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Prostaglandins for preventing postpartum haemorrhage (Review)

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[Intervention Review]

Prostaglandins for preventing postpartum haemorrhage

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ABSTRACT

Background

Prostaglandins have mainly been used for postpartum haemorrhage (PPH) when other measures fail. Misoprostol, a new and inexpensive prostaglandin E1 analogue, has been suggested as an alternative for routine management of the third stage of labour.

Objectives

To assess the effects of prophylactic prostaglandin use in the third stage of labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (7 January 2011). We updated this search on 25 May 2012 and added the results to the awaiting classification section.

Selection criteria

Randomised trials comparing a prostaglandin agent with another uterotonic or no prophylactic uterotonic (nothing or placebo) as part of management of the third stage of labour. The primary outcomes were blood loss 1000 mL or more and the use of additional uterotonics.

Data collection and analysis

Two review authors independently assessed eligibility and trial quality and extracted data.

Main results

We included 72 trials (52,678 women). Oral or sublingual misoprostol compared with placebo is effective in reducing severe PPH (oral: seven trials, 6225 women, not totalled due to significant heterogeneity; sublingual: risk ratio (RR) 0.66; 95% confidence interval (CI) 0.45 to 0.98; one trial, 661 women) and blood transfusion (oral: RR 0.31; 95% CI 0.10 to 0.94; four trials, 3519 women).

Compared with conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH (RR 1.33; 95% CI 1.16 to 1.52; 17 trials, 29,797 women) and use of additional uterotonics, but with a trend to fewer blood transfusions (RR 0.84; 95% CI 0.66 to 1.06; 15 trials; 28,213 women). Additional uterotonic data were not totalled due to heterogeneity. Misoprostol use is associated with significant increases in shivering and a temperature of 38º Celsius compared with both placebo and other uterotonics.

Authors' conclusions

Oral or sublingual misoprostol shows promising results when compared with placebo in reducing blood loss after delivery. The margin of benefit may be affected by whether other components of the management of the third stage of labour are used or not. As side-effects are dose-related, research should be directed towards establishing the lowest effective dose for routine use, and the optimal route of administration.

Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of the management of the third stage of labour especially for low-risk women; however, evidence has been building for the use of oral misoprostol to be effective and safe in areas with low access to facilities and skilled healthcare providers and future research on misoprostol use in the community should focus on implementation issues.

PLAIN LANGUAGE SUMMARY

Prostaglandins for preventing postpartum haemorrhage

An injectable uterotonic is the drug of choice for routine third stage management when the placenta is delivered. Oral or sublingual misoprostol may be used where no injectable uterotonic is available.

After her baby is born, the woman's womb (uterus) contracts and bleeding decreases. If the womb does not contract, postpartum haemorrhage (heavy bleeding) can occur, which can be life threatening. A prostaglandin, oxytocin and ergometrine are all drugs that cause contractions of the womb (uterotonics). This review of 72 randomised controlled trials, involving 52,678 women, found that oral or sublingual prostaglandin (misoprostol) is effective in reducing severe haemorrhage after giving birth and the need for blood transfusions. Misoprostol is not as effective as oxytocin and has more side-effects. The main side-effects are shivering, high temperature and diarrhoea, occurring in a significant proportion of women. Twenty-six of the trials included centres in low- and middle-income countries only. Misoprostol may be useful in places where injectable uterotonics are not available, perhaps because of poor access to skilled healthcare providers. Injectable prostaglandin may be effective in reducing blood loss but has adverse effects of vomiting, abdominal pain and diarrhoea and costs more.

BACKGROUND

Postpartum haemorrhage (PPH) is a major cause of morbidity and mortality during childbirth, especially in low- and middle-income countries. The contribution of PPH to maternal death in low- and middle-income countries is more marked in domiciliary or rural settings where trained staff are scarce, transport facilities are inadequate and the availability of uterotonic agents and blood are limited. According to the latest population-based maternal mortality survey in Ghana, haemorrhage is the main cause, accounting for 24% of the maternal deaths (Ghana 2009).

The third stage of labour is defined as the period from birth of the baby until the delivery of the placenta and its membranes. This stage usually takes less than 10 minutes when active management is used. Active management of the third stage of labour is a term to express the use of uterotonics, early cord clamping and active efforts to deliver the placenta following birth. It is not always clearly defined and universally applied in a standard manner. PPH is usually defined as blood loss of 500 mL or more and severe PPH as 1000 mL or more in the third stage of labour. The 'normal' amount of blood loss is difficult to ascertain because different ways of managing the third stage and assessing the blood loss lead to markedly different amounts.

It has been well demonstrated that active management of the third stage of labour is associated with less blood loss. There seems to be general agreement that if the blood loss exceeds 500 mL close monitoring and additional measures such as administering uterotonics or checking for a cause of bleeding are prudent measures.

Traditionally, oxytocin and ergot preparations have been used as uterotonic agents for PPH prophylaxis mostly as part of active management of the third stage of labour. These agents, although effective in decreasing the blood loss, have the disadvantage of instability in tropical climates (Hogerzeil 1996) and also require the use of syringes and trained personnel for administration. Another disadvantage, mainly related to ergot preparations, is the relatively high incidence of side-effects such as nausea, vomiting and increase in blood pressure.

Prostaglandins have strong uterotonic properties and are used widely in obstetric and gynaecological practice for cervical ripening, together with mifepristone for termination of pregnancy and for induction of labour. Prostaglandin preparations are available in injectable, tablet or gel forms according to their intended use. These agents do not cause hypertension, which enables them to be used in hypertensive patients. In the management of the third stage of labour, prostaglandins have been mainly used for intractable PPH as a last resort when other measures fail. To date, the main disadvantages of prostaglandins have been their cost and availability. Since the mid-1990s, misoprostol, a prostaglandin E1 analogue used orally for the prevention of peptic ulcer disease has also been reported for use in the management of the third stage of labour (El-Refaey 1997). Misoprostol is inexpensive, can be administered orally and is stable at ambient temperatures. There is considerable experience with misoprostol use, both for peptic ulcer disease and as a uterotonic in obstetrics and gynaecology. The main side-effects of prostaglandins are nausea, vomiting and diarrhoea. Shivering and elevated body temperature have been reported with the use of misoprostol in the third stage of labour.

The use of prostaglandins in general, and of misoprostol in particular, could have implications for the efficacy and acceptability of active management of the third stage of labour. The rate and nature of side-effects (nausea, vomiting, diarrhoea, shivering) could influence the immediate relationship between the mother and her baby in the hours following birth.

Active management of the third stage of labour (by use of uterotonics, early cord clamping and active efforts to deliver the placenta) decreases blood loss during the third stage of labour (Begley 2011).

This review is one in a series of reviews evaluating strategies to prevent PPH (Cotter 2001; McDonald 2004) and focuses on the role of prostaglandins in the active management of the third stage of labour.

OBJECTIVES

To determine the effectiveness of prophylactic prostaglandin use compared with placebo or conventional uterotonics as part of the routine management of the third stage of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with a comparison between a prostaglandin and either another uterotonic agent or no uterotonic agent (placebo or nothing) were considered for inclusion in the review. We excluded quasi-random studies.

Types of participants

Women after the birth of their baby were the participants of this review. These women could be at high or low risk for postpartum haemorrhage. The definitions of high risk used by the trialists were accepted in general. These typically included having had a previous postpartum haemorrhage, grand multiparity and multiple pregnancy among others.

Studies including women with caesarean births were eligible.

Types of interventions

In the earlier version of this review we included the use of prostaglandins when used 'as part of active management of the third stage of labour'. Recently, there has been increasing interest in evaluating the individual components of the 'active management' package and at least one trial has evaluated the use of a uterotonic without other components of active management of the third stage of labour. We included the use of a prostaglandin alone within the scope of this review.

The experimental intervention evaluated in this review is the prophylactic use of prostaglandins in the management of the third stage of labour. Prostaglandin preparations are currently available in injectable and tablet forms, therefore different routes may be used and compared either with each other or with conventional injectable uterotonic agents. Different routes of administration are analyzed in separate comparisons.

