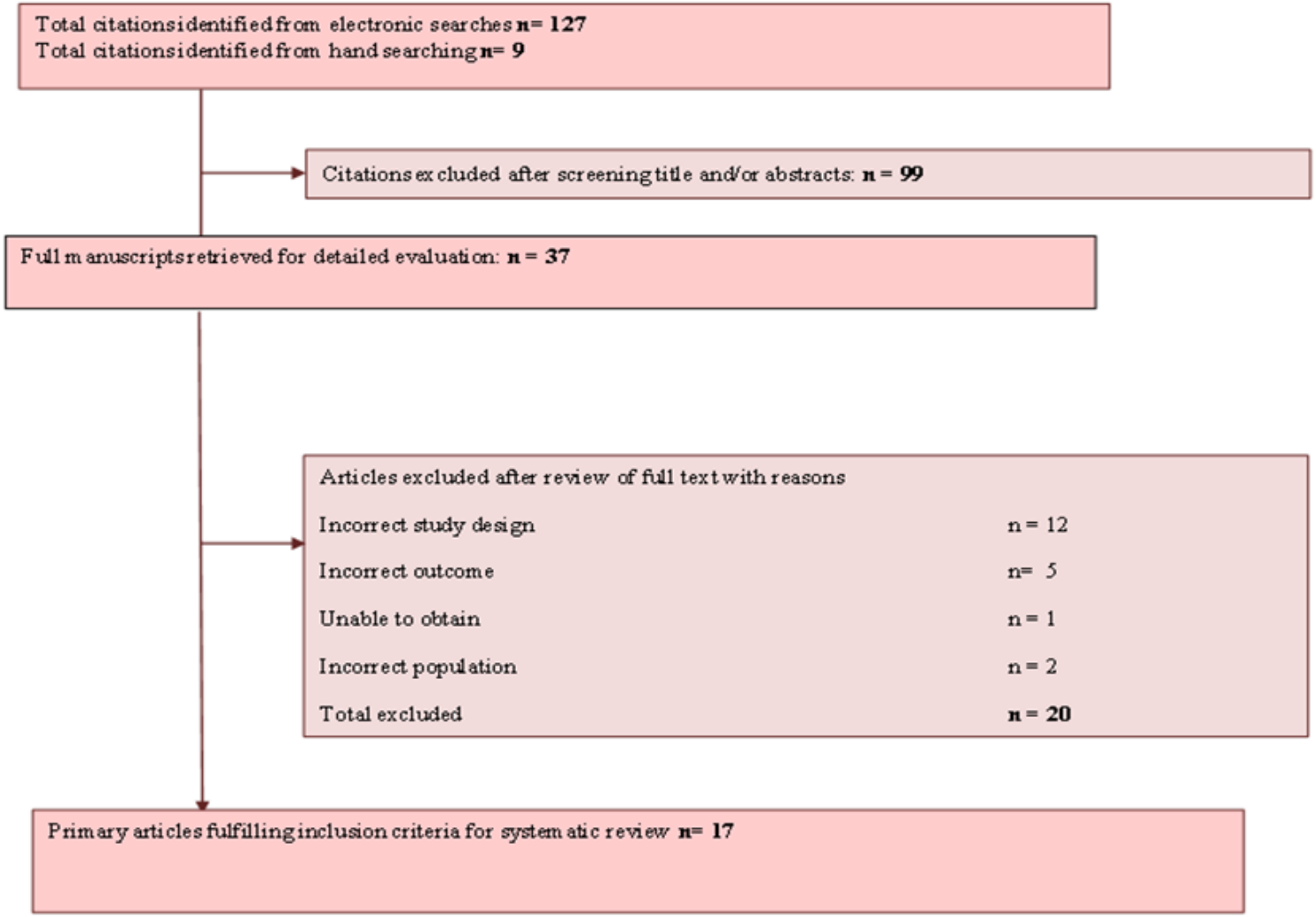

Figure 48 Study selection process in the systematic review of Cell Salvage in ectopic surgery

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Does re-infusion of salvaged blood improve haemoglobin?

The RCT demonstrated a greater increase in haemocrit, from pre operative measurement to post operative measurement in the group that received the intervention (0.095), compared to the control (0.057). The authors did not report if this difference was significant, and the paper contained insufficient data to calculate this, this was also the reason for not calculating mean difference in this analysis. Six case series (308-313) also reported on this outcome, post-operative haemoglobin is given from autologous transfusion patients only. Some studies showed an increase in haemoglobin from pre-operation to post-operation, between 1.3 to 4.8g/l (309-311, 313), whereas others showed a decrease, between 1.3-1.8g/l (308, 312).

Does autologous transfusion increase the likelihood of additional homologous transfusion?

The additional use of homologous blood transfusion in conjunction to autologous transfusion was reported in seven studies (307-309, 311-315). One cohort study reported that 50% (4/8) of participants receiving cell salvage, also received additional homologous blood transfusion. No data on this outcome was provided for the women that did not receive cell salvage. Three out of 6 case series also reported the use of additional homologous blood transfusion, with a total of 44 participants out of 295 (14.9%) receiving additional homologous blood. No data were provided for the groups that did not receive cell salvage.

Is autologous transfusion associated with serious adverse effects?

Infectious morbidity: Post operative infection and fever was reported in 4 studies (299, 306, 311, 316). The RCT demonstrated no significant difference in infectious morbidity between the intervention and control groups overall (RR 0.92 95%CI 0.60, 1.41: p=0.70). No cases of sepsis were reported in either group, and 20 cases of fever and 3 cases of wound infection were reported in the autologous group, and 21 cases of fever

and 4 cases of wound infection were reported in the homologous group: no further details were provided on either of these outcomes. The cohort study by Selo-Ojeme et al also demonstrated no significant difference for the outcome of infectious morbidity (RR 0.90 95%CI 0.42, 1.93: p= 0.79). In this study 6 cases of fever and 1 case of wound infection were reported in the autologous group, and 18 cases of fever and 2 cases of wound infection were reported in the homologous group, again no further details were provided on either of these outcomes. Ten of the participants out of a total 476 (2.1%) who had received cell salvage in the reporting case series developed post operative infection, this included one case of hyperpyrexia and rigors after 100ml of autologous blood was infused in the study by Pathak et al (316), no further details were provided on the other 9 cases reported in the study by Priuli et al (311).

Serious adverse effects: Sixteen studies (299, 306-314, 316-321) reported on serious adverse effects associated with autologous transfusion. None were reported in the RCT or in the cohort studies, in either of the groups that received cell salvage or the groups that did not. The case series however reported 11 maternal deaths (310, 316, 317, 319, 321), although 9 of the deaths were specifically stated by the authors as not being associated with the transfusion they had received. One death was due to mitral stenosis (310), 3 were due to severe irreversible hypovolemic shock (317, 319, 321), and 6 deaths were described as unrelated to the autologous transfusion but further details were lacking (316). A single death reported by Jongen et al from pulmonary oedema was suggested to be associated with autologous transfusion (317), and another case series by Laskey et al reported a case of severe pulmonary oedema from which the patient recovered (321).

Is cell salvage associated with a shorter hospital stay?

Seven studies reported on post operative hospital stay (299, 306, 309-311, 315, 319). The RCT (223) demonstrated no significant difference between the intervention and the

control group, in the proportion of participants that had a post operative hospital stay greater than 7 days (RR 1.33 95%CI 0.49, 3.59: p=0.57). Eight patients (14.3%) receiving cell salvage, and 6 patients (10.7%) receiving donor transfusion experienced a hospital stay greater than 7 days (299). One cohort study by Selo-Ojeme et al also demonstrated no significant difference with post operative hospital stay greater than 8 days (RR 0.64 95%CI 0.07, 5.55: p=0.69)(299, 306). One patient (3%) receiving cell salvage, and 4 patients (5%) receiving donor transfusion experienced a hospital stay greater than 8 days (306), whereas 32 (97%) patients receiving cell salvage, and 81 (95%) patients receiving homologous transfusion experienced a hospital stay of less than 8 days (306) in this study. Five case series reported this outcome, the mean duration of hospital stays reported in the studies were 5.6 days, 6.9 days, 8.6 days (three centres in one study), 7 days, 7.4 days, 8.5 days and 9.8 days.

10.4 DISCUSSION

Main findings

There is a shortage of high quality studies in cell salvage for ectopic pregnancy, with only one RCT, but some data was available from developing countries. From this limited data it could be suggested that simple cell salvage in ectopic pregnancy could be a safe and effective alternative to homologous transfusion. It is however acknowledged that no firm inferences can be drawn from the conclusions of this review as the data lack sufficient quality and are vulnerable to bias. Attempts have been made, where possible to minimise this within our analyses. Post-operative haemoglobin was calculated from autologous transfusion patients only; patients who received additional homologous transfusion were excluded from the analysis of this outcome to reduce bias in outcome measurement. It is possible that the larger increase in haemoglobin and the greater volume of blood received by patients receiving cell salvage may be due to performance bias as it is suggested that women were 3 times

more likely to have higher post operative haemocrit than women who received homologous blood transfusion, as all efforts are made to re-infuse the maximum blood possible (223). Comparatively donor blood (homologous) is often given in much smaller amounts, particularly in low resources settings, where minimal amounts are given, often only enough to sustain the patient's life (299, 306).

Although the RCT included patients with similar characteristics in both intervention and control groups, and had the same criteria for receiving blood transfusion in both groups (299), the authors stated that women receiving autologous blood transfusion "were 6 times more likely to be re- transfused with more than one litre of blood", thus had a greater volume of blood in the autologous group. The increased levels of haemoglobin and haemocrit in the autologous group therefore, may be related to the volume of autologous blood re-infused, rather than it being due to a more effective method per se. The lower volume of blood in the homologous group is likely to be due to a lack of availability, as described earlier.

The proportion of minor and major adverse effects reported within the review was 12% (67/553), however many were suggested to be related to the moribund or clinical state in which the patient presented, rather than the transfusion process (310, 316-319, 321). 81% of the deaths reported in the studies were reported as not being associated with autologous transfusion, although causes of death were not always reported. Serious complications are known to be a possible occurrence due to extracellular haemorrhage when stale and haemolysed blood is autotransfused (322), yet in acute ruptured ectopic pregnancy the intraperitoneal blood remains capable of normal oxygen transport (303), therefore associated procedural complications should be minimal. The deaths reported within the review were mainly due to irreversible hypovolemic shock (317, 319, 321) or pulmonary embolism (317). A quarter of the cases of pulmonary oedema resulted in death (n=1/4), and these cases were thought to be due to rapid

transfusion (314). It might be that this could indicate a particular training need with this procedure given that levels of expertise were good reported. Post operative infection was reported in 13 patients, a further 28 patients (299, 306, 316, 321) were also reported as having minor infections associated with the operative procedure. Prophylactic antibiotics were given to patients in two studies (308, 311), and there was a reduced incidence of infective morbidity in these studies (4% n=9/223) when compared to studies that did not administer prophylactic antibiotics (10% n=34/330) (299, 306, 307, 309, 310, 312-314, 316-321).

Study Limitations

The methodological quality of the studies included in the review was poor. The RCT lacked blinding and adequate concealment of treatment allocation. The cohort studies did not attempt to address sources of bias or give details on the study limitation, and case series studies failed to adequately report the inclusion of consecutive patients, the appropriateness of end points and endpoint assessment, as well as the appropriateness of follow up. It is acknowledged that the study design of most the included studies (case series) are vulnerable to bias and confounding, and that the sample size of the studies included were also predominantly small, therefore more likely to have insufficient power to detect rarer outcomes.

Although the review included data from both developed and developing countries, unlike the method used in caesarean section it is not associated with a high cost or training needs. Furthermore its use in developing countries has been demonstrated in the studies included in the review. Moreover, as the type of cell salvage is alike in all of the included studies the potential for performance bias is reduced.

Existing Research

As discussed previously the reduced need for homologous blood transfusion has been demonstrated in a Cochrane review (323) in elective adult cardiac and orthopaedic surgery with the use of intra-operative cell salvage, but there is no Cochrane review on cell salvage in ectopic pregnancy. There has been one literature review published recently (270) that examined the safety, efficacy, indications and contraindications of cell salvage in both obstetrics and gynaecology, including ruptured ectopic pregnancy. This review did not take a systematic approach, the methodology is unclear, and studies included were omitted from this review. Furthermore since publication of this review three more studies have been published on cell salvage in ectopic pregnancy, including one RCT, hence the need for an up to date systematic review.

Practice and policy implications

Cell salvage could be suggested as a safe and effective intervention to increase haemoglobin levels for women with ruptured ectopic pregnancy in the absence of reliable and safe homologous blood transfusion system. In the absence of data from high quality studies, this review suggests that there seems to be minimal adverse effects associated with cell salvage in ectopic pregnancy. The complications that are reported as associated with the process of cell salvage could be addressed by improving the technique of re-infusion. Pulmonary oedema is often caused by rapid re-infusion, thus training and policy guidance on the conduct of cell salvage, in particular the speed of re-infusion, may reduce this complication. This is also likely to improve outcomes associated with infection and bacterial contamination.

It is acknowledged that no firm inferences can be drawn from the conclusions of this review for the reasons stated above, yet this remains the best evidence available on cell salvage in ectopic pregnancy. Further primary research of sound quality is needed to draw firm inferences on the safety and effectiveness of cell salvage in ectopic pregnancy.

10.5 CONCLUSION

It is possible that cell salvage could be suggested as a safe and effective treatment for haemorrhage from ruptured ectopic pregnancy in the absence of alternative life saving treatment such as a safe, reliable homologous blood transfusion service. Due to the low cost and limited training needs and resources associated with the procedure, cell salvage would seem to be suitable for use low resource settings based on the current available literature. No firm inferences can be drawn from the conclusions of this review due to the quality of the data. It is acknowledged that the study design of most of the included studies (case series) is vulnerable to bias and confounding. However despite this, this remains the best evidence available on cell salvage in ectopic pregnancy to date. Further primary research of sound quality is needed to draw firm inferences on the use of cell salvage in ectopic pregnancy in developing countries.

Table 31 Characteristics of Included Studies

Population	Re-infusion criteria	Intervention	Comparison	Setting	Outcome
Randomised Controlled Trial					
Selo-Ojeme 2007					
139 women with ruptured ectopic pregnancy, Jun 00–May 05. excluded if unable to understand trial, sickle cell disease or leaking chronic ectopic pregnancy.27 excluded not met study criteria	Haemoperitoneum >500mls evidence of haemorrhagic shock	56 patients salvage auto-transfusion	56 patients donor blood transfusion	University hospital, Nigeria	preop haemocrit, haemoperitoneum, postop haematocrit, surgery duration, death, fever, wound infection, >1lt transfused, hospital stay >7days, >0.06 haematocrit difference between pre-operative/post operative value
Cohort Study					
Duncan 1974					
53 patients total: 26 having surgery for major injuries, 8 ruptured ectopic pregnancy, 19 miscellaneous conditions, with potential of blood loss > 1000mls May 71-Feb 73 (45 excluded as cell salvage given for major injury or other procedure)	Significant EBL, potential for further EBL.	8 patients receiving autologous transfusion for ruptured ectopic	no comparison (with donor transfusion alone)	University hospital Texas	volume of blood transfused, additional homologous blood, death
Selo-Ojeme 1997					
123 cases of ruptured ectopic Obafemi Awolowo University hospital Jan 92–Dec 95 (5 excluded received both autologous and homologous transfusion)	NR	33 patients received autologous blood transfusion	85 patients received homologous blood transfusion	University hospital Nigeria	Haemoperitoneum, amount of blood transfused, post operative complications, duration of hospital stay
Case Series					
Stabler 1934					
45 cases of tubal gestation, 34 cases of acute rupture		13 patients received autologous transfusion		UK	Duration of hospital stay, pre and post op Hb, death, haemodynamic condition
Logan 1948					
40 collapsed patients with ectopic pregnancy		40 patients with ectopic pregnancy receiving autologous transfusion		South Africa	Death, amount of blood collected, complications, Hb post op, RBC pre op.
Bourrell 1960					

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31 women with ruptured ectopic pregnancy and laparotomy	7 women having intraoperative blood salvage and autotransfusion. 2 required additional postoperative autologous blood transfusion.	Morocco	EBL, additional homologous blood, post operative hospital stay, volume of blood salvaged/re-infused
Klebanoff 1970			
10 patients receiving cell salvage	4 patients with ectopic pregnancy having cell salvage	Texas	Volume re-infused, pre/post op Hb, duration of hospital stay, death
Pathak: 1970			
1055 cases ruptured ectopic 1954-1967	530 patients received autologous transfusion (168 received only autologous blood)	West Indies	Amount of blood transfused, Hb level (no breakdown between groups), death, major transfusion reactions,
Maleki 1975			
22 patients with ruptured ectopic pregnancy receiving autotransfusion	results of 4 patients with ruptured ectopic reported outcomes	Iran	EBL, amount of blood transfused, Pre op Hb, Post op Hb, additional homologous blood
Merrill 1980			
160 patients with ectopic pregnancy	38 patients with ectopic pregnancy received autotransfusion	Texas	Death, major complication, amount of blood re-infused, additional homologous blood
Laskey 1991			
69 patients with ectopic pregnancy 1988-1989	58 patients with ruptured ectopic pregnancy received autotransfusion	Liberia	Death, major and minor complication
Yamada 1996			
13 patients with ectopic pregnancy	13 patients with ectopic pregnancy having laparoscopy	Japan	EBL, amount of blood re-infused, additional homologous blood,
Jongen 1997			
90 women with ectopic pregnancy seen between 1990 and 1995	48 women who received autologous blood during laparotomy for ectopic pregnancy	Tanzania	Additional use of homologous blood, death, haemoperitoneum
Yamada 2003			
18 patients with suspected large haemoperitoneum from ectopic pregnancy or ovarian bleeding	11 patients with ectopic pregnancy received autologous blood transfusion	Japan	Adverse reactions to transfusion, EBL, amount of blood processed, pre op Hb, post op Hb
Takeda 2006			

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112 women with ectopic pregnancy between 2000-2005 treated by laparoscopic surgery	17 women (15 had ruptured ectopic) who had intraoperative cell salvage and autotransfusion (using the C.A.T.S system and leukocyte reduction filter)	Japan	EBL, amount of re-infused blood, degree of haemoperitoneum, post operative hospital stay, Hb pre and post op, haemodynamic condition
Priuli 2009			
212 patients from 2 hospitals in Benin with ruptured ectopic pregnancy	212 patients received autologous blood transfusion	Benin	Haemodynamic condition, volume of haemoperitoneum, salvaged blood transfused, homologous transfusion, haemoglobin levels pre and post op, post operative course

Table 32 part a: Data of outcomes reported in the included studies (haemoglobin, estimated blood loss,volume of blood salvaged)

Study Year	**Pre operative haemoglobin g/l (SD)**		**Volume of blood salvaged and re-infused (ml) mean and SD or median and range**		**Estimated blood loss median (range)**		**Post operative haemoglobin g/l (SD)**	
Randomised controlled trial								
	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison
Selo-Ojeme 2007	Haemocrit 0.192	Haemocrit 0.204	>1000ml 34 (60%)	>1000ml 11 (19.6%)	1750 (430-3700)	1580 (380-3450)	Haemocrit 0.287	Haemocrit 0.261
Cohort studies								
Duncan 1974	NR	N/A	1306 (584)	N/A	NR	N/A	NR	N/A
Selo-Ojeme 1997	NR	NR	1420	880	1840	1500	NR	NR
Case series (cell salvage only)								
Stabler 1934	4.8 (0.3)		NR		NR		6.1 (0.5)	
Logan 1948	NR		NR		NR		NR	
Bourrel1960	NR		1614ml		2000 (1200-2700)		NR	
Klebanoff 1970	NR		1825 (471)		NR		NR	
Pathak 1970	NR		915 (250-3000)		NR		NR	
Maleki 1975	7 (1.82)		1212 (103)		NR		11.8 (0.28)	
Merrill 1980	NR		1300 (450-8500)		NR		NR	
Laskey 1991	NR		NR		NR		NR	
Yamada 1996	12.2 (1.57)		288 (92)		327 (178)		10.6 (1.28)	
Jongen 1997	NR		NR		NR		NR	
Yamada 2003	11.2 (1.94)		670 (600-2600)		661 (405)		9.4 (1.64)	
Takeda 2006	6.1 (0.9)		1200 (560-2570)		680 (209)		8.4 (1.1)	
Priuli 2009	7.0 (1.8)		1476 (676) 947 (540) 1238 (386)		933 (420) 590 (344) 850 (255)		8.3 (1.8)	

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Table 33 part b: Data of outcomes reported in the included studies (use of homologous blood, post operative stay, infectious morbidity and serious adverse events)

Study Year	**homologous blood product use**		**Post operative hospital stay as stated % or mean number of days (SD)**		**Infectious morbidity**		**Serious adverse effects**	
Randomised controlled trial								
	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison
Selo-Ojeme 2007	NR	NR	>7 days: 8 (14.3%)	>7 days: 6 (10.7%)	20 fever (35.7%) 3 wound infection (5.3%)	21 fever (37.5%) 4 wound infection (7.1%)	None	None
Cohort studies								
Duncan 1974	4 (50%)	N/A	NR	N/A	NR	N/A	None	N/A
Selo-Ojeme 1997	NR	NR	<8 days: 32 (97%) >8 days 1 (3%)	<8 days 81 (95%) >8 days:4(5%)	6 fever (18%) 1wound infection (5%)	18 fever (21%) 2 wound infection (7%)	None	None
Case series (cell salvage only)								
Stabler 1934	NR		8.5 (1.56)		NR		1 death (not transfusion related)	
Logan 1948	NR		NR		NR		2 cases ileus, 1 case jaundice	
Bourrel 1960	NR		9.8 (8-14)		NR		NR	
Klebanoff 1970	NR		7 (0)		NR		1 death (shock)	
Pathak 1970	NR		NR		1 fever		1 hypotension, 6 deaths (not transfusion related)	
Maleki 1975	1 (25%)		NR		NR		None	
Merrill 1980	21 (55%)		NR		NR		2 pulmonary oedema, 2 post operative wound infections (not transfusion linked) 2clinical coagulopathy	
Laskey 1991	NR		NR		NR		1 death, 1 wound infection (not transfusion linked), 1 pulmonary oedema (due to	

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				rapid re-infusion)
Yamada 1996	None	NR	NR	None
Jongen 1997	NR	NR	NR	2 deaths (shock and pulmonary embolism)
Yamada 2003	None	NR	NR	None
Takeda 2006	None	7.4 (6.2)	NR	None
Priuli 2009	22 (10%)	8.6(3) 6.9(7.3) 5.6(0.5)	9 (4.2%)	None

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Table 34 Quality Assessment: reporting checklist of RCT
(Y = Reported: N = Not Reported)

Topic	Consort checklist	
Selo-ojeme 2007		
Title and abstract		
	Identification as RCT in title	N
	Structured summary of trial design, methods, results, conclusions	N
Introduction		
Background objectives	Scientific background, explanation of rationale	Y
	Specific objectives or hypotheses	Y
Methods		
Trial design	Description of trial design, allocation ratio	Y
	Important changes to methods after trial commencement , with reasons	N
Participants	Eligibility criteria for participants	Y
	Settings and locations where data were collected	Y
Interventions	The interventions for each group with sufficient details to allow replication, how, when actually administered	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures, how and when assessed	Y
	Any changes to trial outcomes after commenced, reasons	N
Sample size	How sample size determined	Y
	When applicable, explanation of any interim analyses, stopping guidelines	N/A
Randomisation		
Sequence generation	Method used to generate random allocation sequence	Y
	Type of randomisation; details of restriction	Y
Allocation concealment mechanism	Mechanism to implement random allocation sequence, describing steps taken to conceal sequence until interventions assigned	N
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Y
Blinding	who blinded after assignment to interventions and how	N
	If relevant, description of the similarity of interventions	N/A
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	Y
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N
Results		
Participant flow	For each group, numbers of participants who randomly assigned, received intended treatment, were analysed for primary outcome	Y
	For each group, losses and exclusions after randomisation, with reasons	Y
Recruitment	Dates defining periods of recruitment and follow-up	N
	Why the trial ended or was stopped	N
Baseline data	A table showing baseline demographic and clinical characteristics for each group	Y
Numbers analysed	number of participants included in each analysis and whether the analysis by original assigned groups	Y
Outcomes and estimation	primary and secondary outcome, results for each group, estimated effect size and precision	Y
	binary outcomes, presentation of both absolute and relative effect sizes is recommended	Y
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N
Harms	All important harms or unintended effects in each group	N

Discussion		
Limitations	Trial limitations, addressing sources of potential bias, imprecision, multiplicity of analyses	Y
Generalisability	Generalisability (external validity, applicability) of the trial findings	Y
Interpretation	Interpretation consistent with results, balancing benefits and harms, considering other relevant evidence	Y
Other information		
Registration	Registration number and name of trial registry	N
Protocol	full trial protocol can be accessed, if available	N
Funding	Sources of funding and other support (such as supply of drugs), role of funders	N

Table 35 Quality Assessment: reporting checklist of cohort studies (Y = Reported: N = Not Reported)

STROBE Checklist	**Duncan 1974**	**Selo-Ojeme 1997**
Title and abstract		
Design	N	N
Summary	Y	Y
Introduction		
Background	Y	Y
Objectives	N	N
Methods		
Study design	N	Y
Setting	Y	Y
Participants	Y	N
Variables	N	N
Data sources	N	Y
Bias	N	N
Study size	N	N
Quantitative variables	Y	N
Statistical methods	N	N
Results		
Participants	Y	Y
Descriptive data	N	N
Outcome data	Y	Y
Main results	Y	Y
Other analysis	N	N
Discussion		
Key results	Y	Y
Limitation	N	N
Interpretation	Y	Y
Generalisability	Y	N
Other information		
Funding	N	N

Minors checklist													
Aim	Stabler 1934	Logan 1948	Bourrell 1960	Klebanof 1970	Pathak 1970	Maleki 1975	Merrill 1980	Laskey 1991	Yamada 1996	Jongen 1997	Yamada 2003	Takeda 2006	Priuli 2009
Aim	1	1	1	2	2	2	1	1	2	2	2	2	1
Inclusion of patients	0	0	0	0	1	1	1	1	1	1	1	1	1
Prospective data collection	0	0	0	0	0	2	1	0	1	0	1	0	2
Appropriate end points	0	0	0	0	1	2	1	0	1	1	1	0	1
Unbiased end point	0	0	0	0	0	1	1	0	1	1	1	1	1
Appropriate follow up	0	0	0	1	1	1	1	1	1	1	1	1	1
Loss of follow up <5%	0	1	0	2	1	0	2	0	2	1	2	2	2
Prospective study size calculation	0	0	0	0	0	0	0	0	0	0	0	0	0
Adequate control group	-	-	-	-	-	-	-	-	-	-	-	-	-
Contemporary groups	-	-	-	-	-	-	-	-	-	-	-	-	-
Baseline equivalence	-	-	-	-	-	-	-	-	-	-	-	-	-
Statistical analysis	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 36 Quality Assessment: reporting checklist of case series (Y = Reported: N = Not Reported)

Table 37 Risk of Bias (Y = Reported: N = Not Reported)

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
Selo-Ojeme: 2007							
LOW: Page 109: Computer generated random sequence	LOW: Page 109:Sealed serially numbered envelopes	UNCLEAR: No details provided	UNCLEAR: No details provided	LOW: Page 109: All patients outcomes reported, no loss to follow up	LOW: Page 109 table 2: All outcomes reported on	LOW: No other bias	
Selection				Comparability		Outcome	
Representativeness	Selection of comparison	Ascertainment of exposure	Demonstration of outcomes	Comparability (2 points available)	Outcome assessment	Follow up length	Adequacy of follow up
Duncan 1973							
Y	N	N	Y	N	N	Y	N
Selo-Ojeme 1997							
Y	Y	Y	Y	Y	Y	Y	Y

CHAPTER 11: SYMPHYSIOTOMY FOR OBSTRUCTED LABOUR IN DEVELOPING COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Obstructed labour is a major cause of maternal mortality. Caesarean section is advocated to reduce mortality and morbidity associated with obstructed labour, but caesarean section in developing countries can be associated with many risks and it is not always readily available. In sub-Saharan Africa only 0.5% of all women requiring a caesarean section receive the operation that they need. Symphysiotomy can be an alternative treatment for obstructed labour; it requires fewer resources and does not require specialist surgical skills. Although some research has suggested it compares favourably to caesarean section in developing countries, there is much scepticism around this procedure. The outcomes of symphysiotomy for obstructed labour compared to caesarean section in low to middle income countries have therefore been systematically reviewed and meta-analysed

Methods: Systematic review with meta-analysis. MEDLINE, EMBASE, Cochrane library, CINAHL, African Index Medicus, the Reproductive Health Library, and the Science Citation Index (inception- January 2013) were searched without language restriction. Cohort studies comparing symphysiotomy and caesarean section (as the controls) were selected, with the outcomes of maternal mortality and morbidity and perinatal and neonatal mortality. Relative risks (RR) from the individual studies were pooled using random effects model.

Results: No RCTs and Six cohort studies (1015 women) comparing symphysiotomy and caesarean section for obstructed labour in developing countries were included.

There was no significant difference in maternal mortality with symphysiotomy when compared to caesarean section (RR 0.48 95%CI 0.13, 1.76; p=0.76), and no significant difference in perinatal mortality when compared to caesarean section (RR 1.13 95%CI 0.52,2.43 p=0.76) , even though the number of events were very low. Incontinence and fistulae were both more likely with symphysiotomy than caesarean section (RR 11.76 95%CI 3.43, 40.27; p=<0.001 and RR 7.15 95%CI 1.25, 41.17; p=0.003), however haemorrhage and infection were less likely with symphysiotomy when compared to caesarean section (RR 0.36 95%CI 0.20,0.60; p=0.001 and RR 0.25 95%CI 0.07, 0.92; p=0.04). Scar pain was the only long term outcome where there was a difference between the two groups (p=<0.001), and was more prevalent with caesarean section. **Conclusion:** It could be suggested that symphysiotomy could be a safe alternative to caesarean section in areas where resources are limited or greater risks are involved. Haemorrhage and infection are two leading causes of maternal mortality, both of which are reduced with symphysiotomy, however limited data with very few events reported on this analysis.

11.1 BACKGROUND

Several interventions have been implemented with the aim of reducing maternal mortality, however limited healthcare resources and availability of skilled personnel severely hinder improvements in this. The WHO states that women should have access to comprehensive obstetric care facilities where treatments such as blood transfusion and caesarean section can be performed. The recommended caesarean section rate suggested by WHO is between 5%-15%, yet this data originates from 1985 (324), and is not targeted at developing countries specifically. Therefore the ideal major obstetric intervention rate (e.g. caesarean section) necessary to avoid maternal mortality and severe morbidity today in developing countries is unknown (325).

Caesarean section is suggested to be the most common major operation performed to save a mother's life, yet in Sub-Saharan Africa very few women receive the caesarean section they need (326): this is suggested to be low as 0.5% in some countries, of the total women requiring caesarean section (327). Comparatively, it is suggested by some that the caesarean section rate is too high in some hospitals, and in need of reduction, especially as the safety of the procedure in developing countries is not comparable to that of developed countries. Caesarean section can be associated with severe morbidity and mortality, despite being performed under the safest conditions (328). In addition to this the consequences of a scarred uterus from caesarean section on subsequent pregnancies can be catastrophic, particularly if appropriate obstetric care is not sought or available

Symphysiotomy can be performed as an alternative to reduce the morbidity and mortality associated with obstructed labour, but unlike caesarean section it does not require special surgical skills and can be carried out by a midwife trained in this technique (329). Symphysiotomy is the artificial separation of the symphysis pubis with a surgical instrument, usually a scalpel to enlarge the pelvic diameter, to facilitate the birthing process in cases of obstructed labour (Figure 39). This is normally performed under local anaesthetic by a midwife, doctor or clinical officer, and requires minimal equipment (scalpel, urinary catheter, gloves and local anaesthetic). Symphysiotomy can widen the symphysis by up to 2.5cm (330). Aftercare usually consists of elastic strapping across the front of the pelvis for stability and pain reduction, and knees are usually strapped with bandages in a figure of eight. Bed rest is advised for three to five days, with increasing mobility advocated after five days, bladder catheterisation is also advised for five days (330, 331)

In high income countries caesarean section is used to reduce morbidity and mortality from obstructed labour (332), yet in low income countries where obstructed labour is

more prevalent due to early age pregnancy, malnutrition, skeletal stunting and pelvic immaturity, caesarean section may not be available, or it may carry added risks. Caesarean section may also not be a culturally viable option in some regions, as vaginal delivery is deemed the sanctification of womanhood, even if it is made possible by symphysiotomy (333).

Symphysiotomy is not without risk, yet the benefits and risks of each operative procedure should be outweighed for the patient and the particular setting. Previous research has suggested that symphysiotomy compares favourably with caesarean section in terms of risk for the mother's life (334), yet there remains much scepticism around this practice (335). Further research has been conducted since the latest review (336) (330), there is now more comparative data from cohort studies available, hence the need for an updated systematic review to assess the evidence on this practice.

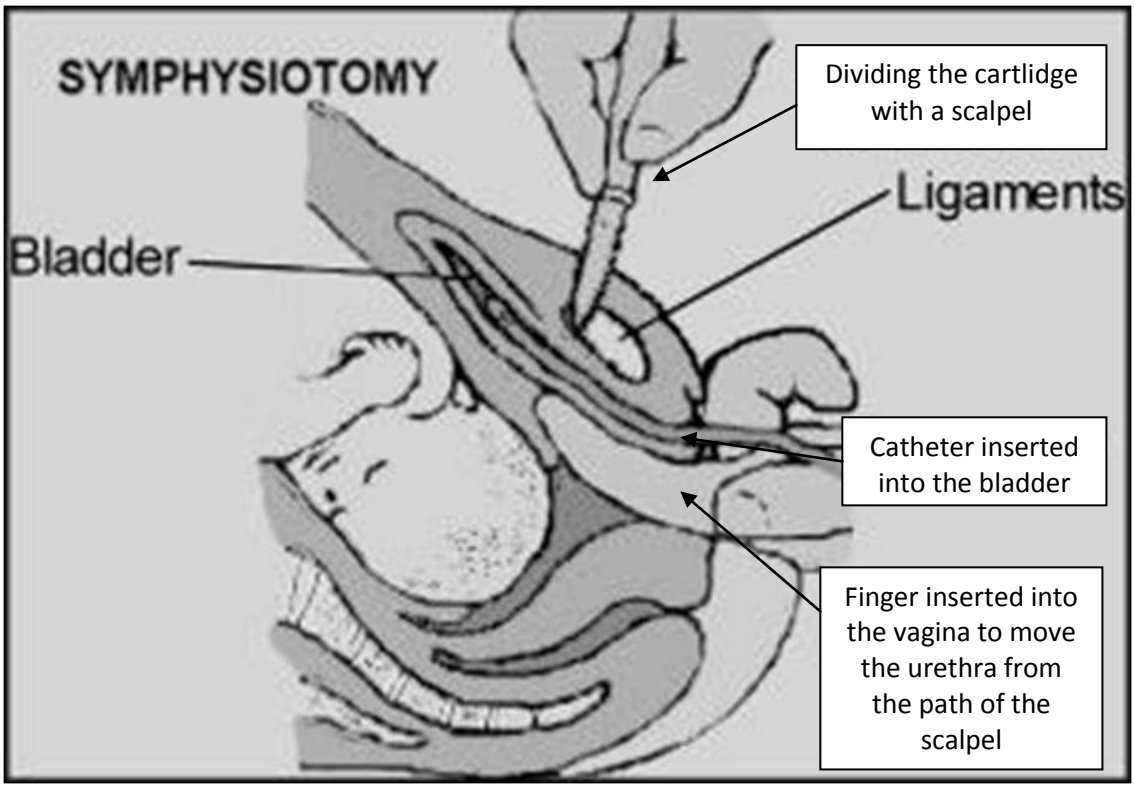

Figure 49 Symphysiotomy: The artificial separation of the symphysis pubis with a scalpel to enlarge the pelvic diameter to facilitate the process of birth.

11.2 METHODS

Data sources and searches

Databases were searched for studies comparing symphysiotomy and caesarean section (as controls) for obstructed labour in developing countries. Following the hierarchy of evidence, the best available evidence was included in the review. PUBMED, EMBASE, Cochrane library, CINAHL, African Index Medicus, the Reproductive Health Library, and the Science Citation Index were searched (from database inception to January 2013). Hand searching complemented electronic searches, and reference lists were checked. The search terms were ‘symphysiotomy’. No language restrictions were applied to the search.

Study selection and data extraction

In the absence of RCTs, cohort studies comparing symphysiotomy and caesarean section (as the controls) for obstructed labour in developing countries were selected following the hierarchy of evidence. Lower levels of evidence were not included in this review, the author and another reviewer aimed to reduce methodological heterogeneity by including the available cohort studies. Initially the electronic searches were scrutinised and full manuscripts of relevant studies were acquired. Final decisions on inclusion or exclusion of manuscripts were made after inspection of these manuscripts by the author and another reviewer (AW and ET). Information was extracted from each article on study characteristics, study quality and outcome data by the author and another reviewer (AW, ET). The outcomes of interest were maternal and perinatal mortality, fistulae, infection, haemorrhage, pyrexia and incontinence in symphysiotomy and caesarean section.

Methodological quality assessment

The cohort studies were assessed for adequacy of reporting using the STROBE checklist (69). Risk of bias in the studies was assessed using the Newcastle Ottawa Scale (71). The studies were evaluated for representativeness of the cohorts of symphysiotomy and caesarean section, selection of the cohorts, ascertainment of the intervention and the outcome, comparability of the cohorts, as well as the length and adequacy of follow-up. The risk of bias was deemed low if a study obtained four stars for selection, two stars for comparability and three stars for ascertainment of exposure (71). Medium risk of bias was suggested to exist in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was classed as having high risk of bias.

Statistical Analysis

Data for effect estimates (Risk Ratios) and corresponding 95% confidence interval were extracted. Effect estimates and their 95% CI were then meta-analysed using the generic inverse-variance method using a random effect model to account for the variability in the setting and clinical indication of the caesarean section or symphysiotomy of the women included. Heterogeneity of treatment effects was evaluated using forest plots, chi square tests and its magnitude determined by computing I^2 statistic. Analyses were performed using REVMAN 5.0 statistical software.

11.3 RESULTS

Six cohort studies set in developing countries were included in the review, 2 prospective comparative cohort studies with consecutive participant inclusion (330, 331), and 4 retrospective cohort studies (336-339). The process of literature search and selection is given in Figure 40. A total of 1015 women were included in our review, 365 cases (woman who had symphysiotomies) and 650 controls (women who had caesarean section). All studies compared the outcomes of symphysiotomy and caesarean section. Study characteristics are shown in Table 32, and the data of the outcomes reported in the studies is provided in Table 33.

Study characteristics

All six cohort studies included in the review compared symphysiotomy and caesarean section for obstructed labour, and were set in developing countries; Nigeria, Papua New Guinea (2 studies), Tanzania, India and Zimbabwe. The earliest study included by Hartfield et al was conducted between 1961 and 1969 and set in Nigeria (331), however the most recent study by Basak et al was conducted between 2005 and 2006 and set in India (330). Both of these studies by Hartfield et al and Basak et al were conducted prospectively and included all women that presented at the labour ward during the study period, during any time of the day. Three studies did not provide any details on the manner in which participants were selected (337-339). All studies

reported similar selection criteria for patients, for example women presenting on labour ward with features of obstructed labour due to cephalopelvic disproportion. Similar patient characteristics were reported in the group that received symphysiotomy and caesarean section in the study by Hartfield et al (331). In the study by Mola et al no significant difference in parity or length of first or second stage of labour between the two groups was reported (339), however in the other study by Mola et al significantly more primigravid participants were reported in the symphysiotomy group (338). The study by van Roosmalen et al reported a lower maternal height in the symphysiotomy group when compared to the caesarean section group (337). Only one study (by Mola et al) reported the inclusion of women with breech presenting fetuses (338), whereas the studies by Basak et al, van Roosmalen et al and Mola et al included vertex presentation only (330, 337, 339). The presentation of the fetus was not reported in the studies by Hartfield et al and Ersdal et al (331, 336). In the studies by Basak et al and Ersdal et al, women with musco-skeletal disorders were excluded (330, 336). Basak et al and Mola et al also excluded women with severe obesity or a macrosomic fetus (>4kg)(330) (338). Mola et al and van Roosmalen et al excluded pregnant women with a dead fetus (337, 338). All studies reported on maternal mortality and neonatal or perinatal mortality, fistula, incontinence, haemorrhage and infection were other commonly reported outcomes.

Study quality

The studies achieved scores of between 8 to 16 out of 22 on the strobe checklist, details were lacking on study design, study size, bias, data sources, variables, statistical methods, participants, descriptive data, study limitations and funding (Table 35). The studies were deemed to have low risk of bias for selection, medium to low risk of bias for comparability, and medium to low risk of bias for outcome on the Newcastle Ottawa Scale (Table 36).

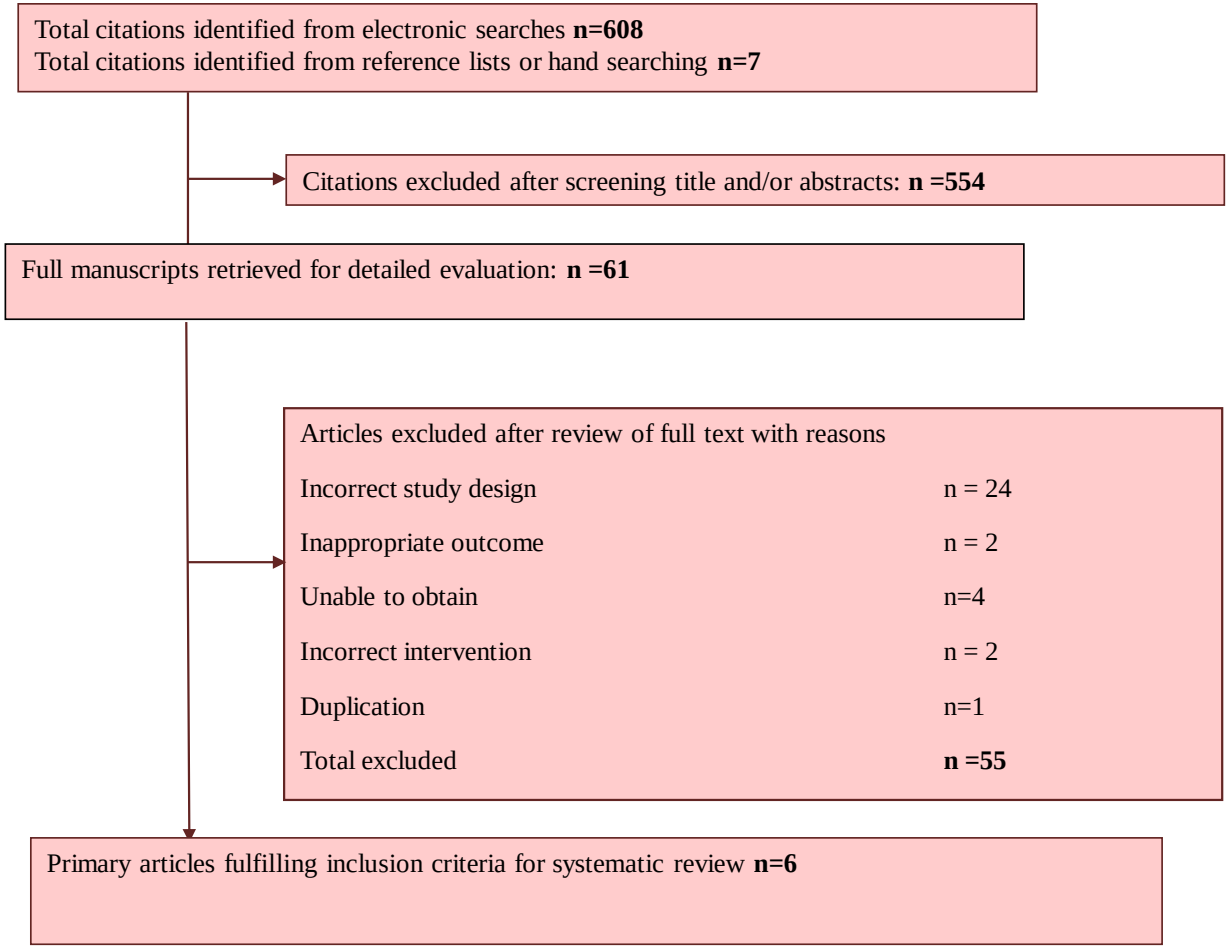

Figure 50 Study selection process in studies included in the review

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Maternal Mortality

Five cohort studies (two prospective and three retrospective) (952 women) reported on maternal mortality (330, 331, 337-339). Meta-analysis demonstrated no significant difference in maternal death with symphysiotomy when compared to caesarean section (RR 0.48 95%CI 0.13, 1.76 p=0.27: Figure 41), however this was only based on 14 events. There was no evidence of heterogeneity in the analysis (I^2= 0% p=0.81).

Perinatal Mortality

Four cohort studies (one prospective and three retrospective) (877 women) reported on perinatal mortality (331, 337-339). Meta-analysis demonstrated no significant difference in perinatal mortality with symphysiotomy when compared to caesarean section (RR 1.13 95%CI 0.52, 2.43 p=0.76: Figure 42), and was based on over 100 events. There was moderate heterogeneity in the analysis (I^2=65% p=0.04).

Fistulae

Two cohort studies (553 women) reported on this outcome (331, 338), meta-analysis demonstrated an increase in fistulae with symphysiotomy when compared to caesarean section (RR 7.15 95%CI 1.25, 41.17 p=0.03: Figure 43, however this was based on 8 events. There was no evidence of heterogeneity in the analysis (I^2=0% p=0.38), although data reporting on this outcome was limited.

Haemorrhage

Two cohort studies (418 women) reported on haemorrhage (330, 331). Meta-analysis demonstrated less cases of haemorrhage with symphysiotomy when compared to

caesarean section (RR 0.36 95%CI 0.20, 0.66;p=0.001: Figure 44). There was no evidence of heterogeneity in this analysis (I^2=0% p=0.57), although data reporting on this outcome was limited.

Infection

Three cohort studies (588 women) reported on infection (330, 338, 339). Meta-analysis demonstrated less infection with symphysiotomy when compared to caesarean section (RR 0.25 95%CI 0.07, 0.92 p=0.04: Figure 45). There was high heterogeneity in the analysis (I^2=74% p=0.02) and data reporting on this outcome was limited. Limited information was provided on the infective complications experienced, the study by Mola et al reported this outcome as wound or genital tract infections without any further description (338), this was also the case for the caesarean section group in the study by Basak et al (330), yet more information was provided on the infectious complications experienced in the symphysiotomy group, where a case of vulval cellulitis is reported. The other study by Mola et al reported wound infections needing drainage or resuturing (339), again no further details were given.

Pyrexia

Two cohort studies (418 women) reported on this outcome (330, 331), meta-analysis demonstrated no significant difference with symphysiotomy when compared to caesarean section (RR 0.75 95%CI 0.43, 1.31 p=0.32: Figure 46. There was moderate heterogeneity in the analysis, although this was not significant (I^2=55% p=0.15), again data reporting on this outcome was limited.

Incontinence

Three cohort studies (723 women) reported on incontinence (331, 338, 339). Meta-analysis demonstrated more cases of incontinence with symphysiotomy when compared to caesarean section (RR 11.76 95%CI 3.43, 40.27 p=<0.0001: Figure 47), although this was only based on 19 events. There was no evidence of heterogeneity in the analysis (I^2=0% p=0.96). No data was provided for baseline prevalence of urinary incontinence in any of the studies, and varying descriptions but no definitions were given in the included studies for this outcome. These included stress incontinence and stress incontinence needing operation treatment.

Long-term follow up

Two cohort studies compared the long-term outcomes of symphysiotomy and caesarean section (Table 34) (331, 336). One study by Hartfield et al reported outcomes between 20 months and 10 years (331), and the other (by Ersdal et al) reported outcomes up to 15 years. The mean reported outcome follow up time was 4 years for symphysiotomy and 2.9 years for caesarean section (336). Long term outcomes for pain when walking (12 events (8/34 vs 4/29), dancing (3 events (1/34 vs. 2/29), jumping (5 events (3/34 vs. 2/29) and carrying (5 events (3/34 vs. 2/29) showed no significant difference between the groups in the study by Ersdal et al (336). Scar pain however was more likely (p<0.001) in the caesarean section group (51.7%) when compared to the symphysiotomy group (2.9%). There were also no differences between the groups for dyspareunia (15 events (10/34 vs 5/29), infertility (2 events (0/34 vs 2/29) or incontinence (6 events) 3/95 vs 3/77). The study by Hartfield et al also reported no significant difference between symphysiotomy and caesarean section for sub-fertility (8 events (4/61 vs 4/48), scanty, irregular or painful menstrual cycle (10

events (3/61 vs 7/48), incontinence, backache, leg pain, abdominal pain or muscle pain (331). Limited data reported on long term outcomes with a sample size of 172 women.

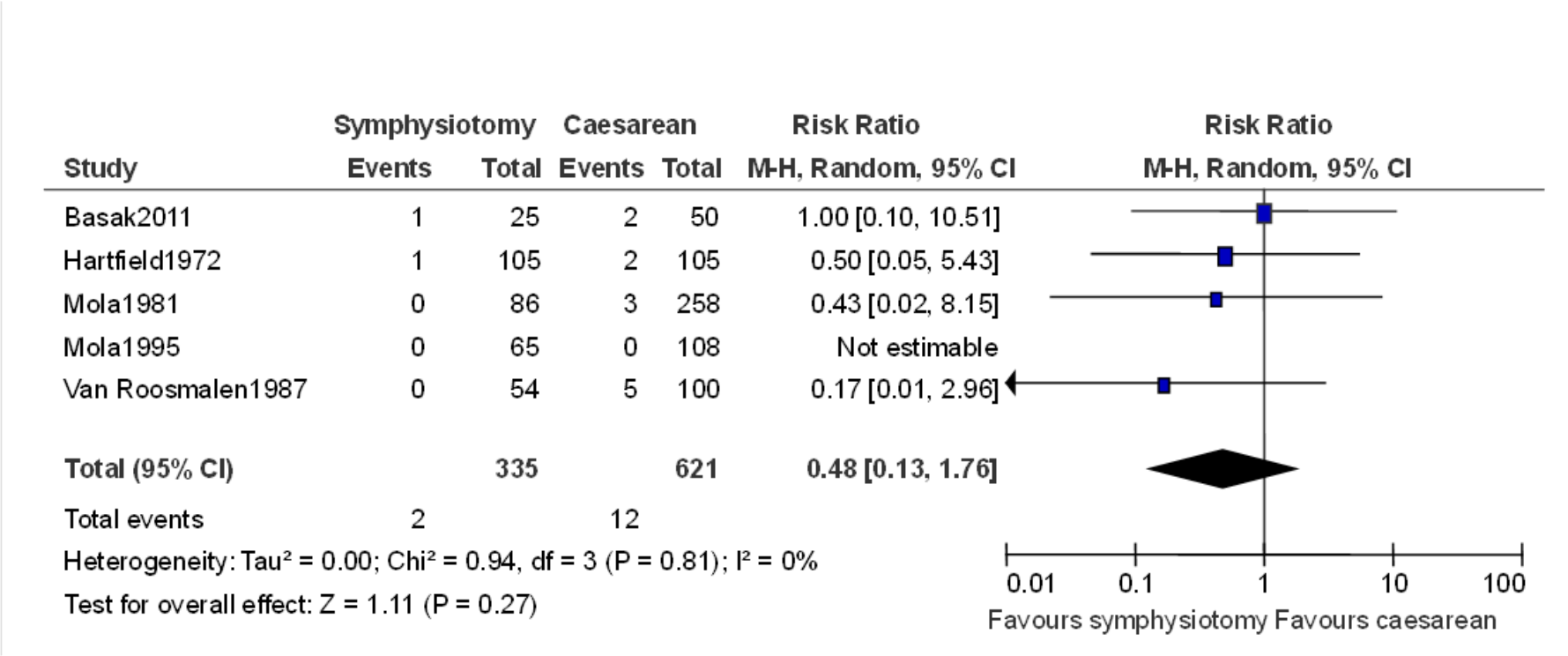

Figure 51 Maternal Mortality in symphysiotomy and caesarean section

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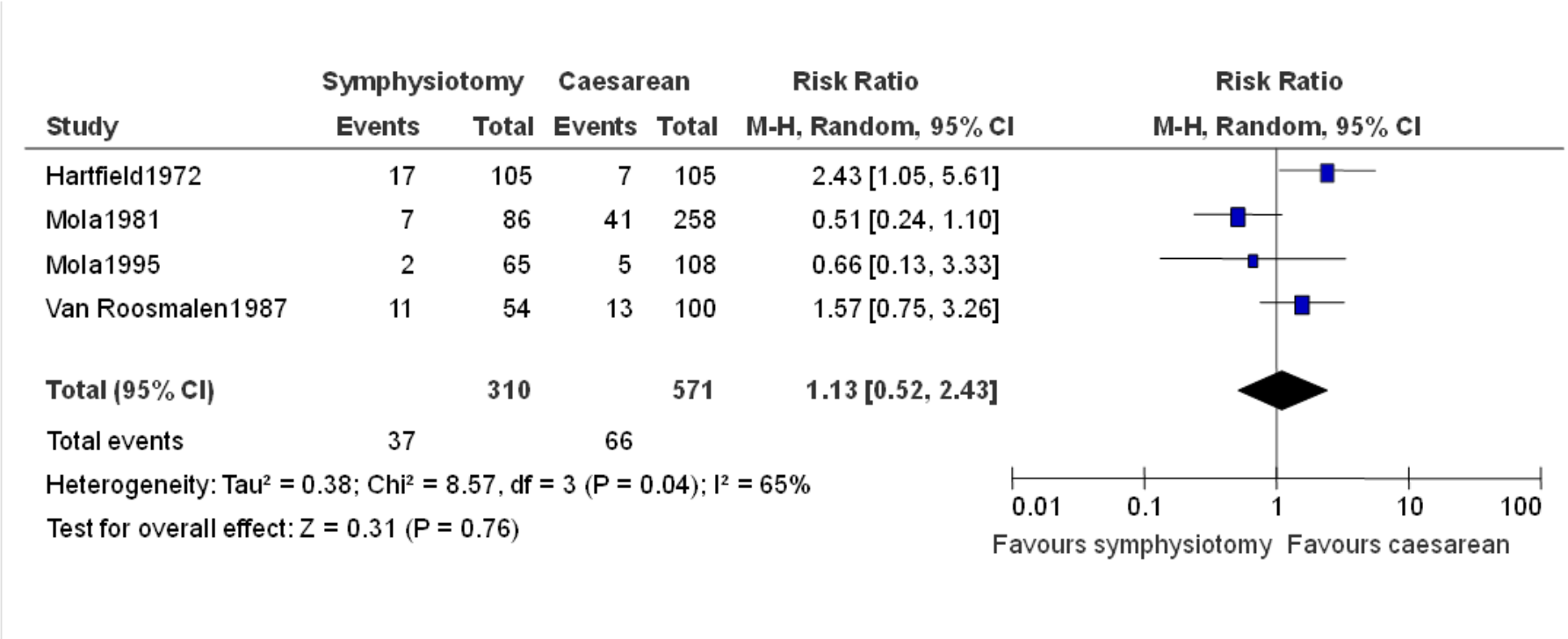