The choice of routine uterotonic drug used during the third stage of labour varies greatly around the world. In this review,

oxytocin (Syntocinon®), ergometrine-oxytocin (Syntometrine®) and ergometrine are grouped together as 'conventional injectable uterotonics'. In cases where the comparison is made between two different types of conventional uterotonics, oxytocin is selected as the conventional uterotonic as it is the drug used in most of the studies included in this review.

The main categories of prostaglandins evaluated in the review are misoprostol (prostaglandin E1 analogue), which is available in tablets and PGF2alpha and E2 preparations that are administered parenterally for use in the third stage of labour. Misoprostol tablets are administered either orally, sublingually or rectally. Since the absorption of misoprostol from these two routes is currently unknown and likely to be different, these routes have been evaluated separately.

Injection of oxytocin or saline, or both, into the umbilical vein (reviewed elsewhere on retained placenta) and intramyometrial injection of prostaglandins other than at caesarean section (not used for routine active management) were not eligible for inclusion in this review.

The following comparisons have been used in the review:

1. oral misoprostol versus no uterotonic/placebo;
2. oral misoprostol versus injectable (conventional) uterotonics;
3. rectal misoprostol versus no uterotonic/placebo;
4. rectal misoprostol versus injectable uterotonics;
5. rectal misoprostol versus intramuscular prostaglandins;
6. sublingual misoprostol versus no uterotonics/placebo;
7. sublingual misoprostol versus injectable uterotonics;
8. intramuscular prostaglandins versus rectal misoprostol;
9. intramuscular prostaglandin versus no uterotonic/placebo;
10. intramuscular prostaglandin versus injectable uterotonics;
11. comparisons of different prostaglandins or different dose/routes of the same prostaglandin;
12. comparisons of different prostaglandins plus injectable uterotonics versus injectable uterotonics or other prostaglandins.

Types of outcome measures

The primary outcomes of this review are blood loss of 1000 mL or more and the use of additional uterotonics in the third stage of labour. Maternal death is included as an outcome but it is unlikely that the review will have power to evaluate this outcome.

Reported blood loss is influenced by the assessment technique. Measurement of blood and clots in jars and weighing of linen are likely to be more precise than clinical estimation used in some studies. The latter is known to underestimate blood loss (Andolina 1999). Also, the duration of measurement and reporting the amount as 'greater than' or 'greater than or equal to' a certain cut-off level (e.g. 500 or 1000 mL) may affect the total reported amount of blood loss especially when this amount is estimated. This becomes less of a problem for comparison between treatment and control groups when the trials blind their assessment processes.

Primary outcomes

1. Severe postpartum haemorrhage (at least 1000 mL);
2. use of additional uterotonics in the third stage of labour.

Secondary outcomes

1. Postpartum haemorrhage (at least 500 mL);
2. mean blood loss (mL);
3. blood transfusion;
4. manual removal of placenta;
5. duration of third stage (minutes);
6. third stage longer than 30 minutes;
7. any side-effect reported;
8. any side-effect requiring treatment;
9. nausea;
10. vomiting;
11. diarrhoea;
12. headache;
13. abdominal pain;
14. high blood pressure;
15. shivering;
16. severe shivering;
17. pyrexia (at least 38 °C);
18. severe pyrexia (at least 40 °C);
19. other.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (7 January 2011). We updated this search on 25 May 2012 and added the results to the awaiting classification section.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, by consulting the third author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third author. We entered the data into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting bias (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5))

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually-randomised trials. We adjusted their sample sizes and standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We also acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

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

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

In the protocol for this review, we specified that if heterogeneity was significant (i.e. P value less than 0.10 or I^2 greater than 50%), we would not use random-effects right away and we would not total the results due to this heterogeneity. However, we discussed the trials and outcomes individually in the text.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes we used the test proposed by Egger 1997, and for dichotomous outcomes we used the test proposed by Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We would have treated the random-effects summary as the average range of possible treatment effects and discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

If we had used random-effects analyses, we would have presented the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it. Subgroup analyses were restricted to the review's primary outcomes.

We carried out the following subgroup analyses.

1. Prespecified low- and high-risk group pregnancies for studies comparing injectable prostaglandins.
2. Different doses of misoprostol used in the studies.

Data relating to high- and low-risk women were analyzed separately as well as together (totals). Recent trials (mostly misoprostol) focused on a general population of women with vaginal or caesarean section delivery without specifying any risk status. Therefore, the high- and low-risk subgroupings were not used in the misoprostol comparisons. However, if future trials falling into these comparisons specifically study a risk group these subgroups will be added to the list of comparisons.

If a particular (risk) group was not specified, this implied that all women are included in that analysis regardless of their risk status. Studies that did not specify the risk status of women included are put in the low-risk category where such distinctions are made.

In meta-analyses with significant heterogeneity (statistical or visual), we discuss the trials individually (i.e. without totals).

Sensitivity analysis

We did not conduct sensitivity analyses for this update, because all of the larger trials in this systematic review were at low risk of bias.

RESULTS

Description of studies

Fifty-three reports of 34 trials were identified and considered for inclusion in this updated review. Eight trials were excluded (*see* Characteristics of excluded studies table). Altogether, 26 trials were included in this 2011 update and this review now includes a total of 72 trials involving 52,678 women - *see* Characteristics of included studies for details. Of these, 49 evaluated misoprostol, eight studies evaluated misoprostol plus oxytocin and the remainder evaluated injectable and intramuscular prostaglandins (12 PGF2alpha and three PGE2). One trial report remains in Studies awaiting classification (Yuan 2003). Two reports are in the Ongoing studies section. (Twelve additional reports from an updated search in May 2012 have been added to Studies awaiting classification for consideration at the next update.)

Settings

The review includes trials conducted in all continents from both low- to middle-income countries and industrialized countries. Twenty-six trials included centres in low- and middle-income countries only. The WHO 2001 trial was conducted in nine countries in Africa, Asia, Europe and Latin America. The Africa 2011 trial was conducted in South Africa, Nigeria and Uganda. In Africa, 10 countries contributed 20 trials (five in South Africa). Sixteen trials were conducted in India and four trials were conducted in China.

The WHO 2001 trial is the largest trial in the review with 18,530 participants from nine countries. The WHO 1999 trial is a pilot dose-finding trial which preceded the WHO 2001 trial and used the same protocol. Side-effects of misoprostol during the first hour after delivery from the WHO 2001 trial are included in the meta-analyses, but further data describing side-effects in the first 24 hours after delivery were published in a separate article and are described in the results section.

Most trials (68/72) were conducted in hospitals where births were performed by skilled caregivers. Two trials (Gambia 2005; Pakistan 2011) were community-based. In Gambia 2005 traditional birth attendants were trained in trial procedures and blood loss measurement provided the interventions (oral misoprostol and oral ergometrine as placebo). Traditional birth attendants were trained in the management of third stage of labour in the Pakistan 2011 trial and provided 600 mcg oral misoprostol to women delivering in the community. In the Guinea-Bissau 2005 trial, midwives administered sublingual misoprostol or placebo to women delivering at primary care centres. In the India 2006c trial, auxiliary nurse-midwives administered oral misoprostol or placebo tablets to women delivering either at primary care centres (approximately 55%) or at home (approximately 45%).

Management of the third stage of labour

In 48 trials, the third stage was managed actively (at least two of the components of active management described, or specified as 'active'); two trials used 'expectant management' (Holland 1991; India 2006c); 10 trials did not mention management of third stage and three were mixed with components of both active or passive management used. The remaining nine trials included women with caesarean section births and did not report any particular form of management.

Risk status

Four studies specifically studied women who were at high risk for postpartum haemorrhage (PPH) (China 2003b; Egypt 1997; Holland 1995; India 2001b). The participants were classified as high risk if they had a history of PPH or conditions such as multiple pregnancy and grand multiparity.

Mode of delivery

Nine trials included only caesarean section births (India 2006a; Iran 2009; Mexico 2009; Switzerland 2006; Tunisia 2009; United Kingdom 1994; United Kingdom 2001b; USA 1990; USA 2005). There were two trials which included both caesarean sections and vaginal births (China 2003b; Turkey 2010).