Figure 52 Perinatal Mortality in symphysiotomy and caesarean section

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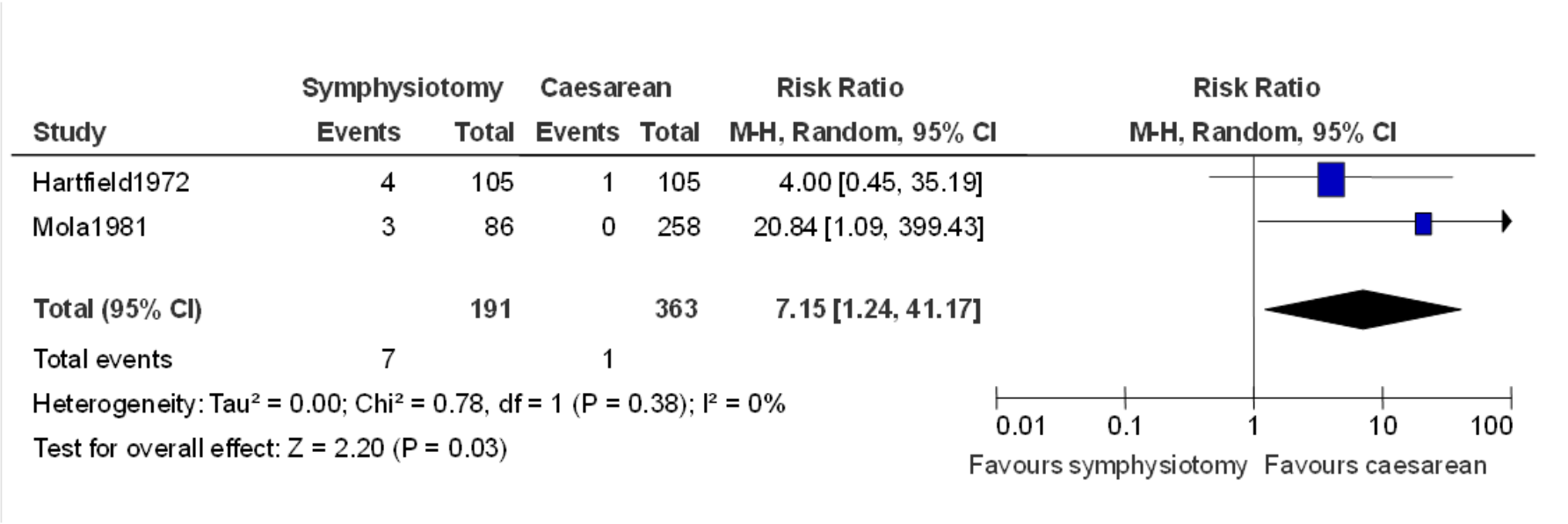

Figure 53 Fistulae in symphysiotomy and caesarean section

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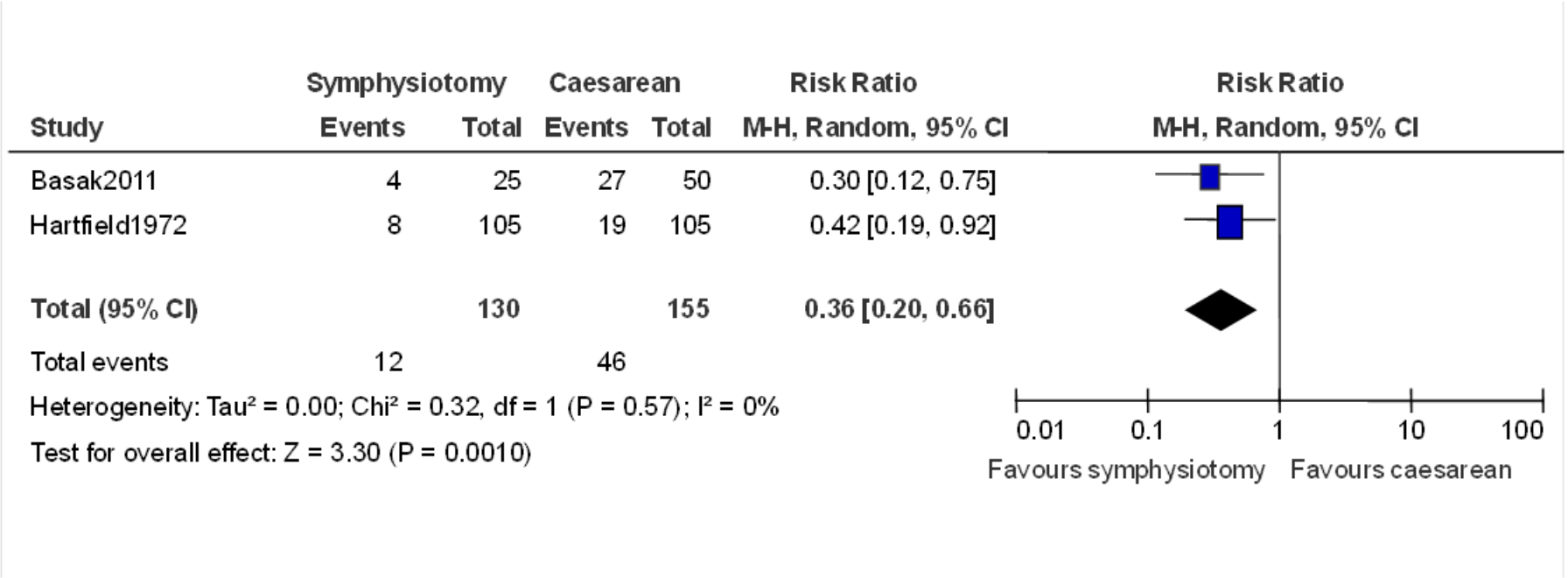

Figure 54 Haemorrhage in symphysiotomy and caesarean section

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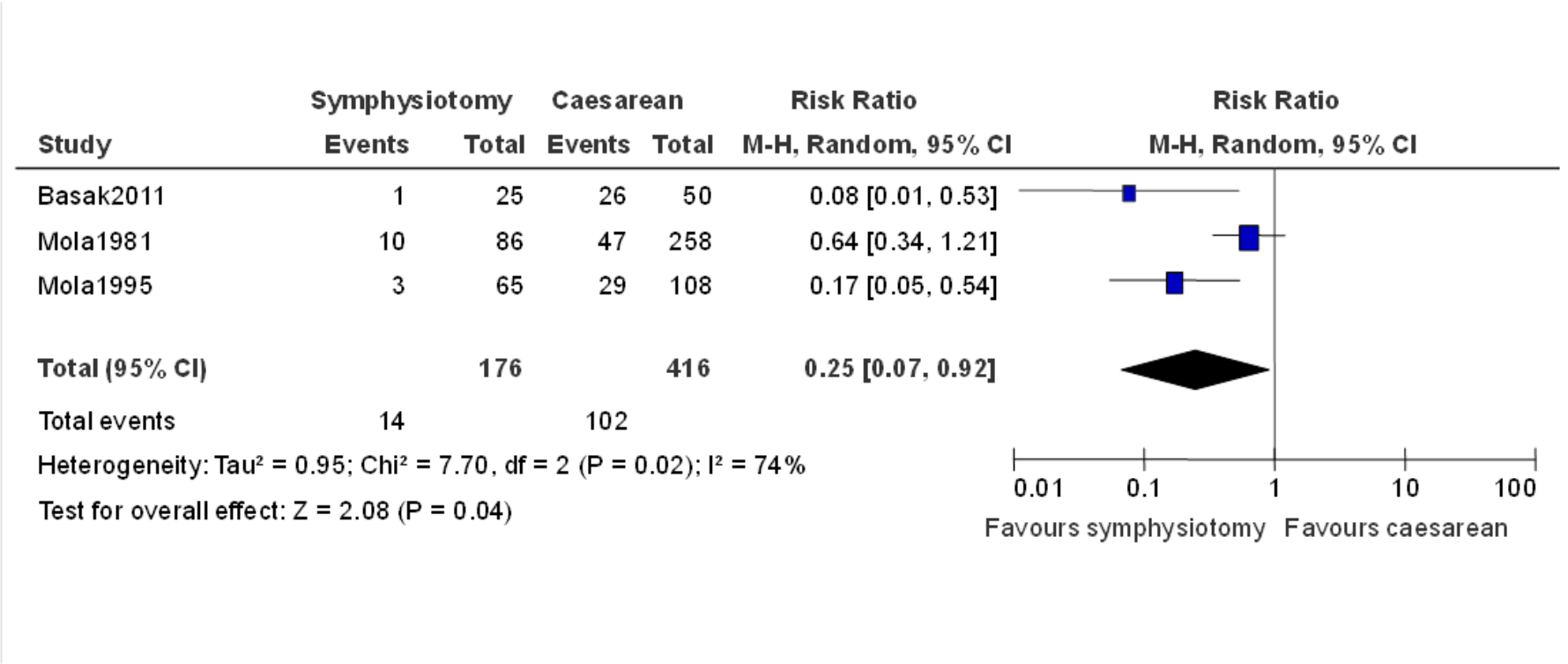

Figure 55 Infection in symphysiotomy and caesarean section

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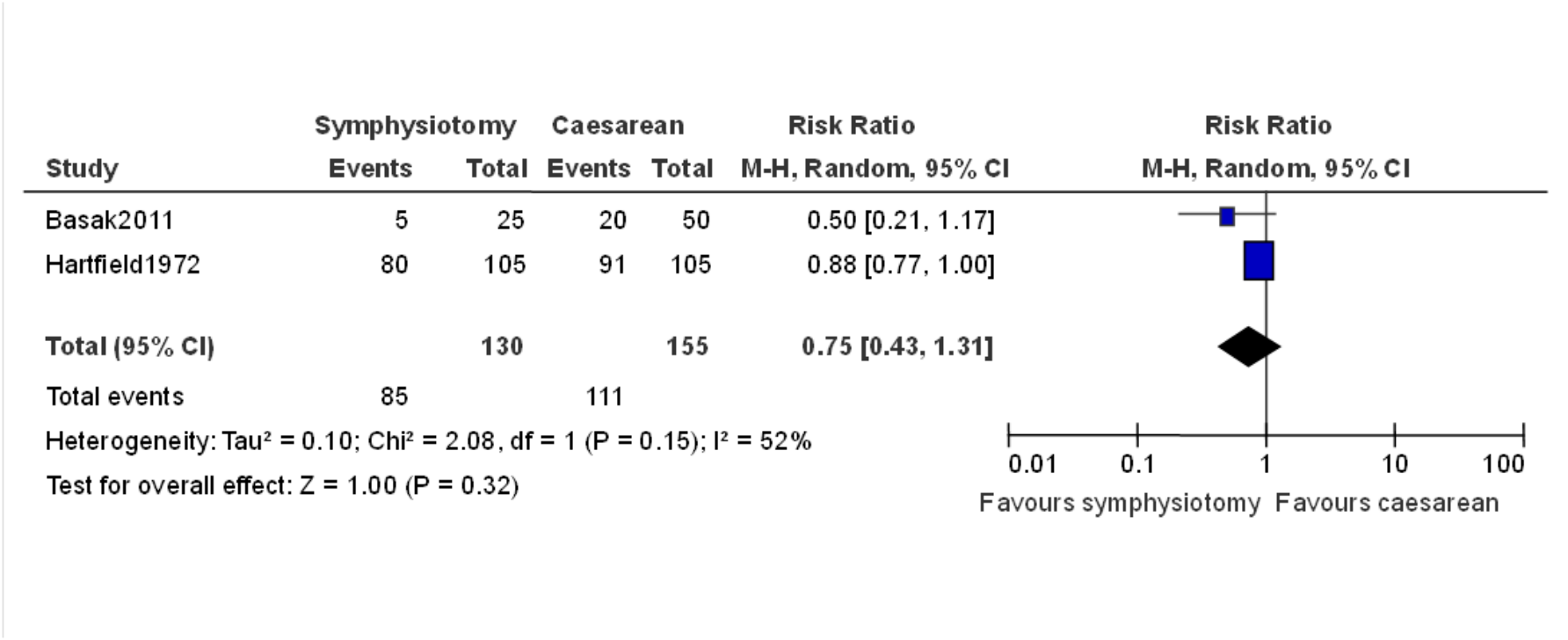

Figure 56 Pyrexia in symphysiotomy and caesarean section

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Study	Symphysiotomy Events	Total	Caesarean Events	Total	Risk Ratio M-H, Random, 95% CI
Hartfield1972	7	105	0	105	15.00 [0.87, 259.32]
Mola1981	8	86	2	258	12.00 [2.60, 55.43]
Mola1995	2	65	0	108	8.26 [0.40, 169.37]
Total (95% CI)		**256**		**471**	**11.76 [3.43, 40.27]**
Total events	17		2		

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 3.92 (P < 0.0001)

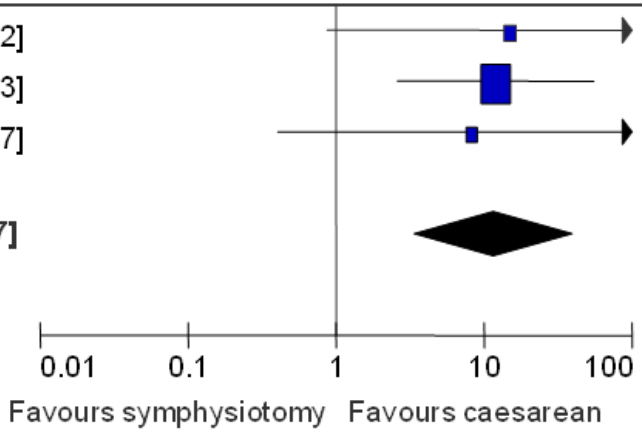

Figure 57 Incontinence in symphysiotomy and caesarean section

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11.4 DISCUSSION

Findings

There was no significant difference for maternal mortality with symphysiotomy when compared to caesarean section, this however was only based on 14 events, with 2 in the symphysiotomy group and 12 in the caesarean section group. There is also no significant difference in perinatal mortality when symphysiotomy is compared with caesarean section (37 vs. 66 events). There are less cases of fistulae and incontinence with caesarean section compared to symphysiotomy (7 vs. 1 and 17 vs. 2), and haemorrhage (12 vs. 46), infection (14 vs. 102) and pyrexia (85 vs. 111) were less frequent with symphysiotomy when compared to caesarean section, although again most of these inferences are based on a small number of events in most of the analyses.

Limitations

The main limitation of this review was the potential selection bias due to the lack of control (i.e. blinding) in the study design. For example women undergoing symphysiotomy may be of lower educational status and from a lower socioeconomic class, thus may prefer this operative procedure due to the lower associated cost and cultural implications with caesarean section. If this group of women were living in poverty their health may also be compromised by malnutrition, anaemia and other conditions (such as malaria, HIV, TB). Moreover symphysiotomy is often reserved for ‘extreme cases’ of obstructed labour, for example when a patient is too ill for the clinician to safely perform a caesarean section, this often occurs in cases where women have experienced significant delays in seeking and receiving treatment. It is possible that these factors could bias outcomes in favour of caesarean section rather than symphysiotomy.

None of the included studies adjusted for confounding factors, such as those given above, or the duration of labour, delay in receiving treatment, or the cadre and experience of operator. The small sample size of the included studies was an additional limitation, thus most inferences were based on limited numbers of events. Although there was no significant difference in maternal mortality with symphysiotomy when compared to caesarean section, most maternal deaths in the symphysiotomy group (331, 337) were due to pre-eclampsia, rather than complications associated with the operative procedure. Whereas deaths from caesarean were due to complications associated with the procedure, such as haemorrhage and infection. The retrospective design of the majority of the cohort studies is also another limitation, as only two were prospective studies.

There was no significant difference in perinatal mortality, although there were slightly fewer perinatal deaths with caesarean section, however this could be biased in favour of caesarean section, as symphysiotomy is normally reserved for extreme cases, often complicated by severe fetal distress. It can also be argued that the skill and experience of clinicians to accurately diagnose the degree of cephalopelvic disproportion, and the correct timing of the treatment (symphysiotomy or caesarean section), could be reflected in the perinatal outcome. As symphysiotomy is a less common procedure, the lack of experience may reflect the slightly higher incidence of perinatal deaths (331). Thus as the experience of the operator increased the results of the operation may have been improved (338). Furthermore, one of the indications for symphysiotomy in some studies were failed trial of vacuum or forceps, this may further add to the higher rates of perinatal mortality (337).

A further limitation could be the disparity in the measurement of the subjective outcomes reported on such as pain. This limitation may also apply to incontinence and

pyrexia as studies reporting this outcome do not give the definition that was used for this outcome therefore it may vary from study to study. There is therefore a possibility that measurement bias maybe present in this analysis. Selection bias may also be present within the studies as none were blinded, although the baseline characteristics reported shown little difference between the two groups, it is likely that experience and opinion of operating clinician may affect participant selection (336), as may parity and maternal age (336, 338) or financial capability to pay for the procedure (330)

Moreover, some outcomes such as incontinence may occur over time with or without symphysiotomy or caesarean section. None of the studies within the review provide information on the prevalence on incontinence within the population studied, nor do they state if this outcome was present prior to the symphysiotomy or caesarean section. As research has suggested that the incidence of incontinence in young women is 12.8%, and increases to 46% for women aged 50-60 years(340), the association with symphysiotomy or caesarean section and incontinence is therefore questionable.

Existing research

A Cochrane review has been published (341), yet in the absence of randomised data, no trials were included within this review thus the authors' concluded that research was needed to provide robust evidence of the effectiveness and safety of symphysiotomy compared caesarean section in clinical situations in which the relative risks and benefits are uncertain. However a systematic review (334) including retrospective case series that were published between 1990-1999, concluded that with training, symphysiotomy poses no greater risks and compares favourably with caesarean section, in terms of risk for the mother's life. Symphysiotomy is also less complex and less expensive than caesarean section. A retrospective review of operative deliveries over ten year period (1986-1995) in Nigeria (342) that included 1719 caesarean sections and 1091 symphysiotomies suggested that the practice of symphysiotomy

reduced the caesarean section rate, and may prevent many cases of maternal mortality and morbidity from operative deliveries in subsequent pregnancies. The maternal and perinatal outcomes of symphysiotomy however were not reported, they also did not compare them to caesarean section, therefore this study was not included within the review.

Policy and practice implication

Obstructed labour remains a leading cause of maternal mortality, and although caesarean section is advocated to reduce morbidity and mortality from obstructed labour (332), there are many associated risks with caesarean section in developing countries, not only for the current pregnancy but for the woman's future reproductive health. Caesarean section scares the uterus and puts it at risk of rupture in future pregnancies. In areas where resources are limited and lengthy transfers between health centres are common, greater risks are associated with caesarean section, thus reinforcing preference for symphysiotomy.

In countries where mortality from caesarean section is low, such as developed countries with current standards of obstetric care, symphysiotomy is obsolete as it is deemed an 'old operation' that was practiced before caesarean section became 'respectable' (343). Even at the peak of the procedures popularity, it is suggested that symphysiotomy was not widely used in Britain and North America (344). There are known associated short and long term complications with both symphysiotomy and caesarean section such as urinary incontinence and pyrexia (345), and our analysis albeit from limited data suggests that incontinence might be greater with caesarean section. However the complications that are responsible for a large proportion of maternal deaths (haemorrhage and infection) are suggested to be lower with symphysiotomy when compared to caesarean section in our meta-analysis.

Although neither procedure is without risk it is suggested that there is an important barrier for symphysiotomy in the mind of the obstetrician (346), and is generally influenced by their perceptions and experience with the procedure. It is however essential to weigh up the risks and benefits of each procedure, in line with the setting, the population and the resources available, and the patients reproductive history and future. The method of delivery chosen should incur the least likelihood of present or future maternal or fetal compromise.

Unanswered questions and future research

Further primary research of sound quality is needed to draw firm inferences on the safety of symphysiotomy for obstructed labour. The outcomes should be compared to the outcomes of caesarean section in developing countries. The appropriateness and ethical grounds of using an RCT to answer this question is debatable. This is because caesarean section is one of the most common surgical procedures performed worldwide and has good data on the benefits and risks associated with the procedure (347). Caesarean section is generally associated with a low complication rate (348); yet like many surgical procedures, this rate can fluctuate with the skill of the operator, the reason for the procedure, the clinical environment and any existing co-morbidities or complications (347), thus the complication rate may differ significantly between developed and developing countries. A comparable body of evidence however, is not available for the risks and benefits associated with symphysiotomy (341), and it is a much less common procedure. Unlike caesarean section given that there is limited data available on the safety and complications associated with this procedure, it would not be possible to fully inform participants of the risks associated with both interventions (i.e. caesarean section and symphysiotomy), in the setting of a RCT. Furthermore, in a facility setting where both options were feasible in terms of equipment and staff training it is likely to be difficult to persuade the operator that both are equally safe. In the community setting, from a practical and organisational point of

view an RCT would be difficult. Therefore an RCT would not be ethical or practical instead a well conducted, well reported large cohort study could be a more ethically sound approach.

11.5 CONCLUSION

Obstructed labour remains a leading cause of maternal mortality. In areas where caesarean section is unavailable or in areas where resources are limited, greater risks can be associated with caesarean section, or when transferring a woman from one facility to another for a caesarean section. Although the inferences made are on the limited data available from both prospective and retrospective cohort studies, at risk of selection and measurement bias, our analysis suggests that symphysiotomy could be a favourable and appropriate alternative. Haemorrhage and infection are common causes of maternal mortality, and from our analysis of limited data (58 and 116 events respectively) these appear to be lower in the symphysiotomy group compared to caesarean section. Long term complaints of patients who underwent symphysiotomy reported similar complaints to those that underwent caesarean section, although scar pain was significantly less frequently reported with symphysiotomy. In summary, symphysiotomy may be useful in certain situation where caesarean section is too risky or unavailable. However no real conclusions can be made from the data available in this review.

Table 38 Characteristics of studies included in the review, comparing the outcomes of symphysiotomy and caesarean section

Study	Study population and selection	Symphysiotomy	Caesarean Section	Outcome
Hartfield 1973	Nigeria, 1961-1969. Aged 16 to 45. Moderate - severe CPD, half patients laboured >24 hours. Consecutive patients having symphysiotomy and C/S matched, No other details provided on selection	(n=105) Symphysiotomy immediately prior to delivery combined with episiotomy. 80% performed by lead obstetrician. Performed under local anaesthetic. After care: Bed rest for 8 -10 days, encouraged to lie on side, reduced 3-5 days later in study.	(n=105) C/S. 80% performed by lead obstetrician 8 C/S under local anaesthetic	MMR and PMR, major maternal complications. Symptoms at 6 weeks follow up, complications at long-term follow up (20 months – 10 years). Mean number of days in hospital, temperature >38.0^{o}C, blood transfusion rate.
Mola 1981	Papua New Guinea 1974 -1980, CPD Majority of women primigravid and had supervised labours. Retrospective study consecutive inclusion of women No further details are provided.	(n=85) Symphysiotomy using the Seedat and Crichton method immediately prior to delivery combined with episiotomy. After care: catheter drainage of bladder for 24 hours, up to 10 days if blood stained and antibiotics. Analgesia and bed rest in lateral position, knees loosely bound for 12 hours. Movement encouraged after 12 hours and to ambulate after 48 hours. Discharged when ambulant, avoid undue exercise for 6 weeks.	(n=258) C/S late in labour	MMR, PMR, fistula, UTI, incontinence, haematoma, osteitis pubis, paralytic ileus, wound or genital tract infection, C/S, 3rd degree tear, problems at 6 weeks.
van Roosmalen 1987	Tanzania 1976-1983 CPD Most women low parity, maternal height lower in the symphysiotomy group. No details reported on selection.	(n=54) Symphysiotomy using the Seedat and Crichton method. Live fetus, vertex presentation.	(n=100) C/S	MMR and serious morbidity. PMR
Mola 1995	Papua New Guinea 1988-1994 Failed attempted at assisted delivery of cephalic presentations. Majority of patient's primigravid. Retrospective, all cases of failed assisted delivery included. No further details provided.	(n=62) Symphysiotomy using the Seedat and Crichton technique. No details reported on after care.	(n=108) C/S	MMR, PMR and morbidity, agars <7 at 5 mins, >24 hours admission to special care baby unit, post operative stay >10 days, need for further surgery.