Blood loss assessment

The majority of the trials (n = 41) used some form of measurement, some using detailed weighing and hematin-dye techniques. Clinical estimation was used in 25 trials, haemoglobin change or level, or both, was used in three and no method was mentioned in the remaining four trials (Colombia 2002; India 2001b; India 2005a; Mexico 2009). Overall, 11 trials used drapes to assess blood loss (China 2003b; Guinea-Bissau 2005; India 2006c; India 2006f; India 2009d; India 2010; Iran 2009; Jamaica 2009; Tibet 2009; Tunisia 2009; United Kingdom 2001c).

Comparisons

Of the 72 trials included in the review, 36 evaluated misoprostol in doses ranging from 50 mcg to 800 mcg and using oral, sublingual, buccal and rectal routes. Misoprostol was compared with placebo in 11 trials (China 2003a; France 2001; Gambia 2005; Guinea-Bissau 2005; India 2006c; Pakistan 2011; South Africa 1998b; South Africa 1998c; South Africa 1998d; South Africa 2001; Switzerland 1999) and with conventional injectable uterotonics in 25 trials. It should be noted that although Gambia 2005 is grouped under placebo trials, it used oral ergometrine as a placebo. In most of the trials, the uterotonic agent was oxytocin 10 international units (IU) intramuscularly or intravenously. In some trials, the uterotonic group received oxytocin or ergometrine-oxytocin depending on the hospital routine (Australia 1999) or depending on whether the woman was hypertensive or not (United Kingdom 2000).

Some trials had several treatment arms. One of the intramuscular prostaglandin trials (Holland 1991) and two misoprostol trials (France 2001; South Africa 1998d) had three arms, one of which was a placebo control group. The WHO 1999 trial was also a three-arm trial comparing misoprostol 600 mcg, 400 mcg orally and oxytocin 10 IU. The United Kingdom 2003 trial had three arms comparing

oral misoprostol 600 mcg, rectal misoprostol 600 mcg, and rectal misoprostol 400 mcg. The India 2008a trial compared intravenous oxytocin with sublingual misoprostol in doses of 100 mcg and 200 mcg, whereas the India 2009b compared it with sublingual misoprostol in doses of 400 mcg and 600 mcg.

One trial compared oral misoprostol with a Tibetan traditional medicine Zhi Byed 11 (Tibet 2009) and one trial used controlled release PGE2 intravaginal insert (Turkey 2010).

Concurrent routine uterotonic use

Two trials from Turkey had four arms, comparing misoprostol 400 mcg after cord clamp followed by misoprostol 100 mcg at four and eight hours postpartum; the same regimen of misoprostol combined with intravenous oxytocin; intravenous oxytocin only; and intramuscular methyl ergometrine only. For blood loss and other early outcomes assessed before the follow-up doses of misoprostol were given, the dosage is regarded as 400 mcg. The only differences between these two trials were that Turkey 2002 used rectal misoprostol and Turkey 2003 used oral misoprostol. The USA 2004 and USA 2005 trials compared 200 mcg buccal misoprostol with placebo in women delivering vaginally and by caesarean section respectively. All women received 20 IU oxytocin infusion at a rate of 10 mL/minute for 30 minutes and then 125 mL/hour for eight hours. Africa 2011 and Nigeria 2011 both used 400 mcg misoprostol plus oxytocin versus only oxytocin.

The review includes unpublished data from Canada 2005, South Africa 1998d, WHO 1999, United Kingdom 2000, WHO 2001 and India 2008b trials.

Risk of bias in included studies

Figure 1 summarizes the risk of bias analysis for all the studies included in this review. Random sequence generation was considered adequate in 51 studies and unclear in 21 studies. Allocation concealment was considered adequate in 48 studies that used sealed envelopes, opaque containers, or identical numbered boxes containing trial medications. Holland 1995 excluded 15% of the women after randomisation, mostly due to women being randomised despite being ineligible (for augmentation of labour), and Turkey 2003 excluded 12.6% of the women after randomisation secondary to them requiring caesarean sections. There were an unspecified but small number of postrandomisation exclusions in South Africa 1998a. These were due to hypertension being discovered after randomisation, which resulted in the exclusion of some women allocated to ergometrine-oxytocin.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