Basak 2011	India May 2005-Sept 2006 Presenting on labour ward, features of obstructed labour (1, obstructed labour due to mild to moderate CPD with fetus alive, vertex presentation, advanced cervical dilatation, well engaged fetal head. 2, obstructed labour after failed instrumental delivery. 3, trapped after coming head in breech delivery, shoulder dystocia). Excluded: musco-skeletal disorders, severe obesity, major CPD, previous C/S, estimated fetal weight >4kg, or dead fetus. Prospective study of all women that presented on labour ward during any time of the day. Retrospective follow up study. Attempts made to time match since index delivery as much as possible. No further details provided.	(n=25) Symphysiotomy 6 required use of forceps and 6 required ventouse. After care: Bed rest preferably on side with iliac strapping in the form of a figure of 8 on the knees for 3 days. Indwelling catheter for minimum of 5 days. Mobilisation to begin on 5th day or when catheter is removed. Discharged at 7 days, advised to avoid weight bearing activities for 3 months	(n=50) C/S	MMR and morbidity (PPH, sepsis, genitourinary trauma, pelvic pain, gait problems). NMR and morbidity due to birth asphyxia, intracranial haemorrhage, cephalohematoma and hypoxic ischemic encephalopathy.
Ersdal 2008	Zimbabwe 1990-1994. Previous normal vaginal deliveries, parity 1-8, previous exclusive vaginal delivery, aged 15-45,no orthopaedic disorders	(n=34) Symphysiotomies earlier than these dates also included, procedures performed by experience doctors.	(n=29) C/S. Often had failed vacuum delivery.	NMR, maternal morbidity (serious soft tissue injuries in birth canal, haemorrhage, sepsis). Pain on walking/ dancing/ jumping/carrying. Pain in scar, dyspareunia, infertility, incontinence.

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*Table 39 Data of outcomes reported (maternal mortality, pain, fistulae, laceration, haemorrhage, infection, pyrexia, incontinence, neonatal mortality, perinatal mortality, length of hospital stay, poor wound healing), comparing symphysiotomy and caesarean section (*pelvic pain)*

Study Year	Hartfield 1973		Mola 1981		Van Roomalen 1987		Mola 1995		Basak 2011	
	sym	cs	sym	cs	sym	cs	sym	cs	sym	cs
Maternal Mortality N(%)	1/105 (1)	2/105 (2.1)	0/86 (0)	3/258 (1)	0/54 (0)	5/100 (5)	0/65 (0)	0/108 (0)	1/25(4)	2/50(4)
Pain N(%)	NR	NR	NR	NR	NR	NR	NR	NR	8/25* (32)	0/50* (0)
Fistulae N(%)	4/105 (4.2)	1/105 (1)	3/86 (3.5)	0/258 (0)	NR	NR	NR	NR	NR	NR
Laceration N(%)	4/105 (4.2)	0/105 (0)	NR	NR	NR	NR	NR	NR	NR	NR
Haemorrhage N(%)	8/105 (8.4)	19/105 (19.9)	NR	NR	NR	NR	NR	NR	4/25 (16)	27/50 (54)
Infection N(%)	NR	NR	10/86 (11.8)	47/258 (18.2)	NR	NR	3/65 (4.6)	29/108 (26.8)	1/25 (4)	26/50 (52)
Pyrexia N(%)	80/105 (84)	91/105 (95.5)	NR	NR	NR	NR	NR	NR	5/25 (20)	20/50 (40)
Incontinence N(%)	7/105 (7.3)	0/105 (0)	8/86 (9.4)	2/258 (0.8)	NR	NR	2/65 (3)	0/108 (0)	NR	NR
Neonatal Mortality N(%)	NR	NR	NR	NR	NR	NR	NR	NR	7/25 (28)	12/50 (24)
Perinatal Mortality N(%)	17/105 (17.8)	7/105 (7.3)	7/86 (8)	41/258 (16)	11/54 (5.9)	13/100 (13)	2/65 (3)	5/108 (4.6)	NR	NR
Days in hospital Mean no days	11.2	11.4	13.3 (9.8)	12.9 (8.2)	NR	NR	NR	NR	NR	NR
Delayed/poor wound healing N(%)	17/105 (17.8)	39/105 (40.9)	NR	NR	NR	NR	NR	NR	NR	NR

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Table 40 Long term follow up outcome data comparing the outcomes of symphysiotomy and caesarean section

Outcome	Ersdal 2008				Hartfield 1973		
	sym	cs	significance (p value)		sym	cs	significance (p value)
Pain on walking n (%)	8/34 (23.5)	4/29 (13.8)	0.33	Dysmenorrhoea n(%)	3/61 (4.9)	3/48 (6.3)	0.76
				Scanty periods n(%)	0/61 (0)	1/48 (2.1)	0.41
Pain on dancing n (%)	1/34 (2.9)	2/29 (6.9)	0.52	Irregular menstrual cycle n(%)	0/61 (0)	3/48 (6.3)	0.15
Pain on Jumping n (%)	3/34 (8.8)	2/29 (6.9)	0.78	Sub-fertility n(%)	4/61 (6.6)	4/48 (8.3)	0.72
Pain on carrying n (%)	3/24 (8.8)	2/29 (6.9)	0.84	Stress incontinence n(%)	2/61 (3.3)	1/48 (2.1)	0.71
Painful scar n (%)	1/34 (2.9)	15/29 (51.7)	<0.01	Utero-vaginal prolapse	1/61 (1.6)	0/48 (0)	0.86
				Frequent backache n(%)	0/61 (0)	2/48 (4.2)	0.23
Dyspareunia n (%)	10/34 (29.4)	5/29 (17.2)	0.41	Occasional backache n(%)	6/61 (9.8)	7/48 (14.6)	0.45
				Frequent leg pain n(%)	2/61 (3.3)	0/48 (0)	0.37
Infertility n (%)	0/34 (0)	2/29 (6.9)	0.12	Occasional leg pain n(%)	7/61 (11.5)	5/48 (10.4)	0.86
				Unexplained abdominal pain n(%)	0/61 (0)	1/48 (2.1)	0.41
Incontinence n (%)	1/34 (2.9)	2/29 (6.9)	0.47	Headache n(%)	0/61 (0)	1/48 (2.1)	0.41
				General muscle pain n(%)	0/61 (0)	1/48 (2.1)	0.41

Table 41 Strobe reporting checklist for cohort studies (Y=reported, N=not reported)

Cohort Studies	**STROBE**	Hartfield 1972	Mola 1981	Van Roosmalen 1987	Mola 1995	Basak 2011	Ersdal 2008
Title and Abstract	design	N	N	N	N	Y	N
	summary	Y	Y	N	Y	Y	Y
Introduction	background	Y	Y	N	Y	Y	Y
	objectives	Y	Y	N	Y	N	Y
Methods	study design	Y	N	N	N	Y	Y
	setting	Y	Y	Y	Y	Y	Y
	participants	Y	N	N	Y	Y	Y
	variables	N	N	N	Y	Y	Y
	data sources	N	N	N	Y	N	Y
	Bias	N	N	N	Y	N	Y
	study size	N	N	N	N	N	N
	quant. variables	Y	N	N	Y	N	N
	stat. methods	N	N	N	Y	N	N
Results	participants	N	Y	Y	N	N	Y
	descriptive data	N	Y	N	N	N	Y
	outcome data	Y	Y	Y	N	Y	Y
	main results	N	Y	N	N	Y	Y
	other analysis	N	Y	N	Y	N	N
Discussion	key results	N	Y	Y	N	Y	Y
	limitation	N	N	N	N	N	N
	interpretation	N	Y	N	Y	N	Y
	generaliability	Y	Y	Y	Y	Y	Y
Other	funding	N	N	N	N	N	Y

Table 42 Risk of Bias for cohort studies (Y=reported, N=not reported)

Cohort Studies		Hartfield 1972	Mola 1981	Van Roosmalen 1987	Mola 1995	Basak 2011	Ersdal 2008
Selection	Representativeness	Y	Y	Y	Y	Y	Y
	Selection on comparison	Y	Y	Y	Y	Y	Y
	Ascertainment of exposure	Y	Y	Y	Y	Y	Y
	Demonstration of outcomes	Y	Y	Y	Y	Y	N
Comparability	Comparability (2 points available)	Y	YY	Y	Y	Y	Y
Outcome	Outcome assessment	N	Y	N	Y	Y	N
	Follow up length	Y	Y	Y	Y	Y	Y
	Adequacy of follow up	N	Y	N	Y	Y	Y

CHAPTER 12: ANTI-SHOCK GARMENT FOR OBSTETRIC HAEMORRHAGE IN DEVELOPING COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: Post-partum haemorrhage is one of the leading causes of maternal mortality. The Anti-shock garment is suggested to be one of the most effective therapeutic procedures to control haemorrhagic shock. It can be used for treatment within a healthcare facility, but also when patients are being transferred to a health facility for treatment. In developing countries many women experience delays in receiving appropriate treatment for haemorrhage. The Anti-shock garment is suggested to improve outcomes when used in conjunction with standard obstetric haemorrhage care. The outcomes of women where the anti-shock garment was used in addition to standard obstetric haemorrhage treatment was systematically reviewed and meta-analysed, and compared to the outcomes of standard obstetric haemorrhage treatment alone.

Methods: Systematic review with meta-analysis. PUBMED, EMBASE, Cochrane library, CINAHL, AMED, African Index Medicus, the Reproductive Health Library, and the Science Citation Index were searched (inception- March 2013) without language restriction. All available studies were included (quasi-experimental studies, case series case and reports) in the absence of randomised data and sufficient data from cohort studies. The outcomes of maternal mortality and morbidity, estimated blood loss and requirements for blood transfusion. Relative risks (RR) from the individual studies were pooled using random effects model.

Results: Two quasi-experimental studies (before and after), two case series and five case reports (1836 women) were included. Maternal mortality and morbidity were less

frequent when the anti-shock garment was used in addition to standard obstetric haemorrhage treatment (mortality: RR 0.54 95%CI 0.34, 0.86; p=0.009. morbidity: RR 0.25 95%CI 0.11, 0.56; p=0.007), although this was based on limited data (69 and 32 events respectively). One case of mortality and five cases of morbidity were reported in the case series studies.

Conclusion: It is possible to speculate that the anti-shock garment may contribute to improving outcomes of women with obstetric haemorrhage, when it is used in addition to standard treatment. The evidence however is based on poor quality data that is vulnerable to bias and confounding, and also a limited number of events.

12.1 BACKGROUND

The Anti Shock Garment

The Anti-shock garment has three sections, one for each leg, and another for the abdomen (Figure 58). The suit compresses the blood vessels in the legs, pelvis and abdomen, shunting the blood to the vital organs in the chest and head (349). It reduces the radius and transmuralpressure of abdominal, uterine, and lower-body blood vessels, therefore decreasing blood flow (350). The Anti shock garment is applied by the following steps. First the garment should be opened and placed under the woman with the top of the garment at her lowest rib. If she is unconscious, she can be rolled her onto her side and the garment be placed underneath her. The Garment should then be stretched and fastened tightly around the patient, starting with the ankle segments labelled 1 in Figure 58). The leg segments (labelled 2 and 3 in Figure 58) should be stretched and fastened around the knees (section 2) and the tights (section 3). Section 4, the pelvic section should be secured tightly at the level of the symphysis pubis. Segment 5 should be placed over the umbilicus, and closed by securing segment 5 with segment 6 (351). The application of the garment should result promptly in a decreased pulse and increased systolic blood pressure. It is not however suitable for

use with a viable fetus in utero (352), so would be suitable for post-partum use, in cases of ectopic pregnancy, or in cases of intrauterine death. Postpartum haemorrhage is the single largest cause of maternal death worldwide. Many clinical and pharmacological interventions are in place to prevent and treat post-partum haemorrhage (270, 353-356), but these are often only suitable for administration by trained staff at the facility level.

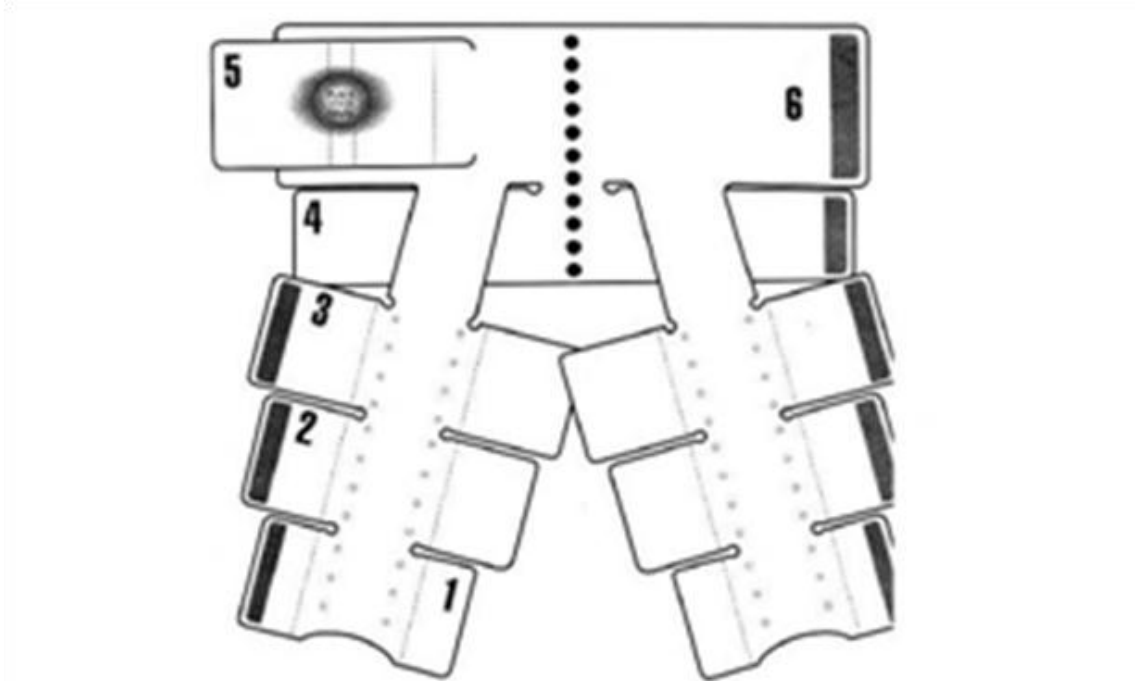

Figure 58 Anti-Shock Garment (sections numbered in order of application of the garment, as described above) source: www.voice-online.co.uk/sites/default/files/imagecache/455/garment.jpg

Births in developing countries take place within the community, without the assistance of a skilled birth attendant (83), many women do not receive essential interventions that can reduce the risk of morbidity and mortality from post-partum haemorrhage (353-355), such as active management of the third stage of labour. Moreover, as many births are attended by unskilled and untrained attendants early warning signs of post-partum haemorrhage may not be detected and timely care not sought.

The decision to access care and to actively seek life-saving treatment may be delayed further by the financial, cultural or geographic barriers faced by many women (15, 136, 162). This is particularly important as women suffering post-partum haemorrhage need to receive appropriate treatment promptly to reduce the risk of mortality and severe morbidity. It is suggested that unless appropriate medical care is received promptly, demise can occur within two hours (12). The use of the Anti-shock garment or G-suit was first documented in obstetrics in 1958 (357), however it was then more readily used with trauma patients. In the 1960's field surgeons in Vietnam reported great success with the use of this garment on injured soldiers (358), and today it is still used in the pre-hospital management of trauma patients (359) (360). The use of the anti-shock garment in post-partum haemorrhage has become more common in the last few decades (352, 360-366), whereas in the 1980's it was suggested to be one of the most effective therapeutic procedures in the United States, in obstetrics and gynaecology to control haemorrhagic shock from post-partum haemorrhage (349).

Although it is used for the treatment of haemorrhagic shock within a healthcare facility (352), or when sufficient quantities of blood are not available to transfuse, it can also be used to improve outcomes of women with obstetric haemorrhage being transferred to a health facility. This may be particularly valuable in rural areas of developing countries where lengthy delays are common with receiving adequate treatment. For example a vehicle first has be found to transfer the patient from the community, then the journey may be long and time consuming due to the distance travelled, or the type of vehicle or terrain. Then once a facility has been reached there may be further delays with surgery or access to blood transfusion (15, 136, 156, 172).

As the Anti-shock garment has been suggested to improve outcomes when used in addition to standard obstetric haemorrhage care (351, 366, 367), the literature available was systematically reviewed and meta-analysed on the outcomes of women

in which the anti-shock garment was used in addition to standard clinical obstetric haemorrhage treatment.

12.2 METHODS

Data sources and searches

Databases were searched for literature on the outcomes of the anti-shock garment on women experiencing obstetric haemorrhage in developing countries. PUBMED, EMBASE, Cochrane library, CINAHL, AMED, African Index Medicus, the Reproductive Health Library, and the Science Citation Index were searched (from database inception to March 2013). Hand searching complemented electronic searches, and reference lists were checked. The search terms were ‘anti-shock garment, anti shock trousers, G-suit, gravity suit, pneumatic suit, PASG and NASG. No language restrictions were applied to the search.

Study selection and data extraction

The best available evidence was included within the review, by following the hierarchy of evidence. In the absence of RCT, and sufficient data from studies of comparative design alone (quasi-experimental studies and case-control studies), case series and reports were also selected, no other studies were available. Initially the electronic searches were scrutinised and full manuscripts of relevant studies were acquired. Final decisions on inclusion or exclusion of manuscripts were made after inspection of these manuscripts by the author and another reviewer (AW and ET). Information was extracted from each article on study characteristics, outcome data and study quality by the author and another reviewer (AW, ET). The outcomes of maternal mortality, morbidity, pre-operative and post-operative haemoglobin, and the need for blood transfusion were focussed on.

Methodological quality assessment

The quasi-experimental studies were assessed for adequacy of reporting using the TREND checklist (368). Risk of bias in the studies was assessed using the Newcastle Ottawa Scale (71), although this tool is designed mainly for cohort and case series studies it is recognised as a tool for assessing risk of bias in non-randomised studies by Cochrane (369). There are no recommended tools to assess risk of bias in quasi-experimental (before/after studies) specifically. Therefore the studies were evaluated for representativeness of the groups, selection of the groups, ascertainment of the intervention and the outcome, comparability of the groups, as well as the length and adequacy of follow-up. The risk of bias was deemed low if a study obtained four stars for selection, two stars for comparability and three stars for ascertainment of exposure (71). Medium risk of bias was suggested to exist in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was classed as having high risk of bias. Case series studies were assessed using the MINORS checklist for adequacy of reporting (70), this contains eight items. Studies are assessed for reliability, consistency and validity. The items are scored between 0 and 2 for the adequacy of the reporting, with the ideal score being 16.

Statistical Analysis

Data for effect estimates (Risk Ratios) and corresponding 95% confidence interval were extracted for the comparative studies. Effect estimates and their 95% CI were then meta-analyzed using the generic inverse-variance method using the random effects model to account for the variability in the population and the setting. Heterogeneity of treatment effects was evaluated using forest plots, chi square tests and its magnitude determined by computing I^2 statistic. Analyses were performed using REVMAN 5.0 statistical software. Data for the case series studies is reported narratively.

12.3 RESULTS

The process of literature search and selection is given in Figure 59. The best available evidence is included in the review following the hierarchy of evidence. Two quasi-experimental studies (before and after) (1806 women) (362, 370), two case series (20 women) (352, 371), and five case reports (10 women) (357, 372-375) were included in the review, no RCTs were available. The characteristics of the studies included are shown in Table 37, and the data for the outcomes reported is provided in Table 38.

Characteristics of the studies

The two quasi-experimental studies (362, 370) included a total of 1806 women experiencing obstetric haemorrhage. Both studies were set in developing countries (Nigeria and Egypt). They were before and after studies and examined the effect of the non-pneumatic anti-shock garment in addition to standard obstetric haemorrhage management, following a period when treatment was standard obstetric haemorrhage management without the use of the anti-shock garment. Both of these studies had similar inclusion criteria for participants, women with obstetric haemorrhage, with signs of shock and blood loss over 750mls, with one sign of haemodynamic instability, for example a pulse above 100bpm or a systolic blood pressure below 100mmHg. The primary outcome measures for these studies were measured blood loss, severe end-organ failure morbidity (renal failure, pulmonary failure, cardiac failure, or central nervous system dysfunctions) and mortality. The two case series (352, 371) included a total of 20 women experiencing obstetric haemorrhage whom developed severe hypovolemic shock, classified by an estimated blood loss greater than 750ml, with a systolic blood pressure below 100mmHg, or a pulse above 100bpm. Both studies were set in Pakistan and also used the non-pneumatic anti-shock garment in addition to standard obstetric haemorrhage management which included administration of

intravenous crystalloid fluids, monitoring of vital signs and blood transfusion to restore haemoglobin to above 7 g/l. The primary outcome measures of the case series were mortality, morbidity (including any complications recorded in the medical notes), mean arterial blood pressure, estimated blood loss, haemoglobin concentration pre and post anti-shock garment, units of blood received in transfusion. The five case reports, reported on ten cases using the 'Gravity suit' or 'MAST suit' for women experience obstetric haemorrhage due to placenta praevia, percreta or acreta, placental abruption, retained placenta or abdominal pregnancy. The location setting of most of the case reports in not stated in the manuscripts. The outcomes reported were morbidity, mortality, blood transfusion and hospital stay.

Study quality

The before and after quasi-experimental studies did not report if consecutive inclusion of participants took place. Instead it was stated that the attending physician/clinician decided if the anti-shock garment would be used or not. In accordance with the TREND checklist the studies adequately reported on most items, however details was lacking on the unit of delivery of the intervention, and the deliverer of the intervention, methods used to assign units to the intervention, blinding, methods used for inputting missing data, flow chart of study participants, description of pre-specified causal pathway, and important adverse events. The studies both achieved scores of 45 out of a possible 59 marks (Table 39). The quasi-experimental studies were deemed to have low risk of bias in selection, ascertainment of exposure, and medium risk of bias in comparability on the Newcastle Ottawa Scale (Table 40). The case series reported adequately on most items achieving scores of 11 and 12 out of a potential 16 marks, sufficient details were lacking on prospective study sample size calculation, an unbiased endpoint assessment and the inclusion of consecutive patients (Table 41).

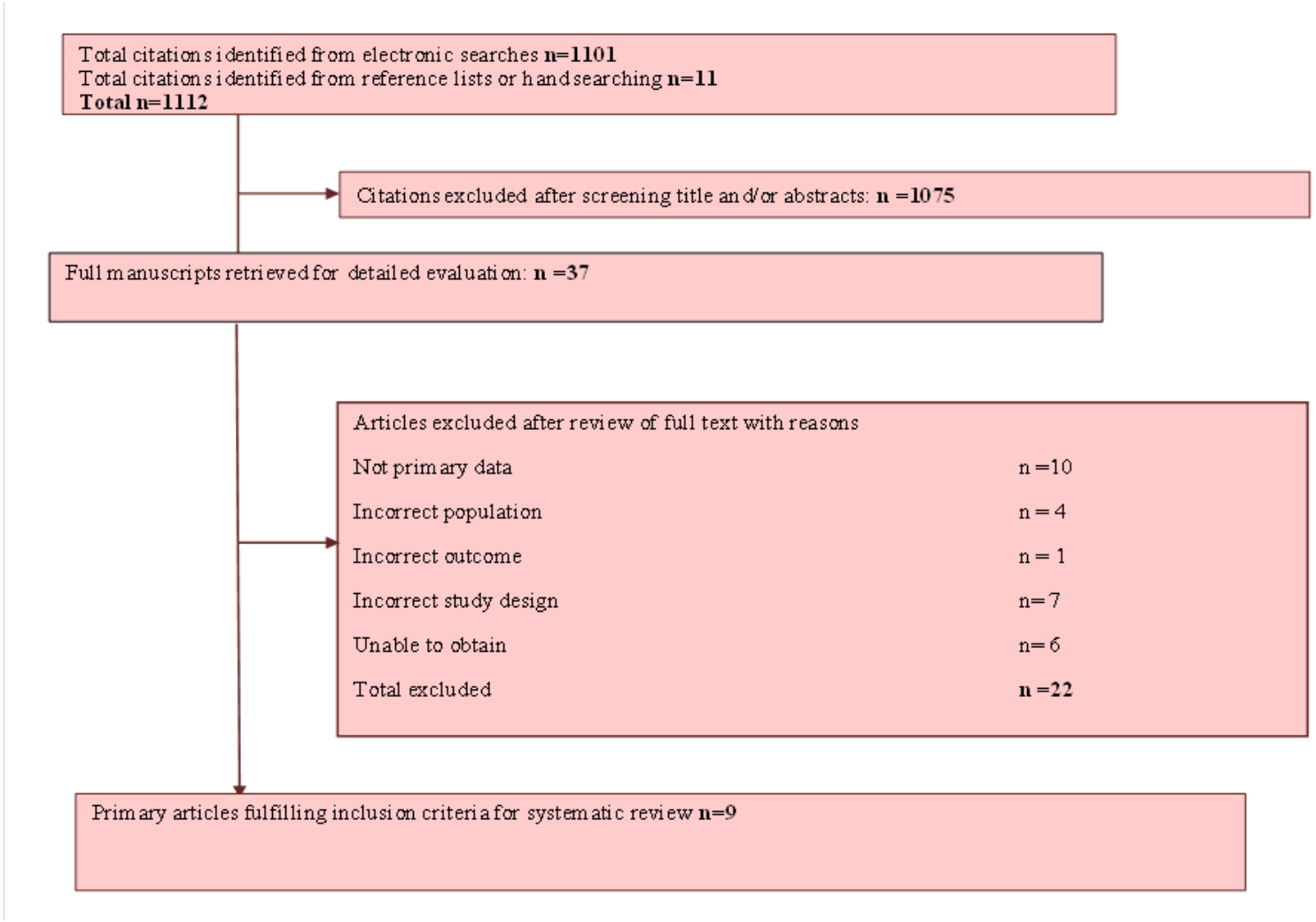

Figure 59 Selection process on studies included in the review

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Maternal Mortality

Meta-analysis of the two quasi-experimental studies demonstrated fewer cases of maternal mortality with the anti-shock garment (RR 0.54 95%CI 0.34, 0.86; p=0.009: Figure 50, this analysis however was based on only 69 events. There was no evidence of heterogeneity in this analysis (I^2=0%). The case series studies and case reports reported a single case of maternal mortality amongst 30 cases (3.3%).