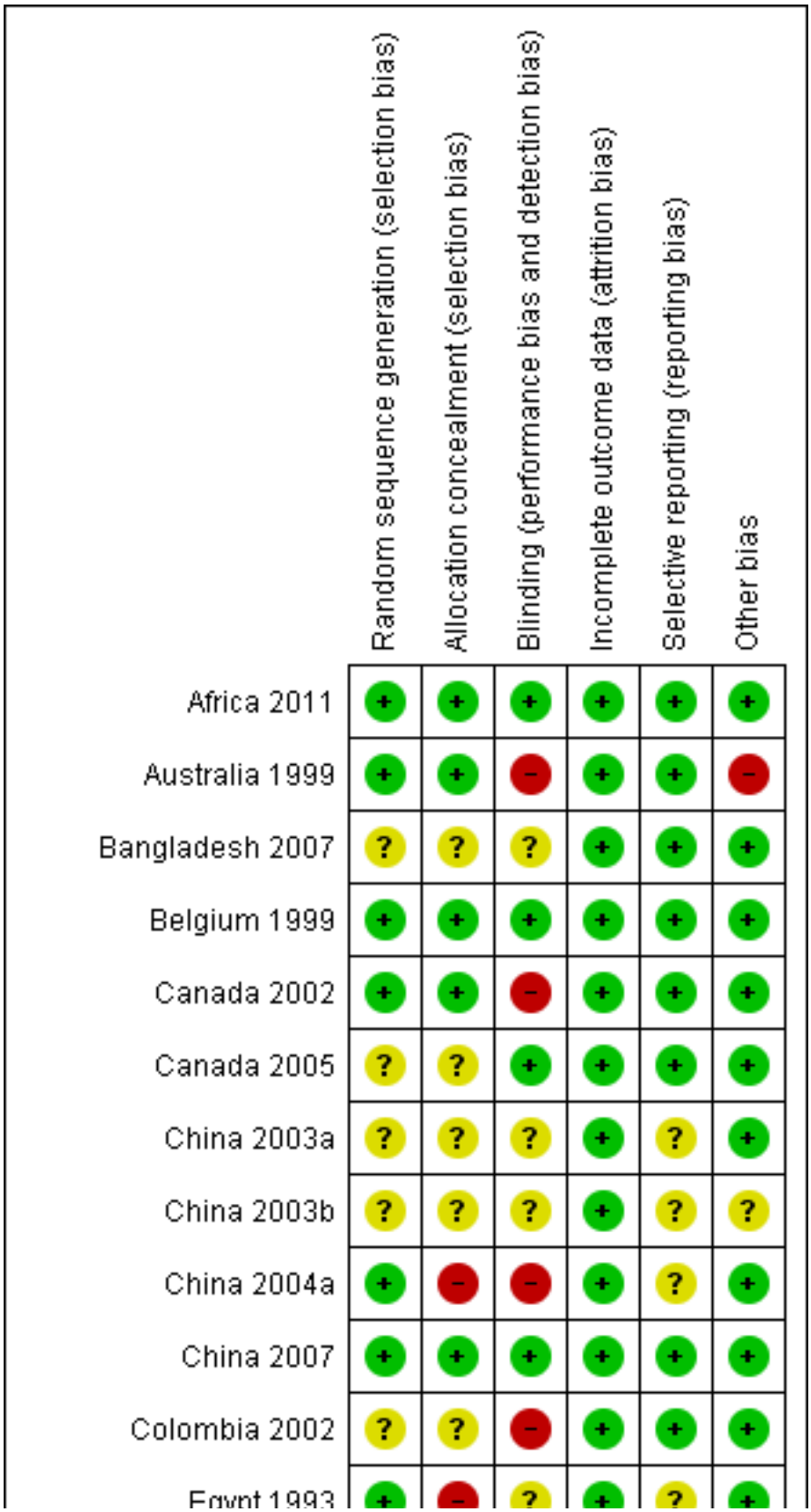
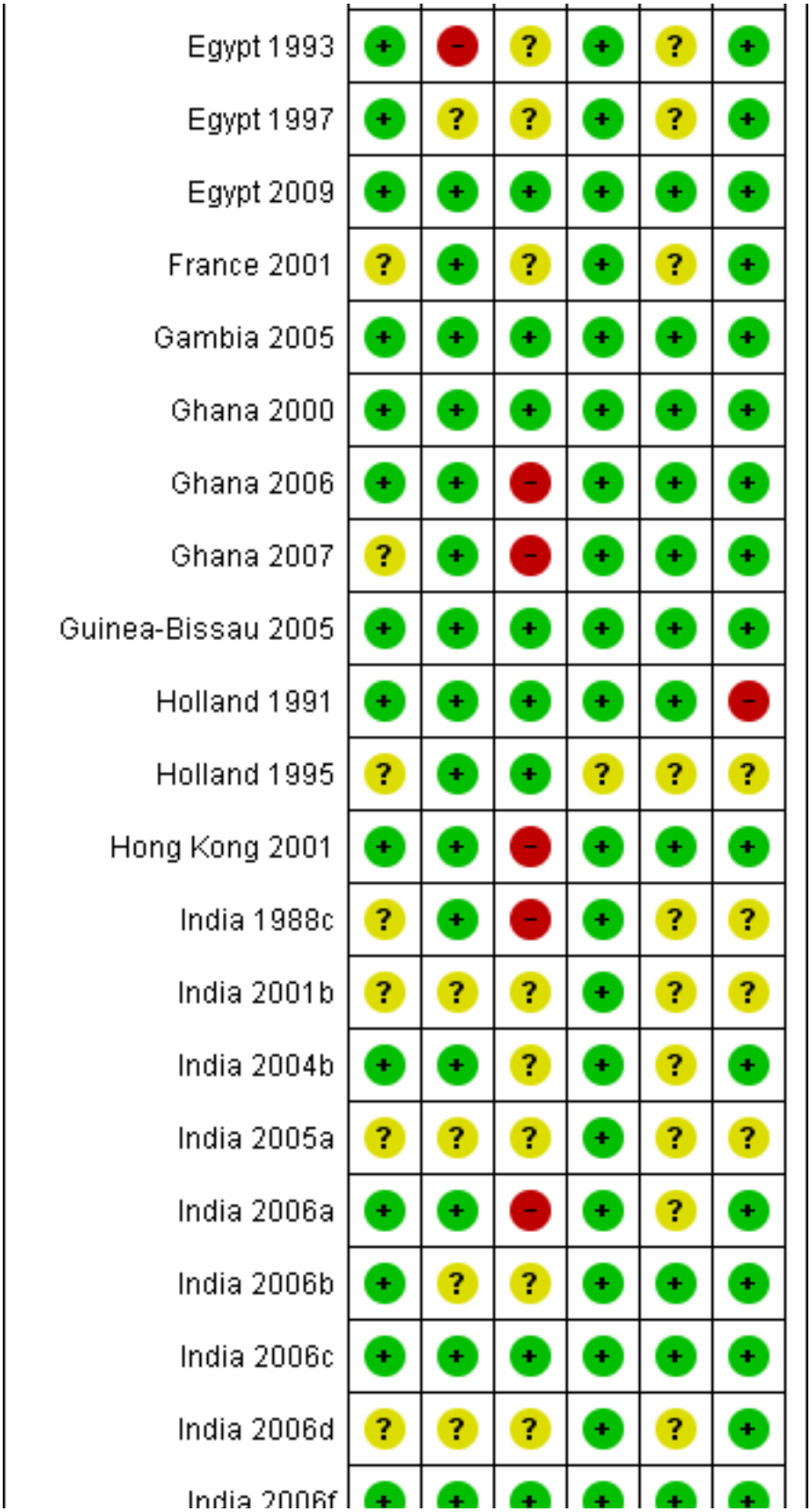


Figure 1. (Continued)



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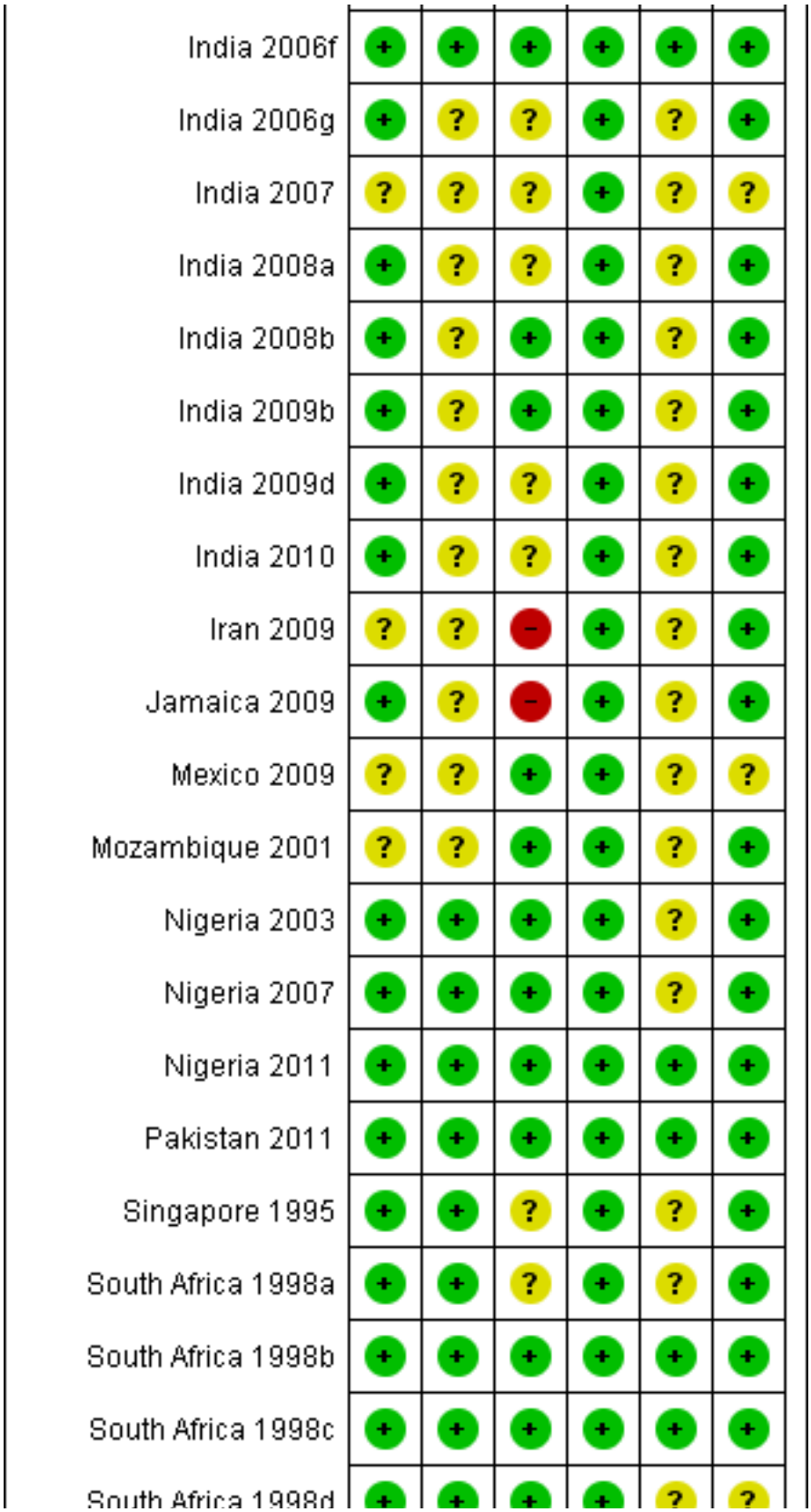
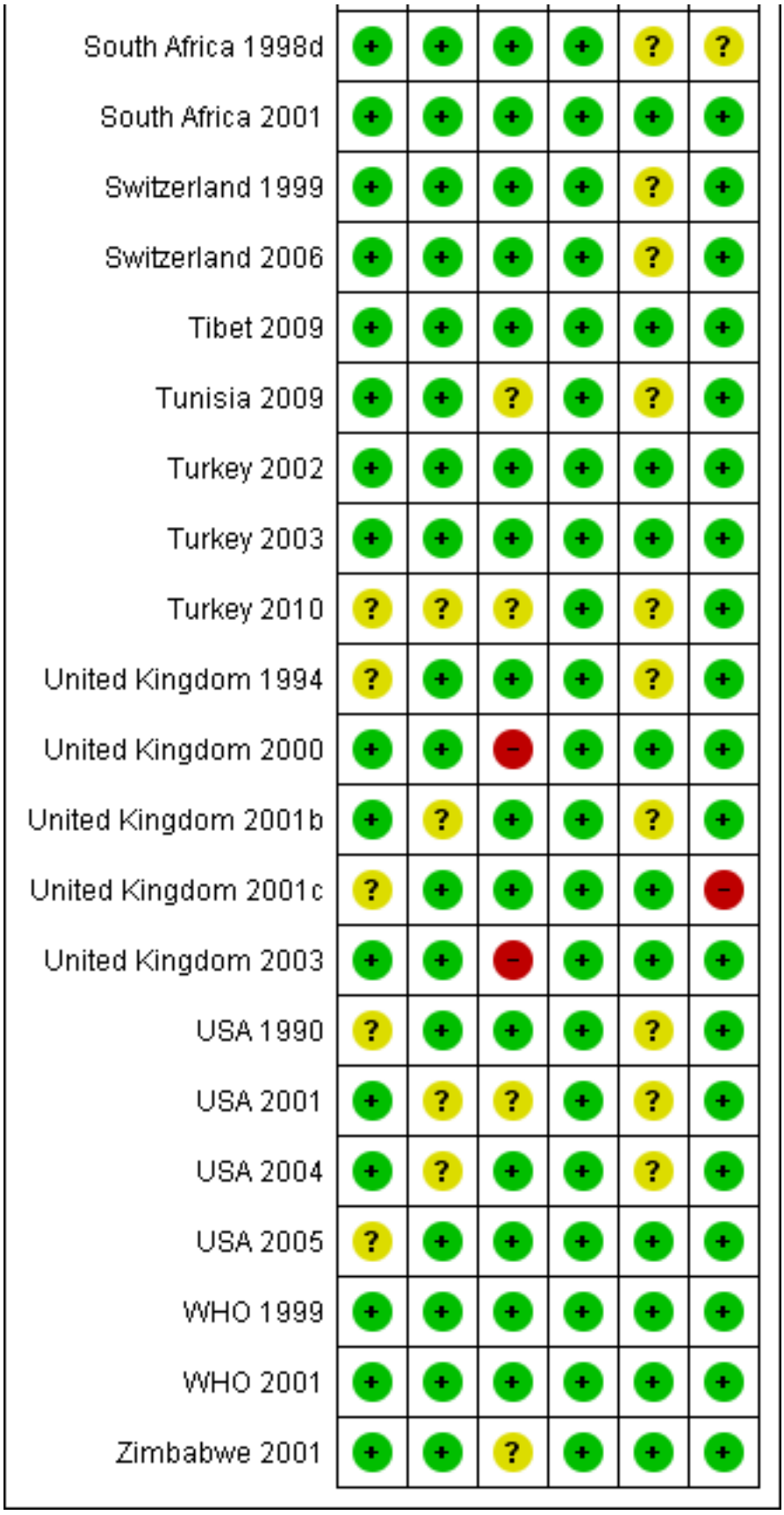