Maternal Morbidity

Meta-analysis of the quasi-experimental studies demonstrated fewer cases of maternal morbidity with the anti-shock garment (RR 0.25 95%CI 0.11, 0.56; p=0.0007: Figure 51), this analysis was based on only 32 events. There was no evidence of heterogeneity in this analysis (I^2=0%). Morbidity included organ system dysfunctions relating to severe obstetric haemorrhage such as acute respiratory distress syndrome, cerebral impairment (including seizures, unconsciousness, or cognitive or motor loss), renal failure and heart failure. Only the before and after study that was set in Egypt (370) provided further clarification on the morbidities experienced by the participants, two women in the pre intervention group were reported to have renal failure and one was reported to have renal impairment. In the intervention group two women were reported to have cerebral impairment. The case series studies and case reports reported five cases of morbidity among the 30 cases (16.6%), which included sepsis, respiratory distress syndrome, pulmonary atelectasis, jaundice and disseminated intravascular coagulation (DIC).

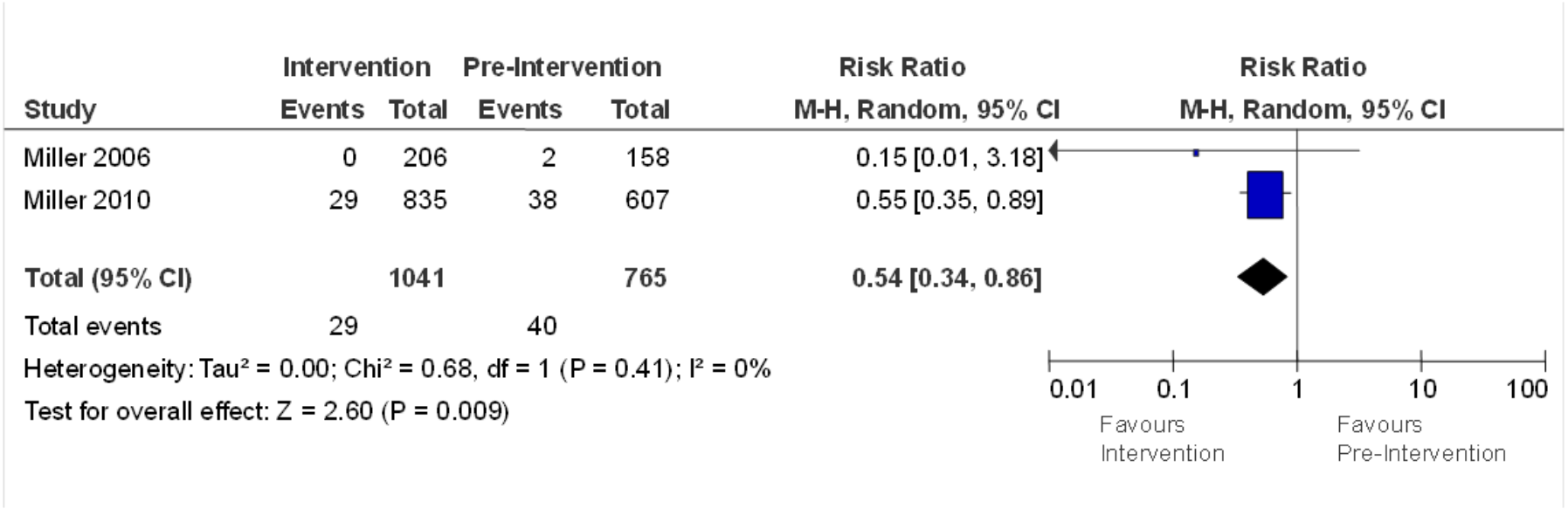

Figure 60 Maternal Mortality in participants being treated with the anti-shock garment or without the anti-shock garment

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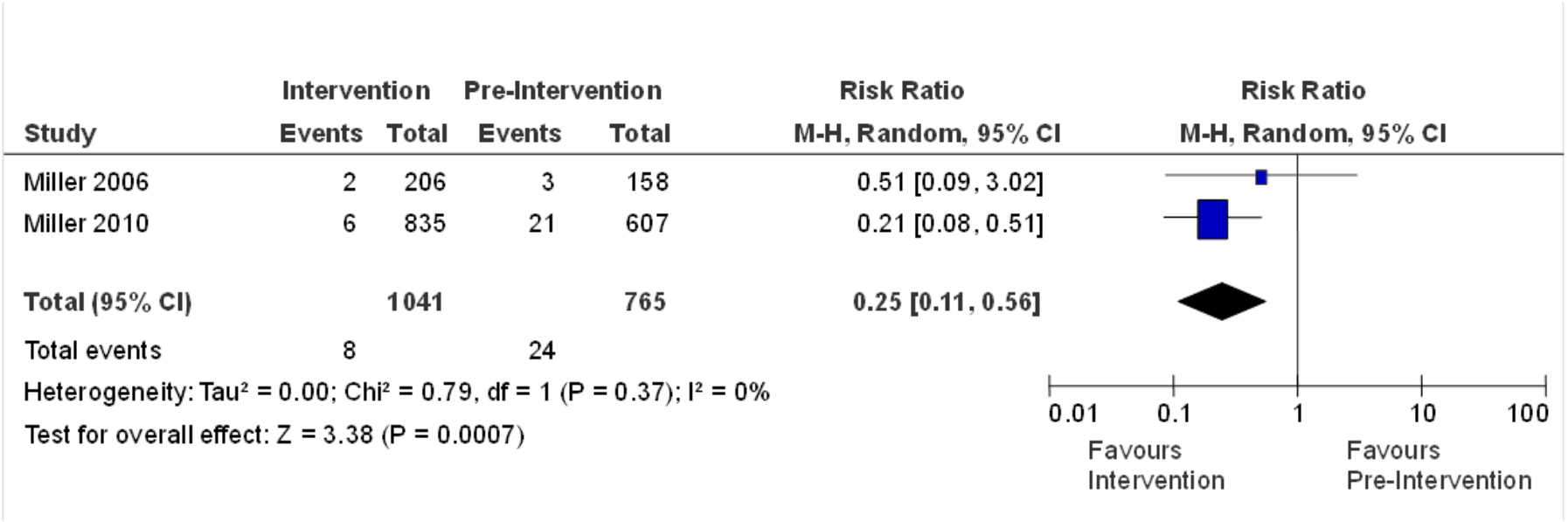

Figure 61 Maternal Morbidity in participants being treated with the anti-shock garment or without the anti-shock garment

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Blood transfusion

Blood transfusion was required by 86.5% (662/765) of patients in the pre-intervention group, and 90.3% (940/1041) of patients in the intervention group, of both of the quasi-experimental studies. When meta-analysed there was no significant difference between the two groups (RR1.11 95%CI 0.87, 1.41; p=0.41: I^2=90% p=0.001: Figure 52). This analysis was based on 1602 events. Case series and case reports documented blood transfusion in 96% (27/28) of the patients. The median amount of blood units transfused was 38 (range 13-63) in the case reports, with a mean of 4.67 (SD 1.37) and 2.54 (SD 1.27) units in the case series studies (Figure 53).

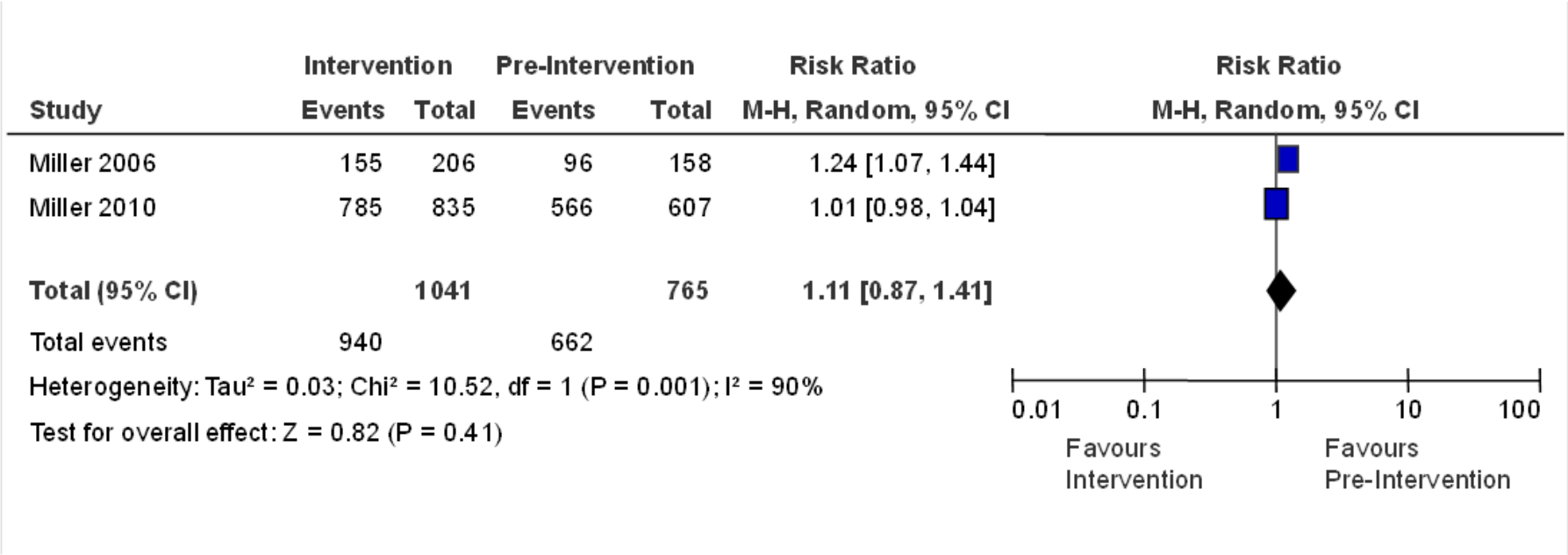

Figure 62 Blood Transfusion received by participants being treated with the anti-shock garment or without the anti-shock garment

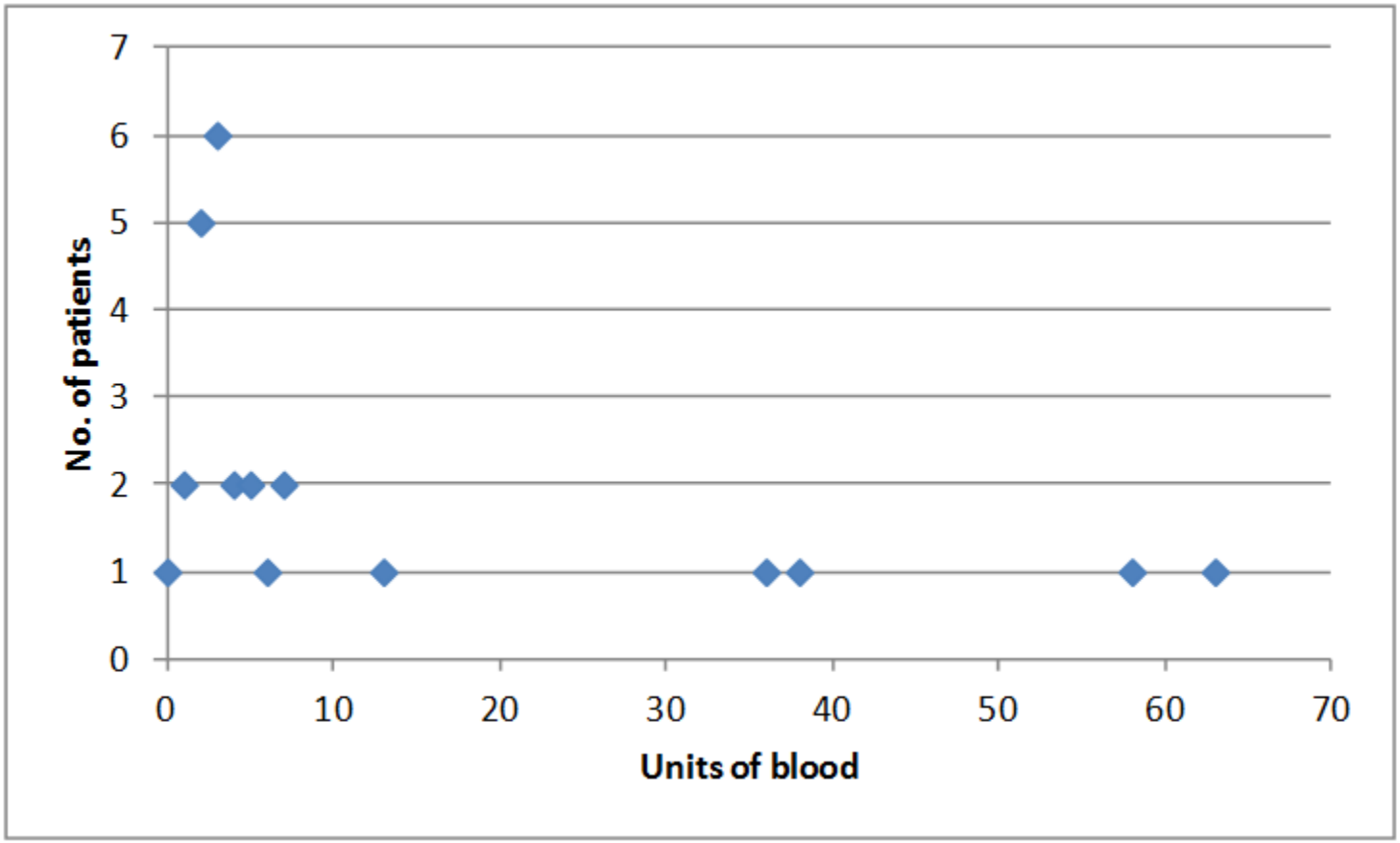

Figure 63 Units of blood transfused in participants being treated with the anti-shock garment

Table 43 Characteristics of studies included in the review

STUDY	Study population and setting	Garment	Pre-intervention	Intervention	Outcomes
Quasi-experimental study (before and after)					
Miller 2006	Egypt: Four tertiary care centre. Obstetric haemorrhage, signs of shock and PPH >750mls, one sign of haemodynamic instability (pulse >100bpm, systolic BP <100mmHg)	Non-pneumatic anti-shock	May-August 2004 n=158 standard evidence based protocol for haemorrhage/shock.	Sept – Dec 2004 n=206 Standard care *plus* Non-pneumatic anti-shock garment	EBL (calibrated blood collection drape)
Miller 2010	Nigeria: Four referral facilities Mar 2004 – Dec 2007(n=452) Egypt: Two referral facilities Jun 2006–May 2008(n=990) PPH >750mls and one sign of haemodynamic instability (pulse >100bpm, systolic BP <100mmHg)	Non-pneumatic anti-shock	(n=607) standard evidence based protocol for haemorrhage/shock.	(n=835) Standard care *plus* Non-pneumatic anti-shock garment	Death, blood loss, severe end-organ failure morbidity (renal failure, pulmonary failure, cardiac failure, CNS dysfunctions), mortality, emergency hysterectomy,
Case series studies					
Hensleigh 2002	Pakistan: June – July 2001 Obstetric haemorrhage, severe shock.	Non-inflatable anti-shock	n=6 managed with anti-shock garment plus standard treatment (1 woman had mitral value stenosis and developed dyspnoea, therefore this data was not analysed). Standard treatment includes intravenous crystalloid fluids, vital sign monitoring, blood transfusion to restore Hb>7 g/l		Mean arterial blood pressure, morbidity (any recorded complications), EBL, controlled haemorrhage, Hb
Brees 2004	Pakistan: Aug– Nov 2003 Obstetric haemorrhage, hypovolemic shock: EBL >750ml, systolic BP <100mmHg, pulse 100bpm,	Non-inflatable anti-shock	n=14 managed with anti-shock garment plus standard treatment. Standard treatment includes intravenous crystalloid fluids, vital sign monitoring, blood transfusion to restore Hb>7 g/l		Morbidity, mortality, EBL, Hb pre and post anti-shock garment, blood transfusion.
Case Reports					
Gardner 1958	One cases of placenta percreta treated with the anti-gravity suit	Gravity suit	1 woman with placenta percreta and placental abruption		Morbidity, mortality, blood transfusion

Pelligra 1979	Three cases of obstetric haemorrhage that were treated with the G-suit	Gravity suit and MAST suit	3 women; one with placental abruption and abdominal pregnancy; one with placenta praevia; one with placenta acreta	Blood transfusion, Mortality, morbidity
Sandberg 1983	Three cases of abdominal pregnancy that were treated with the anti-gravity suite	Antigravity suit	3 women; all abdominal pregnancy, one with placenta acreta, one with retained placenta	Mortality, morbidity, blood transfusion, hospital stay
Andrae 1999	Two cases of obstetric haemorrhage that are treated with MAST (military anti-shock trousers)	MAST trousers	2 women; one with placenta accrete; one with post partum haemorrhage.	Mortality, morbidity,
Ramachandran 2004	One case of abdominal pregnancy followed by massive haemorrhage treated with MAST suit	MAST suit	1 woman with abdominal pregnancy	Morbidity, mortality, blood transfusion

Table 44 Data of outcomes reported in the included studies (blood loss, blood transfusion, morbidity and mortality) in participants that received the anti-shock garment in addition to standard obstetric haemorrhage management, and participants that received only standard obstetric haemorrhage management (NR=not reported)

Quasi-experimental (before and after)	Blood Loss in drape (median, range mls)		Blood Transfusion		Morbidity		Mortality	
	Pre	Intervention	Pre (%)	Intervention (%)	Pre (%)	Intervention (%)	Pre (%)	Intervention (%)
Miller 2006	500 (0-2400)	250 (0-900)	96/158 (61.1)	155/206 (75.2)	3/158 (1.9)	2/206 (0.98)	2/158(1.3)	0/206(0)
Miller 2010	400 (IQR 250-500)	200 (IQR 150-250)	566/607(93.3)	785/835 (94.0)	21/607 (3.5)	6/835 (0.7)	38/607 (6.3)	29/835 (3.5)
Case Series	Blood Loss (median, range mls)		Blood Transfusion (%)	Units transfused mean (SD)	Hb before Mean (SD) g/l	Hb after Mean (SD) g/l	Mortality (%)	Morbidity (%)
Hensleigh 2002	2375 (1200-4000)		6/6 (100)	4.67(1.37)	5.17 (1.96)	8.07 (0.77)	0/6 (0)	0/6 (0)
Brees 2004	3000 (2000-4500)		13/14 (93)	2.54 (1.27)	8.5 (2.89)	7.21(1.86)	1/14 (7)	1/14 (7)
Case Report	Blood Loss (median, range mls)		Blood Transfusion (%)	Units transfused mean (SD)	Hb before Mean (SD) g/l	Hb after Mean (SD) g/l	Mortality	Morbidity (%)
Gardner 1958	NR		1/1 (100)	58	NR	NR	0/1	1/1 (100)
Pelligra 1979	NR		3/3 (100)	Median 38 (13-63)	NR	NR	0/3	2/3 (66)
Sandberg 1983	NR		3/3 (100)	4,000 – 19,000 mls (median 9,000)	NR	NR	0/3	2/3 (66)
Bengt 1999	NR		NR	NR	NR	NR	0/2	0/2
Ramachandran 2003	NR		1/1 (100)	36	11.2	11.8	0/1	0/1

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12.4 DISCUSSION

Findings

Maternal morbidity and mortality from obstetric haemorrhage is reduced when the anti-shock garment is used in addition to standard treatment, when compared to standard treatment alone, although these analyses were based on studies that are vulnerable to bias and a small number of events. There was no significant difference in the incidence of blood transfusion between the two groups; however the case series and case report studies reported 96% of patients requiring blood transfusion.

Limitations

The main limitation of the review is the poor quality of the available studies and the limited number of events included and analysed. With such small numbers it is difficult to make inferences on the effect of the anti-shock garment on the outcomes of women experiencing obstetric haemorrhage. Although two quasi-experimental studies are included, both lacked control in participant selection, as the attending physician decided whether the anti-shock garment was used. With this it is possible that the bias could be in favour of the pre-intervention group in the quasi-experimental studies, as the anti-shock garment may have been used on only those women deemed in grave condition in the intervention phase, therefore such patients may have worse outcomes. This can be demonstrated by the lower blood pressure recordings in the group that were treated with the anti-shock garment, indicating a worse study entry condition for patients in the intervention arm (362, 370). There are further limitations in the before and after study design. It is possible that the effect of time and experience in managing cases of haemorrhage and hypovolemic shock may have improved outcomes as the study progressed, thus bias may be in favour of improved outcomes in the group that were treated with the anti-shock garment.

Due to the nature of the studies included within this systematic review the demographic details of the patients was heterogeneous, reproductive history (gravida and parity), aetiology of haemorrhage, and condition of study entry varied greatly. This was notable even between the quasi-experimental studies; yet there appeared to be no evidence of heterogeneity in the analysis. The intervention also varied across the included quasi-experimental studies and case series, this however is likely to be due to improvements in the design of the garment over time, since its initial use.

Another limitation of the review is that both quasi-experimental studies were conducted by the same study group, although this may reduce heterogeneity in the intervention being evaluated, and the method in which the outcomes are measured, they may have a particular interest in the intervention, that in the absence of a robustly designed study (such as an RCT) may introduce into the results.

Existing Research

Since the publication of two literature reviews in 2007 (367) and 2008 (351) have been conducted by the same author, this systematic review appears to be the first. Since publication of the literature reviews two comparative studies using the Anti-shock garment in the treatment of obstetric haemorrhage have been published (350) (363), therefore an updated review of a systematic design was needed. There is currently no randomised data on the use of anti-shock garment in obstetric haemorrhage.

Policy and practice implications

The anti-shock garment is a low-cost, re-usable intervention that does not require clinical skill for application, thus it could be applied by lay health workers in community settings, where the majority of births occur. As obstetric haemorrhage is a leading cause of maternal mortality and morbidity in developing countries the potential effect could contribute to improvements in maternal outcomes in developing countries. The

findings of this review suggest that it is possible that the use of the Anti-shock garment might improve outcomes for women by reducing maternal mortality and morbidity from obstetric haemorrhage. It is not possible to discuss potential policy implications without further high quality research.

Unanswered questions and future research

Good quality primary research is required to draw firm conclusions on the effect of the anti-shock garment in addition to standard obstetric haemorrhage management in women from developing countries. The outcomes this research could guide policy, practice and further research.

12.5 CONCLUSION

The evidence in this review is based on a small number of events from studies that are vulnerable to bias and confounding, this is the best evidence available to date. There is a suggestion that the anti-shock garment may improve outcomes of women with obstetric haemorrhage, when it is used in addition to standard treatment, but high quality evidence is needed.

Table 45 TREND: reporting criteria in quasi-experimental studies (Y=reported N= not reported)

Topic	TREND checklist	Miller 2010	Miller 2006
Title and abstract			
Title and abstract	Information how units allocated	Y	Y
	Structured summary abstract	Y	Y
	information sample population	Y	Y
Introduction			
Background	Scientific background, explanation of rationale	Y	Y
	Theories used in designing intervention	Y	Y
Methods			
Participants	Eligibility criteria for participants at different levels	Y	Y
	method of recruitment including sampling method	Y	Y
	Recruitment setting	Y	Y
	Setting and location data collected	Y	Y
Interventions	details of intervention for each study condition and how administered	Y	Y
	content	Y	Y
	delivery method	Y	Y
	unit of delivery	N	N
	deliverer	N	N
	setting	Y	Y
	exposure quantity and duration	Y	Y
	time span	N	N
	activities	Y	Y
Objectives	Specific objectives and hypotheses	Y	Y
Outcomes	Completely defined pre-specified primary and secondary outcome measures	Y	Y
	Methods used to collect data	Y	Y
	Information on validated instruments used	Y	Y
Sample size	How sample size determined	N	Y
Assignment method	Unit of assignment to study conditions	Y	Y
	Method used to assign units to study conditions	N	N
	Inclusion of aspects employed to help minimise potential bias	Y	N
Blinding	participants and outcome assessors masked and how	N	N
Unit of analysis	Description of the smallest unit that is being analysed to assess intervention	Y	Y
	If the unit of analysis differs between assignment, analytical method used to account for this	Y	Y
Statistical methods	Statistical methods used to compare study groups	Y	Y
	Methods for additional analyses, subgroup or adjusted analyses	Y	Y
	Methods for imputing missing data	N	N
	Statistical software	Y	Y
Results			
Participant flow	Flow of participants through each stage	N	N
	enrolment	Y	Y
	assignment	Y	Y
	allocation	N	Y
	follow up	Y	N
	analysis	Y	Y

	Description of protocol deviation	N	N
Recruitment	Dates defining periods of recruitment and follow-up	Y	Y
Baseline data	baseline demographic and clinical characteristics for each group	Y	Y
	baseline characteristics for each study condition	Y	Y
	baseline comparisons	Y	Y
	comparison between study population at baseline and target	N	N
Baseline equivalence	Data on study group equivalence at baseline	Y	Y
Numbers analysed	Indication of whether analysis strategy was ITT	N	Y
	Number of participants included in each analysis	Y	Y
Outcomes and estimation	primary and secondary outcome, results for each group, estimated effect size and precision	Y	Y
	inclusion null/negative findings	Y	Y
	Inclusion of results from pre-specified causal pathways	N	N
Ancillary analyses	summary of other analyses performed	Y	N
Adverse events	All important adverse events or unintended effects in each	N	N
Discussion			
Interpretation	Interpretation consistent with results balance benefits harms, considering other evidence	Y	Y
Generalisability	Generalisability of trial findings	Y	Y
Overall evidence	General interpretation of results in context of current evidence	Y	Y

Table 46 Risk of Bias in quasi-experimental studies (Y=reported, N=not reported)

Quasi-Experimental Studies		Miller 2006	Miller 2010
Selection	Representativeness	Y	Y
	Selection on comparison	Y	Y
	Ascertainment of exposure	Y	Y
	Demonstration of outcomes	Y	Y
Comparability	Comparability (2 points available)	Y	YY
Outcome	Outcome assessment	Y	Y
	Follow up length	Y	Y
	Adequacy of follow up	Y	Y

Table 47 Minors checklist of reporting in case series

Case Series	Hensleigh 2002	Brees 2004
Clearly stated aim	2	2
Inclusion of consecutive patients	1	1
Prospective data collection	2	2
Appropriate end points	2	1
Unbiased endpoint assessment	1	1
Appropriate Follow up	2	2
Loss of follow up <5%	2	2
Prospective study size calculation	0	0

CHAPTER 13: INTERPRETATION

The questions stated in the introduction (Table 3) have been addressed through systematically reviewing the evidence on each intervention aimed to reduce maternal mortality in developing countries. This has been achieved through the following objectives:

a) Reviewed, synthesised and assessed the literature on community based interventions

b) Reviewed, synthesised and assessed the literature on task-sharing interventions

c) Reviewed, synthesised and assessed the literature on clinical interventions

d) Made recommendations for practice

e) Made recommendations for research

The findings of these reviews are shown in Table 48. This table also depicts the MDGs that may be influenced by the intervention. Perinatal and neonatal mortality rates were also examined within this thesis where possible, although maternal mortality was the primary focus. Neonatal and perinatal mortality rates are useful when examining interventions to reduce maternal mortality, as greater improvements are often seen in these outcomes first, due to the sample size and power needed to show an effect in maternal mortality.

Overall evidence on interventions to reduce maternal mortality

*Strategies Incorporating the Training and Support of TBA*s: Perinatal and neonatal deaths were significantly reduced with interventions incorporating the training and support of TBAs. There was no significant reduction shown in maternal mortality, greater power being needed to show this, but both randomised and non-randomised studies demonstrated a trend towards reduction. It was suggested that greater reductions in maternal mortality are likely to be shown if the intervention was applied to a wider population. Essential components of the package consisted of appropriate training, access to resources such as clean birth kits, as well as links to effective referral pathways, and continued skill development.

Participatory Learning and Action Cycle with Women's Groups: Maternal and neonatal mortality were significantly reduced with women's participatory learning and action groups.

Groups conducted within a rural setting, containing at least 30% of pregnant women, showed the most marked reductions in mortality rates. Women involved within participatory action groups often demonstrated enhanced awareness of maternal health problems, and can also show the desire and motivation to address them. Participatory learning and action cycles can develop knowledge, skills and critical consciousness, as well as enhance community involvement. Women's groups also have the potential to indirectly improve health outcomes through empowerment and advocacy, which may have repercussions on female education, employment and poverty.

Emergency transportation for pregnant women: Key issues with emergency transport of pregnant women were availability and transport speed, terrain, meteorology, support, dependence for decision-making, cultural issues, cost, and lack of safe, comfortable positioning during transit. Key recommendations for a suitable, efficient, effective, reliable, acceptable and affordable means of transport, were clear guidance to prioritise the use of vehicles; consistent availability of affordable options that were suitable for pregnant women and allowed them to be transported in the optimal left lateral position; a transport type compatible with local terrain, as well as local customs and cultures. Community engagement, education and awareness raising can potentially promote gender equality, and empower women. Collaborations with industry and partnerships with organisations also have the potential to influence the development of global partnerships.

Motivational interviews to reduce unmet contraceptive need: Motivational interviews improved effective contraceptive use between zero to four months after the intervention, yet there appeared to be no significant effect at other time points. A trend towards reduction in subsequent pregnancies or births at 12-24 months appeared to be demonstrated, although no significant effect was shown. This effect was seen on populations mainly from developed settings, at high risk of unintended pregnancy, so the transferability of the review findings to a developing world setting were questionable due to cultural differences and cost implications given that the intervention is intensive. The cost of the intervention, and the size

and the outcome of the overall effect should be assessed. The overall lack of data on the effect of motivational interviewing to improve contraceptive use and unmet contraceptive need in developing countries indicated that a RCT would be necessary to provide good quality evidence. This intervention complies with the WHO in working to promote contraception by producing evidence-based guidelines on service delivery of contraceptive methods, as well as adapt, implement and improve delivery methods to meet the needs of individuals.

Clinical officers performing caesarean section: The provision of caesarean section surgery by clinical officers did not result in a significant increase in maternal or perinatal deaths when compared to doctors. The incidence of wound dehiscence and wound infection however, was more frequent. Greater deployment of clinical officers, in countries with poor coverage of medical doctors can enhance access to emergency obstetric surgery. The role of the clinical officer can be adapted to suit local needs and conditions, therefore clinical officers could be utilised to address other determinants of health within various settings. Although the studies were all non-randomised, they were large and showed consistency in the findings.

Prophylactic antibiotics in surgical abortion and miscarriage surgery: Prophylactic antibiotic administration in surgical abortion significantly reduces infectious morbidity. There is sufficient evidence available from RCTs to guide practice and policy. Although all of the data came from developed countries, the results were deemed transferable to developing countries where the effect could be greater as the risk of developing pelvic infection may be greater. There were however limited data on the prophylactic antibiotic administration in surgical treatment of miscarriage, thus no inferences were drawn. A RCT is needed to guide practice and policy in low resource settings, where the risk of developing pelvic infection may vary from a high resource setting. Prophylactic antibiotics may reduce morbidity and mortality associated with sepsis following surgical treatment of miscarriage in low income countries, particularly in settings where the aetiology of the miscarriage is unknown.

Cell salvage as an alternative to homologous blood transfusion in caesarean section surgery: It was speculated that cell salvage could be beneficial in achieving normal haemoglobin levels for women that have undergone caesarean section, and could possibly be used as an alternative to homologous blood transfusion. However as the studies used to draw these inferences were derived from a developed world setting, and the study design of most of the included studies (case series) were vulnerable to bias and confounding, no firm inferences were able to be drawn from the conclusions of the review. Further primary research of high quality is needed to draw firm inferences on the use of cell salvage in caesarean section.

Cell salvage as an alternative to homologous blood transfusion for ruptured ectopic pregnancy surgery: It is speculated that cell salvage could be used in the treatment for haemorrhage from ruptured ectopic pregnancy in the absence of alternative life saving treatment such as a safe, reliable homologous blood transfusion service. It could also be used if homologous transfusion is not culturally acceptable. Due to the low cost and limited training needs that were associated with the procedure, cell salvage was deemed suitable for use low resource settings however as the data from which these conclusions were drawn lacked sufficient quality and were vulnerable to bias and confounding, no firm inferences were drawn. Primary research of high quality is needed to draw firm inferences on the safety and effectiveness of cell salvage in ectopic pregnancy.

Symphysiotomy for obstructed labour: Symphysiotomy was demonstrated as a possible alternative to caesarean section. This procedure can be performed in instances where resources are limited, when caesarean section is associated with greater risks, or when caesarean section is unavailable or greatly delayed (putting the woman at greater risk of uterine rupture). Haemorrhage and infection are significant contributors to maternal mortality globally, and these complications appeared to be less frequent with symphysiotomy when compared to caesarean section. No additional long term complaints were reported with

symphysiotomy when compared to caesarean section. However this review was based on a limited number of events from cohort studies that were vulnerable to bias and confounding. Well designed studies are needed before any conclusions could be drawn.

Anti-shock garment for women with postpartum haemorrhage: Use of anti-shock garment in addition to standard haemorrhage management appeared to reduce maternal mortality and morbidity from obstetric haemorrhage, when it was used in addition to standard treatment. The anti-shock garment is a low-cost, re-usable intervention that does not require clinical skill for application, thus it could be applied by lay health workers in community settings, where the majority of births occur. These inferences however were again based on a limited number of events from only two quasi-experimental studies, two case series and numerous case reports so were vulnerable to bias and confounding.

Determinants of maternal health

The interventions that have been reviewed in this thesis can be placed in the context of the determinants of maternal mortality framework (16). Each intervention has the pregnant woman at the centre, and aims to improve outcomes by reducing the factors that contribute to maternal death (e.g. untrained birth attendance, unavailability of caesarean section or blood transfusion). The interventions that affect the immediate determinants of maternal health are those that are associated with improving outcomes when pregnancy complications occur (Figure 64), this includes cell salvage in both ectopic pregnancy and caesarean section, and the anti-shock garment.

The interventions that address the intermediate determinants focus on the health status of the woman, and her access to and use of health services, as well as her healthcare seeking behaviour. It includes interventions that affect the care the woman receives, such as clinical officers providing caesarean section to improve availability and accessibility of emergency obstetric surgery, and training and supporting TBAs to improve accessibility of care for women not cared for by skilled birth attendants, and to fill the care 'coverage gaps'. It also

involves antibiotic administration to prevent infective morbidity in abortion, and emergency transportation of pregnant women for timely emergency obstetric care to improve maternal outcomes (Figure 64).

The interventions that address the distant determinants of maternal health are often a more complex package of interventions that affect the family and wider community as well as the individual woman; this includes participatory learning and actions cycles with women's groups, and motivational interviews to improve contraceptive use (Figure 64). Training and supporting TBAs can also affect the distant determinants of maternal health as in many regions their remit of care extends beyond intra-partum care, and includes family planning, malarial prophylaxis and preventing HIV transmission (376, 377).

Life course approach

The life course approach can be used in conjunction with the determinants of maternal health framework when considering both the implementation of interventions, and the possible effects that the interventions may have, other than those intended. Figure 65 demonstrates the span of time in which the reviewed interventions target, from the pre-conception period to the post-partum period; this demonstrates the predictable reproductive journey that many women make. Many of the interventions reviewed have the potential to influence a much wider time span than at point of delivery, the life course approach recognises this (378). For example participatory learning and action cycles with women's groups may not only improve outcomes for those involved at the specific time of involvement, it may also influence future decision making and practices for future generations. This approach can guide the timings of the interventions, suggesting opportunities to address key health issues and key life stages. It is also intended to put women in control of their care, and to make it more responsive to their needs.

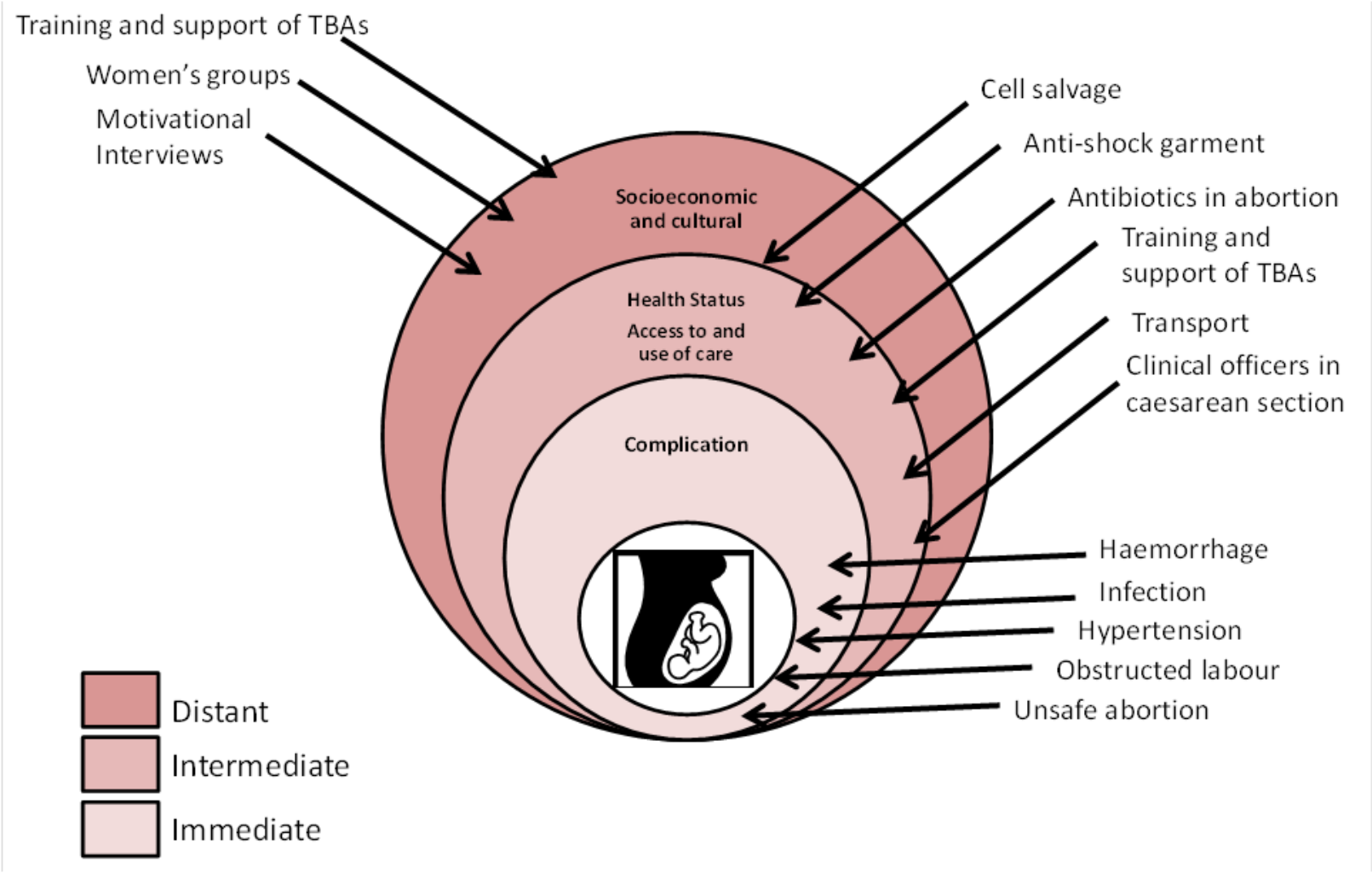

Figure 64 Interventions targeting determinants

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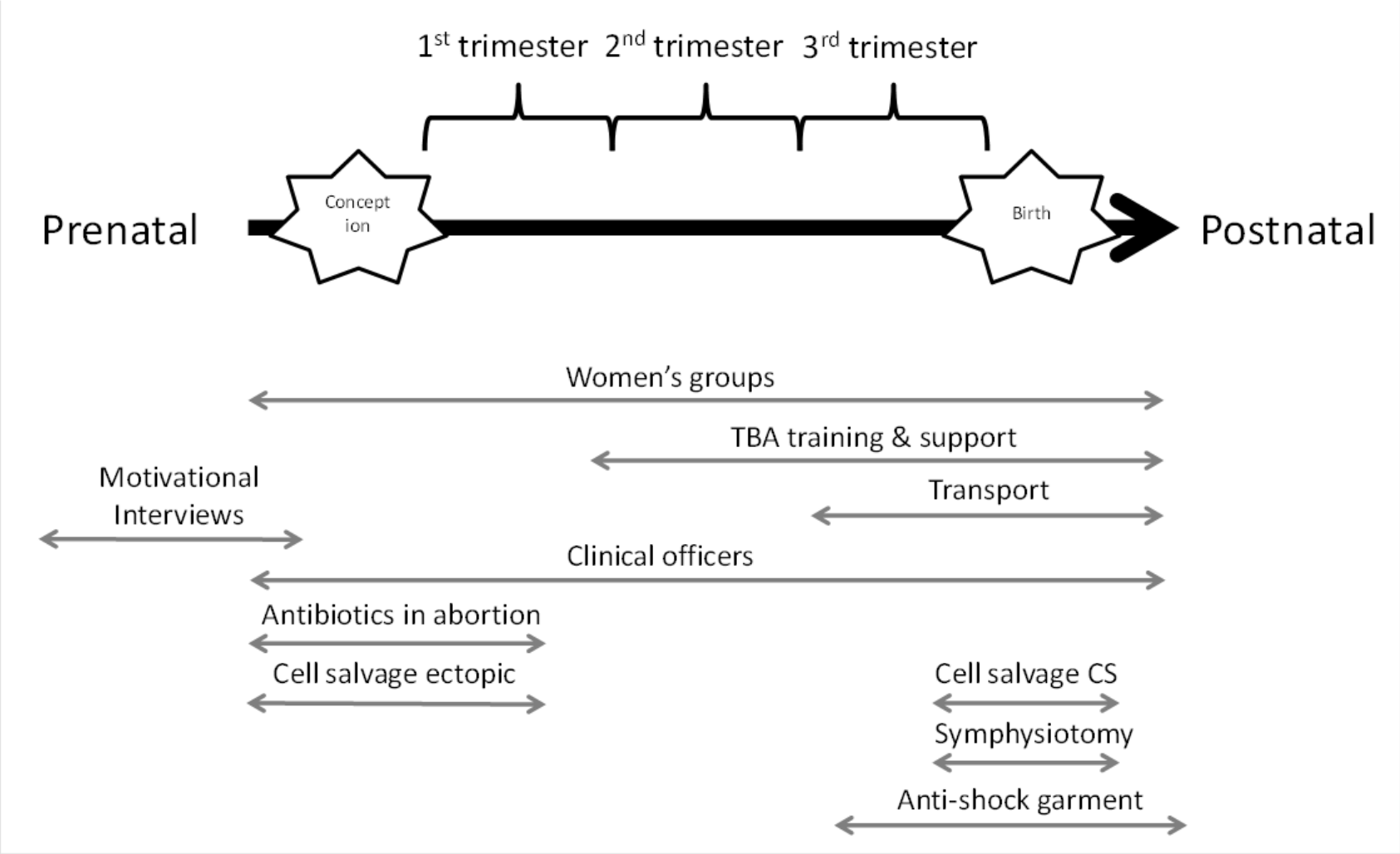

Figure 65 timeline of interventions

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Taking a life course approach to women's health care, encourages consideration of the biological, behavioural, environmental and social exposures throughout each woman's life through four main principles (378) (Figure 65). The first is information; ensuring women have access to consistent, reliable and accurate information about health and their individual health, in a manner in which they can process. This could be delivered through interventions such as women's groups or motivational interviews, but is likely to affect the acceptability and success of all interventions. The second is experience; understanding the relationship between past reproductive experiences, health-seeking behaviours and previous healthcare interactions (i.e. with staff or services), and how these may influence current and future health practices. This principle could have particular bearing on the use of TBAs, or emergency transportation, but again is likely to affect the acceptability and use of all interventions. The third is integration; encouraging greater integration of different health care services across different sectors. It is important to consider the horizontal as Well as the vertical integration of services. This concept applies to all interventions, as the horizontal and vertical implementation is necessary for success. Interventions implemented in isolation are less likely to have a positive impact. This is reiterated in the evaluation of emergency transport projects, as without community involvement, and local services being integrated, barriers to this service being utilised remain (14, 144, 166) (chapter five). This however can be a more complex process, particularly with intervention packages such as training and supporting TBAs. The fourth is data; ensuring the provision of joined-up, person-based, longitudinal data to inform women and healthcare systems about their needs and the services available. This applies to all interventions and is necessary for their implementation, acceptability and utilisation.

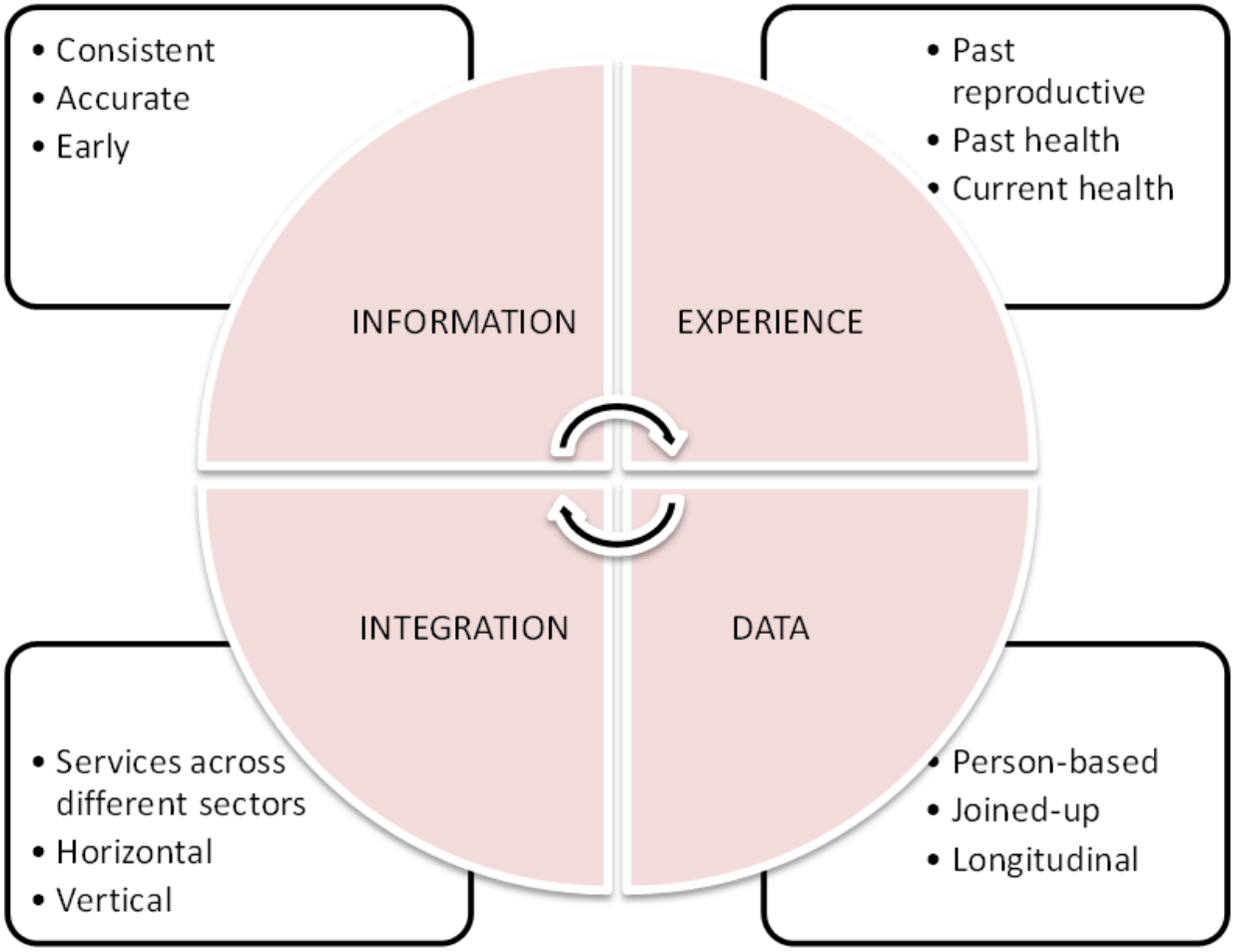

Figure 66 Life course approach

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Impact

The aim of this thesis was to systematically review the evidence on interventions to reduce maternal mortality, however this thesis in isolation will not invoke improvements in maternal health. It is therefore essential to consider the impact of this research, and any policy and practice implementation that has followed.

One of the systematic reviews conducted in this thesis (chapter 8: prophylactic antibiotics for uterine evacuation: a systematic review and meta-analysis) was used to guide application for funding from the Medical Research Council, for an international, multi-centre RCT on sepsis in miscarriage. Funding of £1.6 million was successfully received. The AIMS Trial (Antibiotics In Miscarriage Surgery) commenced in March 2013, and is endorsed by

◊ International Federation of Gynaecology and Obstetrics (FIGO)
◊ WHO (WHO) - through Dr Metin Gulmezoglu)
◊ Royal College of Obstetricians and Gynaecologists
◊ Early Pregnancy – Clinical Studies Group (EP-CSG)
◊ The Association of Obstetricians and Gynaecologists of Malawi
◊ Miscarriage Association
◊ Association of Early Pregnancy Units.

Another systematic reviews (Chapter 7: a comparison of clinical officers with medical doctors on caesarean section outcomes) has contributed to the WHO's recommendations 'Optimizing health worker roles to improve access to key maternal and newborn health interventions through task shifting'. The work of the thesis also complies with the WHOs objectives, in exploring the evidence base for effective delivery strategies of interventions, and increasing coverage of care for mothers and newborns. This in turn has should influence the guidance of professional bodies such as the federation of international gynaecology and obstetrics (FIGO), and the international confederation of midwives (ICM), and the allocation of budgets and resources within health systems, and inform funders of maternal health

projects. The ultimate beneficiaries however will be the mothers and babies that receive the care influenced by this evidence.

The work of this thesis has contributed to publications in the Lancet (64) (Appendix 14), the British Medical Journal (65, 379)(Appendix 12 and 13), and the International Journal of Gynaecology and Obstetrics (380)(Appendix 15). Publication of evidence is key for dissemination of evidence, and increasing the evidence base for practice. This is particularly true for high ranking journals such as the Lancet and British Medical Journal, as not only do they have global reach, they are credible sources of information for practitioners and policy makers worldwide. These high ranking publications have also resulted in dissemination through presentation at prestigious conferences (FIGO: World congress of gynaecology and obstetrics; Royal College of Obstetrics and Gynaecology Blair Bell) and the Houses of Parliament.

Expanding the evidence base for improving maternal and perinatal mortality complies with the objectives of the 'countdown to 2015' movement (381), a programme backed by the WHO, unicef, the department for international development and many other leading organisations. This programme focuses on the progress towards achieving MDGs 4 and 5, in the 75 countries in which 95% of maternal and child deaths occur. The programme emphasises the importance of gathering and synthesising evidence, the keys steps of this thesis.

In addition to communicating research findings to academics and clinicians, engagement, interaction and dialogue with the public can be useful, particularly with seeking funding for projects. Public engagement and interaction can also be vital for support of maternal health improvements, as it can improve female advocacy and empowerment. It can also tackle cultural and societal taboos associated with maternal health. Dissemination of new evidence through academic journal publication is not always suitable for the lay public, so this often needs to be converted into a more accessible means.

The research conducted in this thesis has been used to inform and produce a maternal health resource pack as part of a funded project (at our mothers feet), which involved translation of the evidence into a format suitable for the lay public. The resource pack was distributed amongst charities and non-government organisations, to encourage focus and funding of maternal health projects (appendix 16). It also aimed to encourage investment into specific interventions that have been shown to be effective through the systematic reviews, as well as dispel the myth that costly interventions are the sole solution to addressing maternal mortality.

The research contributing to this thesis has also informed discussions and debates on maternal health and maternal healthcare practices, with organisations interested in commencing maternal health projects (Ammalife, MADE in Europe, Islamic Relief, Muslim Hands, Muslim Charity), but also with community groups that were deterred from, or against supporting maternal health projects due to particular cultural or religious taboos. These took place in community centres and mosques; the evidence from this thesis has also informed workshops on maternal health with schools and youth groups.

Through targeting an academic audience, a clinical audience, potential funders, and the public, and by disseminating information in a means accessible to the various audience types, the intention is to create the maximum possible support for reducing maternal mortality, hence creating the maximum possible impact.