Figure 1. (Continued)



In trials evaluating different interventions in the third stage of labour, PPH is often the primary outcome. Assessment of PPH is prone to bias if the staff making the assessments are not blind to the intervention. In this review, all outcome assessments were blinded in 21 trials. Some outcome assessments were blinded in two trials.

In this review, trials comparing misoprostol with other uterotonics are, in essence, equivalence trials designed to evaluate whether misoprostol is as effective as others given its advantage of oral or rectal route of administration. The majority of such trials have set relatively large margins of equivalence and are therefore, in practical terms, underpowered to test an equivalence hypothesis. The WHO 2001 trial is the largest trial in the review which set an a priori clinical equivalence margin (within 35% efficacy of oxytocin). In this trial the primary outcomes were blood loss greater than or equal to 1000 mL and the use of additional uterotonics. Misoprostol versus placebo or no treatment trials are superiority trials and do not have the problem mentioned above.

The South African trials and the United Kingdom 2001b trial evaluating oral misoprostol used non-identical placebos. The women participating in the South African trials took the medications out of an opaque container with care being taken to conceal the tablets from midwives. Although this method of blinding is not 100% safe, the authors provided the review authors with the information that unblinding was unlikely to occur in the settings in which the trials were conducted. In the United Kingdom 2001b trial, side-effect assessments were blinded.

One study (Holland 1995) was stopped prematurely before reaching a prespecified interim analysis to determine an appropriate sample size. This was due to the manufacturer of the drug issuing a warning about serious cardiovascular side-effects after intramuscular use of sulprostone, a synthetic PGE2 derivative. Another study (Australia 1999), was stopped after recruitment of 863/1862 women following the unsatisfactory results of an interim analysis.

Effects of interventions

The results are based on 37 misoprostol and nine intramuscular prostaglandin trials.

Misoprostol trials

Primary outcomes

Misoprostol versus placebo/no treatment (11 trials, comparisons 01, 02, 03, 04)

Oral misoprostol was used in seven trials (comparison 01: 6225 women total, 5325 in six 600 mcg trials), rectal (comparison 02), sublingual (03) and buccal (04). There were three maternal deaths in misoprostol and one in placebo groups overall in nine trials.

There was significant statistical heterogeneity for the outcome severe postpartum haemorrhage (PPH) in the oral misoprostol versus placebo comparison. Earlier trials (France 2001; South Africa 1998d; South Africa 2001) did not indicate any reduction in severe PPH while the more recent Gambia 2005 (risk ratio (RR) 0.48; 95% confidence interval (CI) 0.09 to 2.59, 2/629 versus 4/599) and India 2006c (RR 0.20; 95% CI 0.04 to 0.91, 2/812 versus 10/808) and Pakistan 2011 (RR 0.57; 95% CI 0.27-1.22, 10/514 versus 19/558) trials suggest some protective effect of misoprostol on severe PPH. The use of additional uterotonics was less when misoprostol was used in four out of six trials but not in the South Africa 1998d trial that had both 600 and 400 mcg treatment arms. As South Africa 1998d is the only study in this comparison suggesting superiority of placebo over oral misoprostol, which is biologically implausible, we re-conducted the analyses excluding this study for the primary outcomes. Oral misoprostol was protective against the use of additional uterotonics (RR 0.87; 95% CI 0.70 to 1.08, five trials, 3585 women) compared with the placebo group. Compared with placebo, oral misoprostol reduced the need for blood transfusions required (RR 0.31; 95% CI 0.10 to 0.94, four trials, 3519 women).

One rectal misoprostol trial South Africa 1998c using 400 mcg did not show a statistically significant difference in severe PPH (RR 0.69; 95% CI 0.35 to 1.37).

The Guinea-Bissau 2005 trial used 600 mcg sublingual misoprostol and showed a statistically significant difference in reducing severe PPH (RR 0.66; 95% CI 0.45 to 0.98, 37/330 versus 56/331).

The USA 2004 and USA 2005 trials used 200 mcg buccal misoprostol in women undergoing vaginal delivery and caesarean section respectively. All women received 20 IU oxytocin infusion in 1 litre of saline. In the USA 2005 trial there were 24/173 versus 22/179 cases of severe PPH in the misoprostol and placebo groups respectively, whereas there were no cases of severe PPH in the USA 2004 trial. In both trials the protocol included oxytocin infusion after delivery of the placenta.

Misoprostol versus conventional injectable uterotonics (39 trials, comparisons 05, 06, 07)

Twenty-one trials compared oral misoprostol (comparison 05), 10 compared rectal (comparison 06) and eight compared sublingual (comparison 07) with injectable uterotonics (oxytocin intramuscular or intravenous, ergometrine, ergometrine + oxytocin). Maternal deaths were reported only in the WHO 2001 trial (2/9264 versus 2/9266) and Ghana 2007 (0/224 versus 1/226). There were no deaths in the Ghana 2006, Canada 2005, Turkey 2002 and WHO 1999 trials. The other trials did not mention whether or not there were any deaths. The funnel plots for the primary outcomes suggest no publication bias (Figure 2; Figure 3).

Figure 2. Funnel plot of comparison: 5 Oral misoprostol versus injectable uterotonics, outcome: 5.2 Severe postpartum haemorrhage (>= 1000 ml).

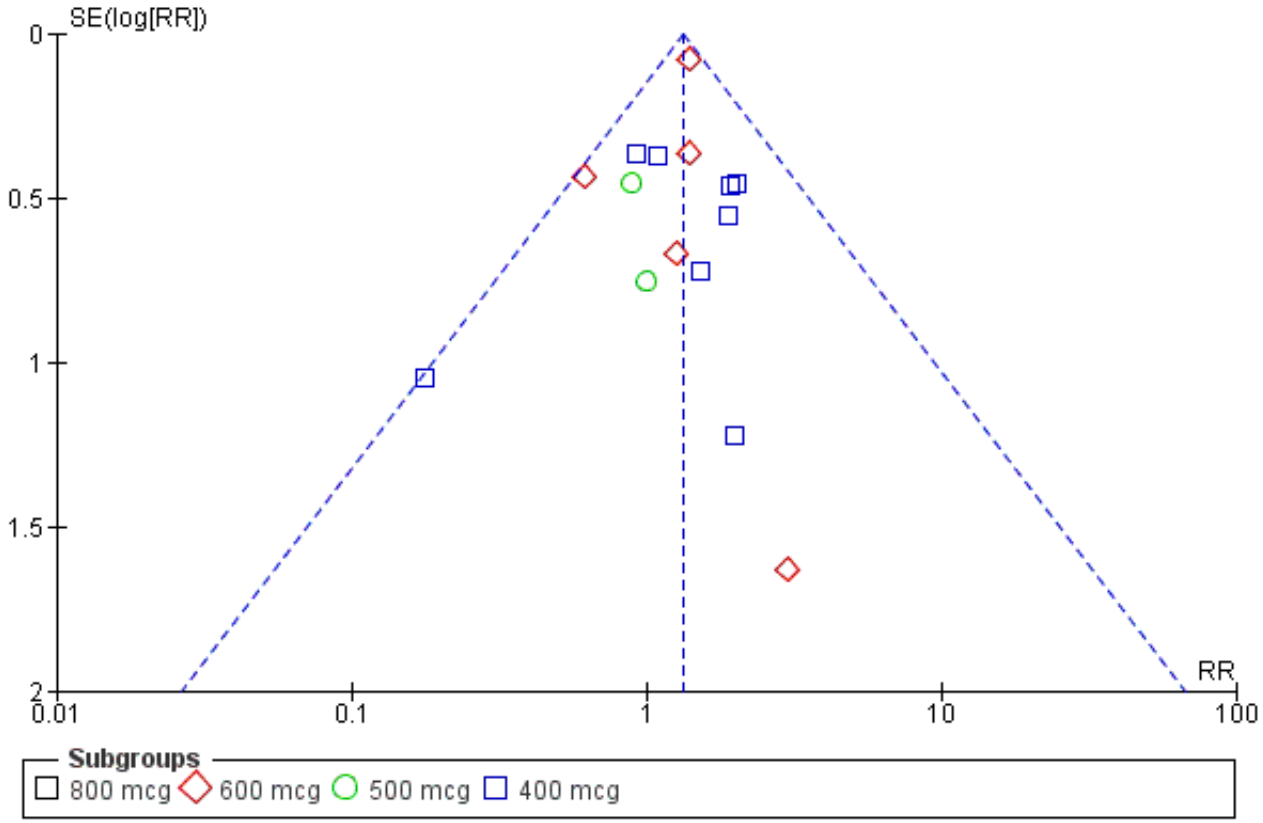
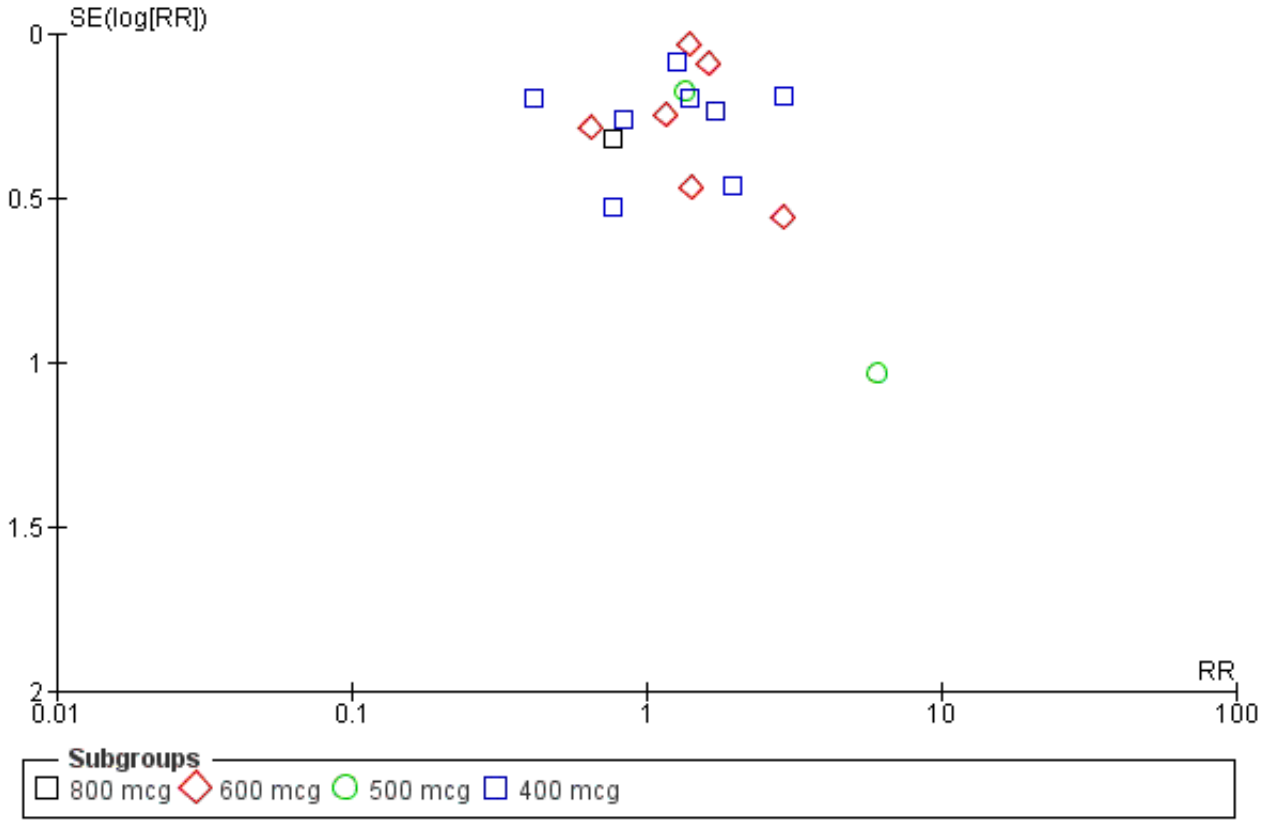


Figure 3. Funnel plot of comparison: 5 Oral misoprostol versus injectable uterotonics, outcome: 5.5 Use of additional uterotonics.