Table 48 Interventions reviewed in the Thesis

Question	Population	Intervention	Comparison	Outcome	Finding	MDGs
Community Based Intervention						
Does training and supporting TBAs reduce maternal, neonatal and perinatal mortality rates in developing countries?	Pregnant women seeking labour and delivery care in developing countries	Training and Supporting TBAs	Standard care	Maternal, perinatal and neonatal mortality	Strategies that incorporate the training and support of TBAs significantly reduces perinatal and neonatal deaths. **Beneficial (suitable for implementation; no further research required)**	
Do women's groups practising participatory learning and action cycles improve maternal and neonatal outcomes in developing countries?	Women	Participatory learning and action cycles	Standard care	Maternal and neonatal mortality	Maternal and neonatal deaths are significantly reduced with women's participatory action and learning groups. Women's groups with at least 30% of pregnant women participating show greater reductions on neonatal and maternal mortality. **Beneficial (suitable for implementation; no further research required)**	
What are the barriers and facilitators of emergency transportation for pregnant women in developing countries?	Pregnant women in developing countries seeking emergency transportation to access emergency obstetric care in	Emergency transport	None	Experiences and opinions of pregnant women or stake holders. Barriers and facilitators of emergency transport of pregnant women.	Individual themes should be appreciated within local context to provide illumination on local barriers and facilitators. Some potential solutions include motorcycle ambulance programme or collaboration with local minibus taxi services, community education and empowerment (raising awareness with women, partners, birth attendants and leaders), subsidies, insurance schemes and vehicle and road maintenance. **Likely to be beneficial (may be**	

					suitable for implementation with close monitoring of outcomes; further research may be required)
Can motivational interviews reduce the unmet need for contraception in developing countries affected by conflict?	Women of reproductive age in developing countries	Motivational interviews	Standard care	Effective contraceptive use, subsequent pregnancy or birth	Motivational interviews increase effective contraceptive use in a population at high risk of unintended pregnancy between zero to four months. This research complies with current global health research on improving family planning, however suitability to a developing world setting is questionable. **Likely to be beneficial (may be suitable for implementation with close monitoring of outcomes; further research may be required)**
Task Sharing Interventions					
Are clinical officers as safe and effective as medical doctors at performing caesarean section?	Pregnant women in developing countries requiring delivery by caesarean section	Clinical officer performing the caesarean section	Medical doctor performing caesarean section	Maternal and neonatal mortality, wound infection and dehiscence	Clinical officers and doctors did not differ significantly in key outcomes for caesarean section. There was an increase in wound infection and dehiscence with clinical officers. **Beneficial (suitable for implementation; no further research required)**
Clinical Intervention					
Do prophylactic antibiotics reduce the incidence of infectious morbidity in surgical abortion and miscarriage surgery?	Women having surgical abortion and women having miscarriage surgery	Antibiotics	Placebo or no drug	Infectious morbidity	Meta-analysis of RCTs showed an average reduction in infectious morbidity in cases of surgical abortion with prophylactic antibiotics by 41%**.** **Beneficial (suitable for implementation; no further research required)** Data on miscarriage was insufficient to draw inferences. High quality

					research is needed. **Unknown effectiveness (not for implementation; may be suitable for research if existing data indicative of benefits)**
Is cell salvage a safe alternative to homologous blood transfusion in caesarean section	Women having caesarean section and blood transfusion	Cell salvage	Homologous blood transfusion	Pre and post operative haemoglobin, blood loss, use of additional homologous blood, length of hospital stay, serious adverse effects	Cell salvage could be suggested as beneficial in achieving normal haemoglobin levels for women that have undergone caesarean section, however further primary research of high quality is needed. **Unknown effectiveness (not for implementation; may be suitable for research if existing data indicative of benefits)**
Is cell salvage a safe alternative to homologous blood transfusion in surgery for ruptured ectopic pregnancy	Women having surgery for ruptured ectopic pregnancy and blood transfusion	Cell salvage	Homologous blood transfusion	Pre and post operative haemoglobin, blood loss, use of additional homologous blood, length of hospital stay, serious adverse effects	Simple cell salvage in ectopic pregnancy could be suggested to be an alternative treatment to donor transfusion. However high quality evidence is needed. **Unknown effectiveness (not for implementation; may be suitable for research if existing data indicative of benefits)**
Is symphysiotomy a safe alternative to caesarean section in developing countries	Women with obstructed labour	Symphysiotomy	Caesarean Section	Maternal mortality, perinatal mortality, fistulae, haemorrhage, infection, pyrexia, incontinence	Symphysiotomy could be suggested to be an alternative to caesarean section in developing countries where the risks associated with caesarean section are high. No additional long term complications are reported with symphysiotomy. High quality evidence is needed **Trade off between benefits and harm (may be suitable for implementation according to local circumstances and**

					priorities. Implementation ideally carried out in the context of research; further research required
Can the anti-shock garment improve outcomes for women with postpartum haemorrhage in developing countries	Women with post-partum haemorrhage requiring transfer to a place of care	Anti-shock garment in addition to Standard care	Standard care	Maternal mortality, maternal morbidity, blood transfusion	Anti-shock garment in addition to standard treatment could be suggested to reduce maternal mortality and morbidity from obstetric haemorrhage. High quality evidence is needed **Unknown effectiveness (not for implementation; may be suitable for research if existing data indicative of benefits)**

APPENDICES

Appendix 1: Search terms for 'Strategies that incorporate the training and supporting of traditional birth attendants reduce perinatal and neonatal deaths: A meta-analysis'

MEDLINE

(((traditional birth attendant[All Fields] OR traditional birth attendant's[All Fields] OR traditional birth attendants[All Fields] OR traditional birth attendants[All Fields]) OR (birth attendance[All Fields] OR birth attendant[All Fields] OR birth attendants[All Fields] OR birth attendants[All Fields] OR birth attending[All Fields])) OR dias[All Fields]) OR comadronas[All Fields]

EMBASE

health care personnel/ or traditional birth attend*.mp.OR birth attend*.mp. OR dais.mp.OR comadronas.mp.

AMED

TX traditional birth attend* OR TX birth attend* OR TX dais OR comadronas

BNI

(traditional birth attend*) OR (birth attend*) OR (dais) OR (comadronas)

Cochrane Library

traditional birth attend:ti,ab,kw OR birth attend:ti,ab,kw OR dais:ti,ab,kw OR comadronas:ti,ab,kw

BIOMED central

traditional birth attend* (All words) in *All fields (full text)* OR birth attend* (All words) in *All fields (full text)* OR dais (All words) in *All fields (full text)* OR comadronas (All words) in *All fields (full text)*

CINAHL

TX traditional birth attend* OR TX birth attend* OR TX dais OR TX comadronas

PsycINFO

traditional birth attend*.mp. OR birth attend*.mp. OR dais.mp.

Science citation index

TS=traditional birth attend* OR TS=birth attend* OR TS=dais OR TS=comadronas

Databases=SCI-EXPANDED Timespan=All Years

African Index Medicus

Traditional birth attend [Key Word] or birth attend [Key Word] or dais [Key Word] or comadronas [Key Word]

Reproductive Health Library

Traditional birth attendant OR dais OR birth attendant OR comadronas

LILACS

Traditional OR birth OR attend$ OR dais OR Comadronas

Appendix 2: Search terms for 'Effect of women's participatory learning and action groups on neonatal and maternal mortality: A systematic review and meta-analysis'

MEDLINE

Community mobilisation.mp. OR Community participation.mp. OR Maternal Health Services/ or Health Knowledge, Attitudes, Practice/ OR participatory action.mp. OR Community-Based Participatory Research/ AND women* Group*.mp. OR participatory[All Fields] AND ("women"[MeSH Terms] OR women's groups[Figure/Table Caption] OR women's groups[Section Title] OR women's groups[Body - All Words] OR women's groups[Title] women's groups[Abstract])

Embase

Community mobilisation.mp. OR Community participation.mp. OR Maternal Health Services/ or Health Knowledge, Attitudes, Practice OR participatory action.mp. OR Community-Based Participatory Research OR women* Group*.mp. (MH "Action Research/ED/EV/OG") OR (MH "Group Exercise/ED/EV/MO/NU/OG/PF") OR (MH "Focus Groups/ED/EP/EV")

Cochrane Collaboration

Participatory action groups

CINAHL

"participatory action groups" OR “women group" OR (MH "Group Exercise") OR (MH "Women's Health Services") OR (MH "Women's Rights") OR (MH "Women's Health") (MH "Randomized Controlled Trials") OR (MH "Clinical Trials") OR (MH "Action Research") OR (MH "Group Exercise") OR (MH "Support Groups")

ASSIA

all(participatory action group) AND all(women)

Science Citation Index

Topic=(participatory action group*) AND Topic=(women*)

African Index Medicus

community mobilisation [Key Word] or community participation [Key Word] or women's groups [Key Word] participatory action [Key Word] or women’s groups [Key Word]

Appendix 3: Search terms for ‘Maternal emergency transport in low and middle income countries: a systematic review and thematic synthesis of qualitative studies.’

MEDLINE

(exp motorcycle/ AND exp ambulance) OR (exp ambulance AND exp bicycle/) OR (emergency/ AND patient referral/) OR (emergency/ AND Transport/) OR (emergency/ AND health care access/) OR (exp ambulance/ AND emergency/) OR (eranger.mp.) OR (exp Motorcycles AND Ambulances/) OR (bicycle.mp AND Ambulances/) OR (Emergencies/ AND “Referral and Consultation"/) OR (Emergencies/ AND access.mp) OR (Ambulances/ AND Emergencies/) AND (Qualitative Research OR exp Qualitative Research OR exp Interview OR Focus Groups/mt OR Focus Groups/ OR observational method/)

Embase

(exp motorcycle/ AND exp ambulance) OR (exp ambulance AND exp bicycle/) OR (emergency/ AND patient referral/) OR (emergency/ AND Transport/) OR (emergency/ AND health care access/) OR (exp ambulance/ AND emergency/) OR (eranger.mp.) OR (exp Motorcycles AND Ambulances/) OR (bicycle.mp AND Ambulances/) OR (Emergencies/ AND “Referral and Consultation"/) OR (Emergencies/ AND access.mp) OR (Ambulances/ AND Emergencies/) AND

(Qualitative Research OR exp Qualitative Research OR exp Interview OR Focus Groups/mt OR Focus Groups/ OR observational method/)

African Index Medicus

Emergency transport [Key Word] or bicycle ambulance [Key Word] or motorcycle ambulance [Key Word] or emergency referral [Key Word] or emergency access [Key Word] or ambulance [Key Word] or (emergency AND ambulance [Key Word])

CINAHL

(TX motorcycle AND TX ambulance) OR (TX ambulance AND TX bicycle) OR (TX emergency AND TX patient referral) OR (TX emergency AND TX Transport) OR (TX emergency AND TX health care access) OR (TX ambulance AND TX emergency) OR (TX eranger) OR (TX Motorcycles AND TX Ambulances) OR (TX bicycle AND TX Ambulances) OR (TX Emergencies AND TX Referral and Consultation) OR (TX Emergencies AND TX access) OR (TX Ambulances AND TX Emergencies) AND (TX Qualitative Research OR TX Interview OR TX Focus Groups OR TX observational method)

Science Citation Index

Topic=(Emergency transport) OR Topic=(bicycle ambulance) AND Topic=(motorcycle ambulance) OR Topic=(emergency referral) OR Topic=(emergency access) OR Topic=(emergency AND ambulance) AND Topic=(Qualitative Research OR Topic= Interview OR Topic= Focus Groups OR Topic=observational method)

Reproductive Health Library

Emergency transport OR bicycle ambulance OR motorcycle ambulance OR emergency referral OR emergency access OR (emergency AND ambulance) AND (Qualitative Research OR Interview OR Focus Groups OR observational method)

Cochrane library

Emergency transport OR bicycle ambulance OR motorcycle ambulance OR emergency referral OR emergency access OR (emergency AND ambulance) AND (Qualitative Research OR Interview OR Focus Groups OR observational method) in title abstract keywords

ASSIA

all((Emergency transport) OR all(bicycle ambulance) OR all(motorcycle ambulance) OR all(emergency referral) OR all(emergency access) OR all(emergency AND ambulance)) AND all((Qualitative Research) OR al(Interview) OR all(Focus Groups) OR all(observational method))

BNI

all((Emergency transport) OR all(bicycle ambulance) OR all(motorcycle ambulance) OR all(emergency referral) OR all(emergency access) OR all(emergency AND ambulance)) AND all((Qualitative Research) OR al(Interview) OR all(Focus Groups) OR all(observational method))

QUALIDATA

emergence AND transport OR bicycle AND ambulance OR motorcycle AND ambulance OR emergency referral OR emergency access OR emergency AND ambulance

Appendix 4: Search terms for 'Can motivational interviews improve contraceptive compliance and reduce unmet contraceptive need in post conflict zones: a systematic review.'

MEDLINE

motivational[All Fields] AND ("interview"[All Fields] OR "interviews as topic"[MeSH Terms] OR "interview"[All Fields])) AND ((("contraception"[MeSH Terms] OR "contraception"[All Fields]) OR ("family planning services"[MeSH Terms] OR ("family"[All Fields] AND "planning"[All Fields] AND "services"[All Fields]) OR "family planning services"[All Fields] OR ("family"[All Fields] AND "planning"[All Fields]) OR "family planning"[All Fields])) OR (("mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields]) OR ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])))

CINAHL

(MH "Motivational Interviewing") OR "Motivational interviewing" AND (MH "Family Planning") OR (MH "Family Planning: Contraception (Iowa NIC)") OR (MH "Family Planning: Unplanned Pregnancy (Iowa NIC)")

ASSIA

all(motivational interviewing intervention) AND all((contraception OR family planning))

African Index Medicus

contraception AND behavioural intervention, motivational AND interview, family planning AND behavioural intervention

EMBASE

motivation/ or motivational interview.mp. AND contraception.mp. or contraception/ OR family planning/

British Nursing Index

all(motivational interview) AND (all(contraception) OR all(family planning))

Science Citation Index

Topic=(contraception) OR Topic=(Family planning) AND Topic=(motivational interview)

Reproductive Health Library

Motivational interview contraception

QUALIDATA

Motivational interviews contraception

Appendix 5: Search terms for 'A comparison of clinical officers with medical doctors on caesarean section outcomes in the developing world: A meta-analysis of controlled studies'

MEDLINE

(((((non-physician[All Fields] AND ("Clinician (Goa)"[Journal] OR "clinician"[All Fields])) OR non physician clinicians[All Fields]) OR medex[All Fields]) OR (("dental assistants"[MeSH Terms] OR ("dental"[All Fields] AND "assistants"[All Fields]) OR "dental assistants"[All Fields] OR "assistant"[All Fields]) AND ("Med Off"[Journal] OR ("medical"[All Fields] AND "officer"[All Fields]) OR "medical officer"[All Fields]))) OR ("Med Off"[Journal] OR ("medical"[All Fields] AND "officer"[All Fields]) OR "medical officer"[All Fields])) OR (clinical[All Fields] AND officer[All Fields])

Embase

(clinical officer or medical officer or assistant medical officer or medex or non physician clinician* or non-physician clinician*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

CINAHL

(TX non physician clinician OR TX medex OR TX non-physician clinician OR TX medical officer OR TX clinical officer OR TX assistant medical officer)

Reproductive Health Library

clinical officer OR medical officer OR assistant medical officer OR medex OR non physician clinicians

Cochrane Collaboration

'clinical officer OR medical officer OR assistant medical officer OR medex OR non physician clinicians in title abstract keywords in Cochrane Reviews'

BIOMED Central

clinical officer (All words) in *All fields (full text)* , and assistant medical officer (All words) in *All fields (full text)* , and medical officer (All words) in *All fields (full text)* , and non physician clinicians (All words) in *All fields (full text)*

Science Citation Index

TS=clinical officer OR TS=medical officer OR TS=assistant medical officer OR TS=medex OR TS=non physician clinician OR TS=non-physician clinician

Databases=SCI-EXPANDED Timespan=All Years

Appendix 6: Search terms for 'Prophylactic antibiotics for uterine evacuation: A systematic review and meta-analysis'

MEDLINE

(abortion, spontaneous.mp. OR spontaneous.mp. OR miscarriage.mp. OR abortion, tubal.mp. OR recurrent miscarriage.mp.OR pregnancy miscarriage.mp. OR miscarriage risk.mp. OR first trimester miscarriage.mp. OR threatened miscarriage.mp. OR surgical evacuation of the uterus.mp. OR evacuation of retained products of conception.mp. OR pregnancy loss.mp. OR incomplete miscarriage.mp. OR early pregnancy loss.mp. ORclinical spontaneous abortion.mp.OR complete miscarriage.mp.OR missed miscarriage.mp.) AND (sepsis.mp. OR therapy sepsis.mp.) OR (exp infection OR (infection/ or infection.mp. OR infection rate.mp.) OR (bacteremia.mp) OR (endotoxemia OR hemorrhagic septicemia) OR (fever OR pyrexia.mp). OR (postoperative infection OR post-operative infection.mp.) OR (surgical infection) OR (blood poisoning.mp. OR bloodstream infection) OR (septicemia.mp. OR blood infection.mp.) AND (abortion, incomplete.mp. OR septic abortion OR abortion, septic.mp. OR septic abortion.mp. OR abortion, threatened.mp.OR embryo death OR embryo loss.mp) OR (induced abortion OR abortion, induced.mp. OR induced abortion.mp. OR spontaneous abortion.mp. OR abortion, missed.mp.OR missed abortion.mp. OR medical abortion OR abortion, medical.mp.OR recurrent spontaneous abortion.mp. OR legal abortion OR abortion, legal.mp. OR eugenic abortion.mp. OR therapeutic abortion OR abortion, therapeutic.mp. OR abortion.mp.OR pregnancy termination OR termination of pregnancy.mp. OR recurrent OR recurrent abortion.mp.OR illegal abortion OR exp imminent abortion OR legal abortion/ OR incomplete abortion OR second trimester abortion OR selective abortion/ OR surgical abortion OR fetus death) AND prophylactic.mp. AND (anti-bacterial agents.mp.OR anti bacterial agents.mp. OR anti bacterial.mp OR antiinfective agent/ OR exp antibiotic agent OR

antibiotic.mp. OR antibiotic therapy OR antibiotic treatment.mp. OR antibiotic agent.mp. OR antibiotic prophylaxis.mp. OR prophylactic antibiotic.mp. OR prophylaxis, antibiotic.mp. AND (clinical trial OR randomized controlled trial OR RCT OR randomization OR randomization OR randomi?ed controlled trial$.tw. OR rct.tw. OR random allocation.tw.OR randomly allocated.tw. OR allocated randomly.tw.OR (allocated adj2 random).tw.

BIOMED Central

(Spontaneous abortion OR miscarriage OR tubal abortion OR recurrent miscarriage OR pregnancy miscarriage OR miscarriage risk OR first trimester miscarriage OR threatened miscarriage OR surgical evacuation of the uterus OR evacuation of retained products of pregnancy OR pregnancy loss OR incomplete miscarriage OR early pregnancy loss OR clinical spontaneous abortion OR complete miscarriage OR missed miscarriage) OR (incomplete abortion OR missed abortion OR septic abortion OR threatened abortion OR embryo loss OR induced abortion OR medical abortion OR recurrent spontaneous abortion OR legal abortion OR therapeutic abortion OR abortion OR termination of pregnancy OR recurrent abortion OR illegal abortion) AND (Sepsis, OR therapy sepsis OR

infection:ab,ti OR bacteremia OR endotoxemia OR hemorrhagic septicaemia OR haemorrhagic septicaemia OR pyrexia OR postoperative infection OR post-operative infection OR post operative infection OR surgical infection OR blood poisoning OR systemic inflammatory response syndrome OR septicaemia) AND prophylactic (anti-bacterial agents OR anti-bacterial OR antibiotic OR antibiotic therapy OR antibiotic treatment) OR prophylaxis OR antibiotic agent OR antibiotic prophylaxis OR prophylactic antibiotic)

Embase

(abortion, spontaneous.mp. OR spontaneous.mp. OR miscarriage.mp. OR abortion, tubal.mp. OR recurrent miscarriage.mp.OR pregnancy miscarriage.mp. OR miscarriage risk.mp. OR first trimester miscarriage.mp. OR threatened miscarriage.mp. OR surgical evacuation of the uterus.mp. OR evacuation of retained products of conception.mp. OR pregnancy loss.mp. OR incomplete miscarriage.mp. OR early pregnancy loss.mp. ORclinical spontaneous abortion.mp.OR complete miscarriage.mp.OR missed miscarriage.mp.) AND (sepsis.mp. OR therapy sepsis.mp.) OR (exp infection OR (infection/ or infection.mp. OR infection rate.mp.) OR (bacteremia.mp) OR (endotoxemia OR hemorrhagic septicemia) OR (fever OR

pyrexia.mp). OR (postoperative infection OR post-operative infection.mp.) OR (surgical infection) OR (blood poisoning.mp. OR bloodstream infection) OR (septicemia.mp. OR blood infection.mp.) AND (abortion, incomplete.mp. OR septic abortion OR abortion, septic.mp. OR septic abortion.mp. OR abortion, threatened.mp.OR embryo death OR embryo loss.mp) OR (induced abortion OR abortion, induced.mp. OR induced abortion.mp. OR spontaneous abortion.mp. OR abortion, missed.mp.OR missed abortion.mp. OR medical abortion OR abortion, medical.mp.OR recurrent spontaneous abortion.mp. OR legal abortion OR abortion, legal.mp. OR eugenic abortion.mp. OR therapeutic abortion OR abortion, therapeutic.mp. OR abortion.mp.OR pregnancy termination OR termination of pregnancy.mp. OR recurrent OR recurrent abortion.mp.OR illegal abortion OR exp imminent abortion OR legal abortion/ OR incomplete abortion OR second trimester abortion OR selective abortion/ OR surgical abortion OR fetus death) AND prophylactic.mp. AND (anti-bacterial agents.mp.OR anti bacterial agents.mp. OR anti bacterial.mp OR antiinfective agent/ OR exp antibiotic agent OR antibiotic.mp. OR antibiotic therapy OR antibiotic treatment.mp. OR antibiotic agent.mp. OR antibiotic prophylaxis.mp. OR prophylactic antibiotic.mp. OR prophylaxis, antibiotic.mp. AND (clinical trial OR randomized controlled trial OR randomised controlled trial OR randomization OR randomization OR randomi?ed controlled trial$.tw. OR rct.tw. OR random allocation.tw.OR randomly allocated.tw. OR allocated randomly.tw.OR (allocated adj2 random).tw.

PsychInfo

(abortion, spontaneous.mp. OR spontaneous.mp. OR miscarriage.mp. OR abortion, tubal.mp. OR recurrent miscarriage.mp.OR pregnancy miscarriage.mp. OR miscarriage risk.mp. OR first trimester miscarriage.mp. OR threatened miscarriage.mp. OR surgical evacuation of the uterus.mp. OR evacuation of retained products of conception.mp. OR pregnancy loss.mp. OR incomplete miscarriage.mp. OR early pregnancy loss.mp. ORclinical spontaneous abortion.mp.OR complete miscarriage.mp.OR missed miscarriage.mp.) AND (sepsis.mp. OR therapy sepsis.mp.) OR (exp infection OR (infection/ or infection.mp. OR infection rate.mp.) OR (bacteremia.mp) OR (endotoxemia OR hemorrhagic septicemia) OR (fever OR pyrexia.mp). OR (postoperative infection OR post-operative infection.mp.) OR (surgical infection) OR (blood poisoning.mp. OR bloodstream infection) OR (septicemia.mp. OR blood infection.mp.) AND (abortion, incomplete.mp. OR septic abortion OR abortion, septic.mp. OR septic abortion.mp. OR abortion, threatened.mp.OR embryo death OR embryo loss.mp) OR

(induced abortion OR abortion, induced.mp. OR induced abortion.mp. OR spontaneous abortion.mp. OR abortion, missed.mp.OR missed abortion.mp. OR medical abortion OR abortion, medical.mp.OR recurrent spontaneous abortion.mp. OR legal abortion OR abortion, legal.mp. OR eugenic abortion.mp. OR therapeutic abortion OR abortion, therapeutic.mp. OR abortion.mp.OR pregnancy termination OR termination of pregnancy.mp. OR recurrent OR recurrent abortion.mp.OR illegal abortion OR exp imminent abortion OR legal abortion/ OR incomplete abortion OR second trimester abortion OR selective abortion/ OR surgical abortion OR fetus death) AND prophylactic.mp. AND (anti-bacterial agents.mp.OR anti bacterial agents.mp. OR anti bacterial.mp OR antiinfective agent/ OR exp antibiotic agent OR antibiotic.mp. OR antibiotic therapy OR antibiotic treatment.mp. OR antibiotic agent.mp. OR antibiotic prophylaxis.mp. OR prophylactic antibiotic.mp. OR prophylaxis, antibiotic.mp.

WPRIM

All:prophylactic or All:anti-bacterial agents or All:anti-bacterial or All:antibiotic or All:antibiotic therapy or All:antibiotic treatment or All:prophylaxis or All:antibiotic prophylaxis or All:prophylactic antibiotic

All:abortion or All:threatened abortion or All:embryo loss or All:missed abortion or All:medical abortion or All:recurrent spontaneous abortion or All:induced abortion or All:termination of pregnancy or All:recurrent abortion or All:illegal abortion or All:imminent abortion or All:legal abortion or All:incomplete abortion or All:second trimester abortion or All:selective abortion or All:septic abortion or All:surgical abortion or All:therapeutic abortion or All:hormonal abortion or All:artifical abortion or All:habitual abortion or All:multiple abortion or All:premature exit of products of conception or All:elective abortion

All:sepsis or All:therapy sepsis or All:infection or All:bacteremia or All:endotoxemia or All:hemorrhagic septicemia or All:pyrexia or All:postoperative infection or All:post-operative infection or All:surgical infection or All:blood poisoning or All:systemic inflammatory response syndrome or All:SIRS or All:blood stream infection or All:bloodstream infection or All:septicemia or All:blood infection

All:spontaneous abortion or All:miscarriage or All:tubal abortion or All:recurrent miscarriage or All:pregnancy miscarriage or All:miscarriage risk or All:first trimester miscarriage or All:threatened miscarriage or All:surgical evacuation of uterus or All:evacuation of retained products of conception or All:pregnancy loss or All:incomplete miscarriage or All:early

pregnancy loss or All:clinical spontaneous abortion or All:complete miscarriage or All:missed miscarriage

IMSEAR

((abstract:abortion) OR (abstract:miscarriage))

AIM

abortion [Key Word] or miscarriage [Key Word]

LILACS

abortion or miscarriage [Words] and sepsis or infection or pyrexia or blood poisoning or septicemia [Words] abortion or miscarriage [Words] and anti-bacterial or antibiotic or prophylaxis [Words]

IMEMR

abortion or miscarriage [KeyWords] and anti-bacterial or antibiotic or prophylaxis [KeyWords] abortion or miscarriage [KeyWords] and sepsis or infection or pyrexia or blood poisoning or septicemia [KeyWords]

PAHO

abortion [Words] or miscarriage [Words]

Appendix 7: Search terms for 'Cell salvage in caesarean section: A systematic review and meta-analysis'

MEDLINE

(cell AND salvage).ti,abOR (blood AND salvage).ti,ab(erythrocyte AND salvage).ti,ab OR (autologous AND transfusion).ti,ab OR autotransfusion.ti,ab AND (c*esarean section).ti,ab OR (obstetric*).ti,ab

CINAHL

(TX cell salvage OR TX blood salvage OR TX cell salver OR TX eythrocyte salvage OR TX autologous transfusion OR TX autotransfusion) AND (TX c*esarean section OR TX obstetric*)

EMBASE

(blood transfusion/ or blood autotransfusion/ or erythrocyte transfusion/ or cell salvage.mp. OR blood salvage.mp. or blood autotransfusion/ or blood salvage/ or blood transfusion/ OR erythrocyte salvage.mp. OR blood autotransfusion/ or autologous transfusion.mp. OR autotransfusion.mp. or blood autotransfusion/ OR cell salver.mp) AND (c*esarean section.mp. OR obstetric*.mp.)