Oral misoprostol was associated with a statistically significant higher risk of severe PPH (RR 1.33; 95% CI 1.16 to 1.52, 17 trials, 29,797 women). While the large WHO 2001 trial results dominated the meta-analysis, the majority of trials showed similar results with no statistically significant heterogeneity across different doses or trials. Although the results were not totalled due significant statistical heterogeneity, overall, the use of additional uterotonics showed a similar trend among different dose groups. There was also a trend towards fewer blood transfusions with misoprostol (RR 0.84; 95% CI 0.66 to 1.06, 15 trials, 28,213 women).

Three 400 mcg rectal misoprostol versus injectables trials reported on severe PPH and there were similar numbers of women with this outcome in the two groups (RR 1.14; 95% CI 0.70 to 1.85, three trials, 1780 women). More women who received misoprostol required additional uterotonics (RR 1.64; 95% CI 1.16 to 2.31). One study using 800 mcg rectal misoprostol (Ghana 2007) reported only one case of severe PPH reported in the control group.

Seven trials compared sublingual misoprostol versus injectables. Use of additional uterotonics reported by all the trials were less likely among misoprostol group compared with injectables (RR 0.61; 95% CI 0.44 to 0.85, seven trials, 1013 women).

Concurrent routine uterotonic use (comparisons 08, 09, 10 and 11)

Oral misoprostol combined with oxytocin were compared with conventional uterotonics in the Africa 2011, Nigeria 2011 and Turkey 2003 trials. Oral misoprostol when combined with oxytocin was more effective than placebo and oxytocin in decreasing PPH (RR 0.71; 95% CI 0.53 to 0.95, three trials, 3205 women) and although not totalled due to heterogeneity, a similar trend can be observed for severe PPH. It should be noted here that for outcomes assessed within four hours, including all blood loss outcomes, the effective dose was 400 mcg in Africa 2011 and Nigeria 2011, whereas Turkey 2003 added 100 mcg to the initial 400 mcg dose after four and eight hours.

The Turkey 2002 trial compared rectal misoprostol and oxytocin, Tunisia 2009 compared sublingual misoprostol and oxytocin with conventional uterotonics in women who had caesarean sections, whereas Mexico 2009 used a combination of intravaginal misoprostol and oxytocin.

Side-effects

Oral misoprostol 600 mcg was consistently associated with higher rates of prostaglandin-related side-effects such as nausea, vomiting, diarrhoea as well as for 'any' shivering, severe shivering and pyrexia (greater than 38 °C) when compared with placebo as well as with conventional uterotonics. Not all of the side-effects were totalled due to heterogeneity under Comparison 5.0, however, in the meta-analyses both severe shivering and diarrhoea were more likely to occur among the misoprostol group participants: RR 7.24; 95% CI 4.74-11.08, five trials, 20823 women and RR: 1.83; 95% CI 1.34-2.50; 13 trials, 27011 women, respectively. For 'any' shivering, the individual trial RRs ranged between 1.43 and 69.10.

Further analysis of side-effects during the first 24 hours in the WHO 2001 trial showed that in comparison to oxytocin, women who received misoprostol had a higher incidence of 'any' shivering (RR 4.70; 95% CI 1.90 to 11.20), and of pyrexia (RR 6.3; 95% CI 3.70 to 10.80) in the period two to six hours after delivery. Diarrhoea was also more common in the misoprostol group in the period two to six hours (RR 21.00; 95% CI 5.10 to 86.50) and seven to 12 hours (RR 7.70; 95% CI 2.30 to 25.40).

The results of three trials (India 2009b; South Africa 1998d; WHO 1999) where 600 mcg and 400 mcg doses of oral misoprostol were compared indicate that side-effects are dose-related (any shivering RR 1.37; 95% CI 1.12 to 1.69) (Analysis 16.14). This might not apply, however, to rectal misoprostol, as there were no significant differences in the one trial (United Kingdom 2003) that evaluated 600 mcg and 400 mcg doses of rectal misoprostol. A comparison of 600 mcg rectal versus 600 mcg oral misoprostol in the same trial showed that rectal misoprostol resulted in less pyrexia, 'any' shivering, and severe shivering (RR 0.27; 95% CI 0.16 to 0.46) (Analysis 18.8) than oral misoprostol. Severe shivering was also observed more frequently among all different doses of misoprostol compared with injectable uterotonics (Analysis 5.19).

Intramuscular prostaglandin trials (comparisons 12, 13, 14, 15)

One trial (Holland 1991) was a three-arm trial with a placebo arm in addition to sulprostone and oxytocin. Thirteen trials compared injectable prostaglandins with conventional injectable uterotonics. The occurrence of primary outcomes such as a blood loss of 1000 mL or more and the use of additional uterotonics were too few to give reliable estimates.

Intramuscular prostaglandins had less mean blood loss when compared with no uterotonic use in the one trial with 46 women (Holland 1991) that examined this outcome (-224 mL mean difference (MD); 95% CI -420.35 to -27.65 mL). Other outcomes evaluated in this study were not statistically significant.

When compared with conventional uterotonics, intramuscular prostaglandins resulted in less blood loss and shorter duration of the third stage of labour (-1.25 minutes MD; 95% CI -1.42 to -1.08 minutes). Blood loss data were not totalled because of heterogeneity due to one small trial having the results in the opposite direction. Five other trials showed less blood loss with injectable prostaglandin.

Vomiting, abdominal pain and diarrhoea were more common with intramuscular prostaglandins.

Intramuscular prostaglandin F2alpha was compared with rectal misoprostol 400 mcg in one small trial with 120 women (India 2006d). There were more women requiring additional uterotonics (2/60 versus 10/60) but the study was too small to give any guiding evidence. Another small trial compared intramyometrial injection of PGF2alpha with intramyometrial oxytocin in women having caesarean section births (USA 1990).

One small study compared two different intramuscular prostaglandins and observed that intramuscular carboprost was less likely to result in PPH (less than 500 mL) but more likely to cause nausea and diarrhoea compared with intramuscular methylergometrine maleate (MEM) (India 2007).

DISCUSSION

This review includes comparisons of intramuscularly, orally, and rectally administered prostaglandins with placebo, and with conventional injectable uterotonics. We did not combine misoprostol with other prostaglandins in the meta-analyses. Misoprostol tablets are used via oral, rectal, sublingual or buccal routes while other prostaglandins are used intramuscularly (or intramyometrial during caesarean section). In terms of outcomes, we gave emphasis to blood loss of at least 1000 mL and the use of additional uterotonics as the most clinically relevant outcomes. We recorded maternal death data systematically but did not anticipate having sufficient power to analyse this outcome.

Misoprostol for PPH prevention in the community: While the results of earlier trials comparing misoprostol (used orally or rectally) with placebo or no treatment were somewhat equivocal, the results of the recent trials are more promising (Gambia 2005; Guinea-Bissau 2005; India 2006c; Pakistan 2011). It is important to note that all four recent trials have design and setting differences that make the summing up of their results difficult. The Gambia 2005 trial had a lower than expected number of events and although the direction of effect favours misoprostol the trial is not powered adequately. In addition, oral ergometrine was assumed to be equivalent to placebo and although the value of oral ergometrine is questionable (WHO 1994), it may not be zero. However, we kept this comparison in the misoprostol versus placebo comparison, because the authors' a priori assumption was that the direction and the pharmacokinetics of oral ergometrine suggests that it is unlikely to be effective. The third stage management was 'active'. This trial is the one of the two trials that used traditional birth attendants to administer the trial interventions. The Guinea-Bissau 2005 trial used sublingual misoprostol within the context of active management and showed greater effect with higher blood loss (i.e. 1000 mL compared to 500 mL). Almost half of the women in this trial (150/330 and 170/331 in the misoprostol and placebo groups) experienced blood loss of 500 mL or more which is unusual in postpartum haemorrhage (PPH) trials with active management. The India 2006c trial used oral misoprostol in the context of 'expectant' management of the third stage of labour. Therefore, its findings are more applicable to settings where this type of third stage management is the norm. It is not known whether with other components of active management being in place the same magnitude of effect would hold or not. The Pakistan 2011 trial used 600 mcg oral misoprostol versus placebo delivered via traditional birth attendants at home births and the third stage management was 'active'. Recent analysis by Hofmeyr et al. using the data from 46 studies included in the earlier version of this review concluded that 400 mcg of misoprostol were found to be safer than doses larger than 600 mcg and just as effective (Hofmeyr 2009).