Cochrane library

'cell salvage OR blood salvage OR erythrocyte salvage OR autologous transfusion OR autotransfusion OR cell salver AND c*esarean section OR obstetric* in title abstract keywords'

African Index Medicus

cell salvage [Key Word] or blood salvage [Key Word] or erythrocyte salvage [Key Word] or autologous transfusion [Key Word] or autotransfusion [Key Word] or cell salver [Key Word]

LILACS

cell OR salvage OR or OR blood OR salvage OR or OR erythrocyte OR salvage OR or OR auto logous OR transfusion OR or OR autotransfusion OR or OR cell OR salver

Reproductive Health Library

cell salvage OR blood salvage OR erythrocyte salvage OR autologous transfusion OR autotransfusion OR cell salver AND c*esarean section OR obstetric*

Science Citation Index

TS= cell salvage OR TS= blood salvage OR TS= erythrocyte salvage OR TS= erythrocyte salvage OR TS= autologous transfusion OR TS= autotransfusion OR TS= cell salver AND (TS=c*esarean section OR TS=obstetric*) Databases=SCI-EXPANDED Timespan=All Years

Appendix 8: Search terms for 'Cell salvage in ectopic pregnancy: A systematic review'

MEDLINE

(cell AND salvage).ti,abOR (blood AND salvage).ti,ab(erythrocyte AND salvage).ti,ab OR (autologous AND transfusion).ti,ab OR autotransfusion.ti,ab AND (ectopic AND pregnancy).ti,ab OR (tubal AND pregnancy).ti,ab

CINAHL

(TX cell salvage OR TX blood salvage OR TX cell salver OR TX eythrocyte salvage OR TX autologous transfusion OR TX autotransfusion) AND (TX tubal pregnancy OR TX ectopic pregnancy)

EMBASE

(blood transfusion/ or blood autotransfusion/ or erythrocyte transfusion/ or cell salvage.mp. OR blood salvage.mp. or blood autotransfusion/ or blood salvage/ or blood transfusion/ OR erythrocyte salvage.mp. OR blood autotransfusion/ or autologous transfusion.mp. OR autotransfusion.mp. or blood autotransfusion/ OR cell salver.mp) AND (tubal pregnancy.mp. or uterine tube pregnancy/ OR ectopic pregnancy.mp. or ectopic pregnancy/)

Cochrane library

'cell salvage OR blood salvage OR erythrocyte salvage OR autologous transfusion OR autotransfusion OR cell salver AND ectopic OR tubal pregnancy in title abstract keywords'

African Index Medicus

cell salvage [Key Word] or blood salvage [Key Word] or erythrocyte salvage [Key Word] or autologous transfusion [Key Word] or autotransfusion [Key Word] or cell salver [Key Word]

LILACS

cell OR salvage OR or OR blood OR salvage OR or OR erythrocyte OR salvage OR or OR auto logous OR transfusion OR or OR autotransfusion OR or OR cell OR salver

Reproductive Health Library

cell salvage OR blood salvage OR erythrocyte salvage OR autologous transfusion OR autotransfusion OR cell salver AND ectopic OR tubal pregnancy

Science Citation Index

TS= cell salvage OR TS= blood salvage OR TS= erythrocyte salvage OR TS= erythrocyte salvage OR TS= autologous transfusion OR TS= autotransfusion OR TS= cell salver AND (TS=ectopic OR TS=tubal pregnancy)

Databases=SCI-EXPANDED Timespan=All Years

Appendix 9: Search terms for 'Symphysiotomy for obstructed labour in developing countries, an alternative to caesarean section: A systematic review and meta-analysis.'

PUBMED

"symphysiotomy"[MeSH Terms] OR "symphysiotomy"[All Fields] OR "pubiotomy" [All Fields]

Science Citation Index

Topic=(symphysiotomy) OR Topic=(pubiotomy)

Embase

Symphysiotomy.mp. OR pubiotomy.mp.

CINAHL

"symphysiotomy OR pubiotomy"

COCHRANE collaboration

"symphysiotomy OR pubiotomy"

African Index Medicus

symphysiotomy OR pubiotomy

Reproductive Health Library

symphysiotomy OR pubiotomy

Appendix 10: Search terms for 'Anti-shock garment for obstetric haemorrhage in developing countries: A systematic review and meta-analysis' RHL: Gravity suit OR MAST suit OR Pneumatic suit OR NASG OR PASG OR G-suit OR Anti-shock trouser OR Anti-shock garment

PUBMED

((((((anti-shock[All Fields] AND ("clothing"[MeSH Terms] OR "clothing"[All Fields] OR "garment"[All Fields])) OR ("gravity suits"[MeSH Terms] OR ("gravity"[All Fields] AND "suits"[All Fields]) OR "gravity suits"[All Fields] OR ("anti"[All Fields] AND "shock"[All Fields] AND "trousers"[All Fields]) OR "anti shock trousers"[All Fields])) OR G-suit[All Fields]) OR (anti-gravity[All Fields] AND suit[All Fields])) OR ("gravity suits"[MeSH Terms] OR ("gravity"[All Fields] AND "suits"[All Fields]) OR "gravity suits"[All Fields] OR ("pneumatic"[All Fields] AND "suit"[All Fields]) OR "pneumatic suit"[All Fields])) OR PASG[All Fields]) OR NASG[All Fields] AND obstetric

AMED

AB anti-shock garment OR AB anti shock trousers OR AB G-suit OR AB gravity suit OR AB pneumatic suit OR AB PASG OR AB NASG AND obstetric

CINAHL

AB anti-shock garment OR AB anti shock trousers OR AB G-suit OR AB gravity suit OR AB pneumatic suit OR AB PASG OR AB NASG AND obstetric

Science Citation Index

TS=anti-shock garment OR TS=anti shock trousers OR TS=G-suit OR TS=gravity suit OR TS=pneumatic suit OR TS=PASG OR TS=NASG AND TS=maternal (Databases=SCI-EXPANDED Timespan=All Years) AND obstetric

COCHRANE collaboration

anti-shock garment OR anti-shock trousers OR G-suit OR anti-gravity suit OR pneumatic suit OR PASG OR NASG AND obstetric

Embase

(Gravity suit or MAST suit or Pneumatic suit or NASG or PASG or G-suit or Anti-shock trouser or Anti-shock garment).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] AND obstetric

African Index Medicus

anti-shock garment OR anti shock trousers OR G-suit OR gravity suit OR pneumatic suit OR PASG OR NASG AND obstetric

Appendix 11: Contributions to the chapters of the thesis

Chapter 1: Introduction

Amie Wilson

Chapter 2: Methodology

Amie Wilson

Chapter 3: Strategies that incorporate the training and supporting of traditional birth attendants reduce perinatal and neonatal deaths: A meta-analysis

Amie Wilson: Conception of the systematic review, literature search, study selection, data extraction, quality assessment, data interpretation, discussion

Ioannis Gallos: Literature search, data extraction, quality assessment

Nieves Plana: Data extraction, data analysis

David Lissauer: Data interpretation and discussion, critical input to manuscript

Javier Zamora: Data extraction, data analysis

Khalid Khan: Critical input to manuscript

Christine MacArthur: Critical input to manuscript

Arri Coomarasamy: Study selection, data extraction, data interpretation, discussion

Chapter 4: Effect of women's participatory learning and action groups on neonatal and maternal mortality: A systematic review and meta-analysis

*Amie Wilson: Conducted the sy*stematic review, literature search, quality assessment, data extraction, critical input to published manuscript. This chapter was written by Amie Wilson, it is different to the published manuscript.

Christine MacArthur: Systematic review, literature search, quality assessment, data extraction, critical input to manuscript

Arri Coomarasamy: Systematic review, critical input to manuscript

Nadine Steward: extracted data for the meta-analysis

Audrey Prost: extracted data for the meta-analysis, first draft of the published report (different to the text in this chapter) and collated subsequent inputs.

Tim Colburn: Meta-analysis, meta-regressions, and assessment of publication bias and small-study effects,

Andrew Copas: Advice on meta-analysis, meta-regressions, and assessment of publication bias and small-study effects

Jolene Skordis-Worrall: Comparative cost-effectiveness analysis, wrote the corresponding sections of the report.

Mikey Rosato: Figures

Christina Pagel: Effect for all Countdown countries, appendix

David Osrin: edited final version of the report.

All authors on the manuscript commented on the report and contributed data for the tables.

Chapter 5: Maternal emergency transport in low and middle income countries: a systematic review and thematic synthesis of qualitative studies.

Amie Wilson: Conceived the systematic review, literature search, study selection, data extraction, data analysis and interpretation and discussion, quality assessment of the studies.

Sarah Hillman: Performed the literature search, data extraction, performed data analysis, quality assessment of the studies, assisted with the discussion.

Mikey Rosato: Provided critical input

John Skelton: Provided critical input

Anthony Costello: Provided critical input

Julia Hussein: Provided critical input

Christine MacArthur: Provided critical input

Arri Coomarasamy: Assisted with the systematic review, study selection, provided critical input.

Chapter 6: Can motivational interviews improve contraceptive compliance and reduce unmet contraceptive need in post conflict zones: a systematic review.

Amie Wilson: Conceived the systematic review, literature search, study selection, data extraction, data analysis, data interpretation and discussion, quality assessment of the studies and risk of bias

Krishnarajah Nirantharakumar: Literature search, study selection, data extraction and provided critical input.

Surenthirakumaran Rajendira: quality assessment of the studies.

Christine MacArthur: Provided critical input.

Arri Coomarasamy: Provided critical input.

Chapter 7: A comparison of clinical officers with medical doctors on caesarean section outcomes in the developing world: A meta-analysis of controlled studies

Amie Wilson: Systematic review, literature search, study selection, and data extraction, quality assessment, data analysis, data interpretation

David Lissauer: Systematic review, literature search, study selection, and data extraction, data interpretation, assisted with manuscript

Shakila Thangaratinam: Data analysis, quality assessment, critical feedback on the manuscript

Khalid S Khan: Critical feedback on the manuscript

Christine MacArthur: Critical feedback on the manuscript

Arri Coomarasamy: Systematic review, study selection, data analysis, data interpretation, assisted with manuscript

Chapter 8: Prophylactic antibiotics for uterine evacuation: A systematic review and meta-analysis

Amie Wilson: Systematic review, literature search, study selection, data extraction, data analysis, data interpretation, discussion

Rita Champaneria: Systematic review, literature search, study selection, data extraction, quality assessment

David Lissauer: Data interpretation, discussion

Christine MacArthur: Critical feedback to the manuscript

Arri Coomarasamy: Data analysis, data interpretation, discussion

Chapter 9: Cell salvage in ectopic pregnancy: A systematic review

Amie Wilson: Systematic review, literature search, study selection, data extraction, data analysis, quality assessment, data interpretation, discussion

Hoda Harb: Systematic review, literature search, study selection, data extraction, quality assessment, data interpretation

Christine MacArthur: Critical feedback to manuscript

Arri Coomarasamy: Critical feedback to manuscript

Chapter 10: Cell salvage in caesarean section: A systematic review and meta-analysis

Amie Wilson: Systematic review, literature search, study selection, data extraction, data analysis, quality assessment, data interpretation, discussion

Hoda Harb: Systematic review, literature search, study selection, data extraction, quality assessment

Ioannis Gallos: Data analysis

Christine MacArthur: Critical feedback to manuscript

Arri Coomarasamy: Critical feedback to manuscript, data interpretation

Chapter 11: Symphysiotomy for obstructed labour in developing countries, an alternative to caesarean section: A systematic review and meta-analysis.

Amie Wilson: Systematic review, literature search, study selection, data extraction, data analysis, quality assessment, data interpretation, discussion

Ewa Truchanowicz: Systematic review, literature search, study selection, data extraction, quality assessment

Christine MacArthur: Critical feedback to manuscript

Arri Coomarasamy: Critical feedback to manuscript

Chapter 12: Anti-shock garment for obstetric haemorrhage in developing countries: A systematic review and meta-analysis

Amie Wilson: Systematic review, literature search, study selection, data extraction, data analysis, quality assessment, data interpretation, discussion

Ewa Truchanowicz: Systematic review, literature search, study selection, data extraction, quality assessment

Christine MacArthur: Critical feedback to manuscript

Arri Coomarasamy: Critical feedback to manuscript

Chapter 13: Interpretation

Amie Wilson

Appendix 12: Published manuscript

BMJ

BMJ 2011;343:d7102 doi: 10.1136/bmj.d7102 (Published 1 December 2011)

RESEARCH

Effectiveness of strategies incorporating training and support of traditional birth attendants on perinatal and maternal mortality: meta-analysis

Amie Wilson *doctoral researcher*[1], Ioannis D Gallos *specialist registrar*[1], Nieves Plana *research fellow*[2], David Lissauer *clinical lecturer in obstetrics and gynaecology*[1], Khalid S Khan *professor of women's health and clinical epidemiology*[3], Javier Zamora *professor of biostatistics*[2], Christine MacArthur *professor of maternal and child epidemiology*[4], Arri Coomarasamy *professor of gynaecology and reproductive medicine*[1]

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Abstract

Objective To assess the effectiveness of strategies incorporating training and support of traditional birth attendants on the outcomes of perinatal, neonatal, and maternal death in developing countries.

Design Systematic review with meta-analysis.

Data sources Medline, Embase, the Allied and Complementary Medicine database, British Nursing Index, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, BioMed Central, PsycINFO, Latin American and Caribbean Health Sciences Literature database, African Index Medicus, Web of Science, Reproductive Health Library, and Science Citation Index (from inception to April 2011), without language restrictions. Search terms were "birth attend*", "traditional midwife", "lay birth attendant", "dais", and "comadronas".

Review methods We selected randomised and non-randomised controlled studies with outcomes of perinatal, neonatal, and maternal mortality. Two independent reviewers undertook data extraction. We pooled relative risks separately for the randomised and non-randomised controlled studies, using a random effects model.

Results We identified six cluster randomised controlled trials (n=138 549) and seven non-randomised controlled studies (n=72 225) that investigated strategies incorporating training and support of traditional birth attendants. All six randomised controlled trials found a reduction in adverse perinatal outcomes; our meta-analysis showed significant reductions in perinatal death (relative risk 0.76, 95% confidence interval 0.64 to 0.88, P<0.001; number needed to treat 35, 24 to 70) and neonatal death (0.79, 0.69 to 0.88, P<0.001; 98, 66 to 170). Meta-analysis of the non-randomised studies also showed a significant reduction in perinatal mortality (0.70, 0.57 to 0.84, p<0.001; 48, 32 to 96) and neonatal mortality (0.61, 0.48 to 0.75, P<0.001; 96, 65 to 168). Six studies reported on maternal mortality and our meta-analysis showed a non-significant reduction (three randomised trials, relative risk 0.79, 0.53 to 1.05, P=0.12; three non-randomised studies, 0.80, 0.44 to 1.15, P=0.26).

Conclusion Perinatal and neonatal deaths are significantly reduced with strategies incorporating training and support of traditional birth attendants.

Introduction

Perinatal and maternal mortality rates are high in developing countries, with more than 358 000 mothers[1] and six million babies dying annually.[2] The millennium development goals were set up to encourage improvement in social and economic conditions in the world's poorest countries by 2015. Progress towards achieving goal 4 (reducing child mortality) and goal 5 (improving maternal health) has been uneven.

At present, about 60 million births in developing countries occur outside healthcare facilities.[3] An estimated 52 million births occur without the assistance of a skilled birth attendant.[3] Women often give birth outside of health facilities with the help of a

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Extra material supplied by the author (see http://www.bmj.com/content/343/bmj.d7102?tab=related#webextra)

Web table: Study characteristics

Appendix 13: Published manuscript

BMJ

RESEARCH

A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world: meta-analysis of controlled studies

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ABSTRACT

Objective To review the effectiveness and safety of clinical officers (healthcare providers trained to perform tasks usually undertaken by doctors) carrying out caesarean section in developing countries compared with doctors.

Design Systematic review with meta-analysis.

Data sources Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, BioMed Central, the Reproductive Health Library, and the Science Citation Index (inception-2010) without language restriction.

Study selection Controlled studies.

Data extraction Information was extracted from each selected article on study characteristics, quality, and outcome data. Two independent reviewers extracted data.

Results Six non-randomised controlled studies (16 018 women) evaluated the effectiveness of clinical officers carrying out caesarean section. Meta-analysis found no significant differences between the clinical officers and doctors for maternal death (odds ratio 1.46, 95% confidence interval 0.78 to 2.75; P=0.24) or for perinatal death (1.31, 0.87 to 1.95; P=0.19). The results were heterogeneous, with some studies reporting a higher incidence of both outcomes with clinical officers. Clinical officers were associated with a higher incidence of wound infection (1.58, 1.01 to 2.47; P=0.05) and wound dehiscence (1.89, 1.21 to 2.95; P=0.005). Two studies accounted for confounding factors.

Conclusion Clinical officers and doctors did not differ significantly in key outcomes for caesarean section, but the conclusions are tentative owing to the non-randomised nature of the studies. The increase in wound infection and dehiscence may highlight a particular training need for clinical officers.

INTRODUCTION

Many developing countries have a shortage of trained doctors. Rural areas are particularly affected, as doctors predominantly congregate in urban areas.[1] Various problems have been linked with the depletion in the workforce, including HIV (either because of death, sickness, or fear of exposure to the disease), the migration of trained staff, and the lack of resources and personal income.[1-4]

In some developing countries clinical officers were temporarily posted to alleviate the shortage of medical doctors.[2,5] However, they have now become a more permanent strategy, being described as the "backbone" of healthcare in several settings.[5] Clinical officers have a separate training programme to medical doctors, but their roles include many medical and surgical tasks usually carried out by doctors, such as anaesthesia, diagnosis and treatment of medical conditions, and prescribing. The perceived benefits of using clinical officers compared with doctors are reduced training and employment costs as well as enhanced retention within the local health systems.[3,4,6]

The scope of practice of a clinical officer within obstetrics is often determined by the country in which they work.[2] In 19 out of 47 sub-Saharan African countries, clinical officers are authorised to provide obstetric care, yet in only five countries are they permitted to carry out caesarean sections and other emergency obstetric surgery.[2] Given that caesarean section is the most common major surgical procedure in sub-Saharan Africa[7] and must be delivered in a timely fashion to save a mother's life,[8] clinical officers could potentially play an important part in increasing accessibility and availability of emergency obstetric care, particularly caesarean section. However, uncertainty exists about their role,[1] training, effectiveness, and safety. Given the central role that clinical officers increasingly have in the provision of obstetric care, we systematically reviewed and meta-analysed the effectiveness of clinical officers in caesarean section.

METHODS

We searched databases for relevant literature on clinical officers within obstetrics in the developing world, with particular attention to maternal and perinatal mortality rates and adverse outcomes. We searched Medline, Embase, Cochrane Central Register of

Appendix 14: Published Manuscript

Women's groups practising participatory learning and action to improve maternal and newborn health in low-resource settings: a systematic review and meta-analysis

Audrey Prost, Tim Colbourn, Nadine Seward, Kishwar Azad, Arri Coomarasamy, Andrew Copas, Tanja A J Houweling, Edward Fottrell, Abdul Kuddus, Sonia Lewycka, Christine MacArthur, Dharma Manandhar, Joanna Morrison, Charles Mwansambo, Nirmala Nair, Bejoy Nambiar, David Osrin, Christina Pagel, Tambosi Phiri, Anni-Maria Pulkki-Brännström, Mikey Rosato, Jolene Skordis-Worrall, Naomi Saville, Neena Shah Mare, Bhim Shrestha, Prasanta Tripathy, Amie Wilson, Anthony Costello

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See Comment pages 1693 and e12

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Summary

Background Maternal and neonatal mortality rates remain high in many low-income and middle-income countries. Different approaches for the improvement of birth outcomes have been used in community-based interventions, with heterogeneous effects on survival. We assessed the effects of women's groups practising participatory learning and action, compared with usual care, on birth outcomes in low-resource settings.

Methods We did a systematic review and meta-analysis of randomised controlled trials undertaken in Bangladesh, India, Malawi, and Nepal in which the effects of women's groups practising participatory learning and action were assessed to identify population-level predictors of effect on maternal mortality, neonatal mortality, and stillbirths. We also reviewed the cost-effectiveness of the women's group intervention and estimated its potential effect at scale in Countdown countries.

Findings Seven trials (19 428 births) met the inclusion criteria. Meta-analyses of all trials showed that exposure to women's groups was associated with a 37% reduction in maternal mortality (odds ratio 0·63, 95% CI 0·32–0·94), a 23% reduction in neonatal mortality (0·77, 0·65–0·90), and a 9% non-significant reduction in stillbirths (0·91, 0·79–1·03), with high heterogeneity for maternal (I^2=58·8%, p=0·024) and neonatal results (I^2=64·7%, p=0·009). In the meta-regression analyses, the proportion of pregnant women in groups was linearly associated with reduction in both maternal and neonatal mortality (p=0·026 and p=0·011, respectively). A subgroup analysis of the four studies in which at least 30% of pregnant women participated in groups showed a 55% reduction in maternal mortality (0·45, 0·17–0·73) and a 33% reduction in neonatal mortality (0·67, 0·59–0·74). The intervention was cost effective by WHO standards and could save an estimated 283 000 newborn infants and 41 100 mothers per year if implemented in rural areas of 74 Countdown countries.

Interpretation With the participation of at least a third of pregnant women and adequate population coverage, women's groups practising participatory learning and action are a cost-effective strategy to improve maternal and neonatal survival in low-resource settings.

Funding Wellcome Trust, Ammalife, and National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care for Birmingham and the Black Country programme.

Introduction

Between 1990 and 2010, substantial improvements were noted in maternal and child survival—maternal mortality decreased by 47% and the mortality in children younger than 5 years fell by 37%.[1] However, in 2011, an estimated 273 465 mothers died from complications of pregnancy and childbirth and 2·9 million infants did not survive the first month of life, representing 43% of all deaths in children younger than 5 years.[2,3] Achievement of the Millennium Development Goals 4 and 5 requires a doubling of the reduction in maternal mortality ratio and a renewed focus on neonatal survival.[2] Community-based interventions are crucial for the attainment of these goals.[4]

In a systematic review and meta-analysis of community-based intervention studies, reductions were noted in the neonatal mortality (12 studies, risk ratio 0·76, 95% CI 0·68–0·84), but the evidence of reductions in maternal mortality was inconclusive (ten studies, 0·77, 0·59–1·02).[5] This and other reviews included different approaches to community interventions,[6,7] and the policy implications of their findings are uncertain. One approach involved home visits to counsel mothers, provide newborn care, and facilitate referral.[8,9] Another involved home-based counselling combined with community activities to improve newborn care.[10,11]

A third approach involved women's groups in a four-phase participatory learning and action cycle. Phase 1 was to identify and prioritise problems during pregnancy, delivery, and post partum; phase 2 was to plan and phase 3 implement locally feasible strategies to address the priority problems; phase 4 was to assess their

Appendix 15: Published Manuscript

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REVIEW ARTICLE

A systematic review and thematic synthesis of qualitative studies on maternal emergency transport in low- and middle-income countries

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ABSTRACT

Background: Most maternal deaths are preventable with emergency obstetric care; therefore, ensuring access is essential. There is little focused information on emergency transport of pregnant women. *Objectives:* The literature on emergency transport of pregnant women in low- and middle-income countries (LMICs) was systematically reviewed and synthesized to explore current practices, barriers, and facilitators for transport utilization. *Search strategy:* MEDLINE, EMBASE, BNI, Cochrane Library, CINAHL, African Index Medicus, ASSIA, QUALIDATA, RHL, and Science Citation Index (inception to April 2012) were searched without language restriction. *Selection criteria:* Studies using qualitative methodology and reporting on emergency transportation in LMICs were included. *Data collection and analysis:* Thematic framework and synthesis through examination and translation of common elements were used to analyze and synthesize the data. *Main results:* Twenty-nine articles were included. Eight major themes were identified: time for transport; transport options; geography; local support; autonomy; culture; finance; and ergonomics. Key issues were transport availability; transport speed; terrain; meteorology; support; dependence for decision making; cultural issues; cost; and lack of safe, comfortable positioning during transport. *Conclusion:* Themes should be appreciated within local contexts to illuminate barriers and facilitators. Potential solutions include motorcycle ambulance programs, collaboration with taxi services, community education, subsidies, and vehicle maintenance.

1. Introduction

Transport and health are inextricably linked, with transport services relating to numerous aspects of healthcare. Transport systems ensure attendance of healthcare providers and adequate medical supplies. Numerous reports have suggested mobility and transport as key requirements and determinants for health [1].

In many low-income countries, less than 1% of the population has access to conventional emergency transport (e.g. ambulance) [2]. A shortage of vehicles means that few people have access to transport for work or health purposes, even though transport systems were recognized as a fundamental human need 3 decades ago. For many, access to transport is not within easy reach; in Ethiopia, approximately half of rural households were reported to travel distances greater than 15 km for public transport [3].

Most births in low-income countries occur outside of health facilities [1] and, as most obstetric complications are unpredictable, timely access to emergency care is essential for reducing deaths. Transport has a critical role in achieving Millennium Development Goals 4 and 5 (which include reducing child and maternal mortality, and achieving access to healthcare), targeting the second delay of "reaching care." Research on transport in low- and middle-income countries (LMICs) often relates to pollution or the spread of communicable diseases. There is little focused and rigorously evaluated research on emergency transport of pregnant women [4], as well as limited synthesis and insight [3,4].

The aim of the present systematic review was to examine qualitative literature on maternal emergency transport to explore people's experiences of using transport, the options available, and the barriers and facilitators encountered. There was a focus on qualitative studies to elicit insights on how transport systems work and what might be done to improve the acceptability and availability of different transport modalities, in order to enhance policy and program interventions relating to transport.

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Appendix 16: NGO resource pack

at our mothers' feet

At Our Mothers' Feet is a campaign run by **MADE in Europe** in partnership with **Ammalife** and with the support of **UK aid** from the UK Department for International Development.

The campaign aims to raise awareness of global maternal health issues amongst UK Muslim communities and inspire them to take action to promote better maternal health for all women.

Content developed by
Ammalife - www.ammalife.org
and **MADE in Europe** - www.madeineurope.org.uk

Design by Onetogether.co.uk

NGO Resource Pack

madeineurope.org.uk

TOP 20 GLOBAL MATERNAL HEALTH INTERVENTIONS

at our mothers' feet

AOMF_Resourcepack_32pp_2013.indd 1-2 27/01/2013 21:49

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