With the addition of four non-hospital based trials, it is possible to make some inferences for those settings although all four trials have important differences. All four trials were conducted either at home or at primary care centres and it is reassuring to see that there were no major adverse events related to misoprostol use. The Guinea-Bissau, Pakistan and India trials were conducted by caregivers trained in third stage management although only the Guinea-Bissau 2005 had fully qualified midwives.

The addition of several smaller misoprostol versus injectable uterotonic trials confirm the findings of the earlier version of the review. Overall, injectable uterotonics are more effective than misoprostol. Various injectables were used in the included trials. The data with regard to the comparative efficacy of oxytocin 10 international units (IU) versus ergometrine suggest that there are no major advantages of either of them (McDonald 2004). Ergot preparations seem to be somewhat more effective in reducing blood loss but are associated with a higher rate of side-effects and the choice should be made according to the trade-off between the benefit and harm (Carroli 2001).

The results of the large WHO 2001 trial, conducted in nine countries with the participation of 18,530 women, dominate the systematic review's comparison between misoprostol 600 mcg and injectable uterotonics, mostly 10 IU of oxytocin. This comparison demonstrates that oral misoprostol up to 600 mcg is associated with a higher risk of blood loss and the use of additional uterotonics (up to 16% of women will require additional uterotonic treatment) when compared with a policy of injectable uterotonics. There is a consistent increase in all prostaglandin-related side-effects. Considering that the observed rate of side-effects is already high, it is unlikely that higher doses of oral misoprostol (to increase efficacy) could be used for the routine prevention of PPH among healthy women although the Ghana 2006 trial used 800 mcg oral misoprostol.

Although in almost all of the trials these side-effects were reported as not severe, they cause discomfort. For example, women in the WHO 2001 trial rated to have severe shivering needed extra blankets or other comfort measures. Amant reported that women who had shivering had their teeth chattering for 10 to 20 minutes and had no control over their body movements during this period (Amant 2001). On the other hand, in the case of pyrexia (greater than 38 °C), the staff may be concerned for the woman about the risk of postpartum infections and the need for initiating any unnecessary antibiotic treatment. Furthermore, fever may delay blood transfusion.

The largest trial (WHO 2001), used oxytocin both intramuscularly or intravenously. While it is obvious that intravenous injection provides faster availability of the drug, pharmacokinetic data show that with the intramuscular route oxytocin is circulating in the blood within two to three minutes (Gibbens 1972). Furthermore, the pharmacokinetics of oral misoprostol demonstrate that misoprostol acid reaches its peak in the plasma between 20 to 30 minutes after oral administration (Zieman 1997), well after the mean time from delivery until placental expulsion observed in the WHO 2001 (8.3 minutes, standard deviation (SD) 14.6) and Mozambique 2001 (9.0 minutes, SD 3.6) trials. Therefore, we do not think that the route of administration of oxytocin will affect its efficacy.

The nine studies which enrolled women undergoing caesarean section births have been included together with the others in the analysis. The amount of blood loss during and after caesarean section may be different, due to additional bleeding not directly related to the contractility of the uterus and, due to inevitable contamination with other fluids. However, a differential effect between different uterotonics is unlikely. Therefore, a sensitivity analysis according to the mode of delivery was not conducted. The problems associated with measurement of blood loss at caesarean section may, however, obscure any smaller differences in efficacy and push the results towards 'no difference'. In this review, these studies were analyzed within the group of studies that included women at low risk for PPH, when appropriate. Different from the prior version of the review, there are two studies (China 2003b; Turkey 2010) which included both caesarean sections and vaginal births in their study and comparison groups. It should be noted that unlike all the other studies, Turkey 2010 compared a controlled release PGE2 vaginal insert with intravenous oxytocin.

With the data available so far, there do not seem to be major differences between intramuscular prostaglandins and conventional injectable uterotonics (oxytocin or ergometrine) in reducing blood loss in the third stage of labour. These trials had few women who experienced the primary outcomes of this review, although the mean blood loss (a secondary outcome) was reduced by 22 mL to 34 mL on average for women who received intramuscular prostaglandins, based on the dose. Vomiting and diarrhoea were common side-effects with intramuscular prostaglandins. The studies reported, however, that side-effects did not need treatment. The concerns of safety, cost and side-effects are important limitations of intramuscular prostaglandins.

One article (Tibet 2009) compared a traditional Tibetan herbal medicine (ZB11) used for prevention of PPH with oral misoprostol and concluded that misoprostol is more effective in reducing the rates of PPH, however, there were no differences between the two groups in terms of severe PPH and mean blood loss.

Further evidence has been building around the use of oral misoprostol plus injectable uterotonics versus uterotonics. Three trials (Africa 2011; Nigeria 2011; Turkey 2003) have shown that the combination has been more effective in reducing severe PPH compared with uterotonics alone, although side-effects like shivering and fever were more frequent with the combination. Based on the results of these studies, it is important to underline the effectiveness of a dose as low as 400 mcg versus placebo in women who received oxytocin. Given that in settings where oxytocin is available, it will reduce PPH significantly, it is not clear whether routine concurrent use should be a priority.

A WHO systematic review on the cause of maternal deaths identified obstetric haemorrhage as the largest cause of maternal death in Africa and Asia where the majority of maternal deaths occur (Khan 2006). Prevention of PPH with appropriate, evidence-based interventions such as oxytocin and misoprostol when oxytocin is not available could prevent a substantial proportion of deaths in these two regions.

AUTHORS' CONCLUSIONS

Implications for practice

The uterotonic of choice in settings where active management is practiced is oxytocin 10 IU administered intravenously or intramuscularly. Oxytocin retains more than 85% active drug after storage for one year at under 30 °Celsius. Getting oxytocin used as widely as possible should be the primary aim for births occurring outside hospitals at peripheral levels of the healthcare system. If these conditions for oxytocin use cannot be met then misoprostol could be used based on the current evidence. The empirical dosage most used in trials to date is 600 mcg orally. Promising results against placebo have also been reported in individual trials of 400

mcg orally (over and above the routine use of oxytocin) and 600 mcg sublingually.

More efforts should be devoted to making injectable uterotonics available, especially using strategies such as that of disposable prefilled syringes, e.g. Uniject (PATH 2001; Tsu 2009). Developing the skills to administer injections in areas where this is not currently available will have the additional benefit of enabling other effective treatments such as parenteral antibiotics or anticonvulsants to be used. However, recent studies have been promising to show that oral misoprostol use has been effective and safe in community settings with low access to facilities and skilled healthcare providers. These recommendations are in line with the most recent WHO Essential Medicines List which approved misoprostol "for the prevention of PPH in settings where oxytocin is not available or cannot be safely used" (WHO 2011).

Intramuscular prostaglandins are not preferable to conventional uterotonics in the routine management of the third stage of labour especially for low-risk women.

Implications for research

The recent misoprostol versus placebo trials conducted outside hospitals showed promising results and future research on misoprostol use in the community should focus on implementation issues such as giving misoprostol in advance during the antenatal period to women or to traditional birth attendants for use after childbirth or other means of improving access to and safe use of uterotonics in home births. As side-effects are dose-related and life-threatening hyperpyrexia has been reported with 800 mcg orally (Chong 1997), research should be directed towards establishing the lowest effective dose for routine use, and the optimal route of administration.

For the settings in which active management of the third stage is the norm, there is no need for further trials comparing misoprostol with injectable uterotonics. Future research in the third stage of labour could focus on investigating the effectiveness of the particular components of active management.

Intramuscular prostaglandins may be studied for the management of high-risk cases since they are unlikely to find widespread use in low-risk cases due to their costs and side-effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Africa 2011

Methods	Multicentre, randomised, double blind, placebo-controlled trial.
Participants	1099 women without significant obstetric complications expected to give birth vaginally at 6 different hospitals in South Africa, Uganda and Nigeria. Those who delivered via caesarean or had an assisted vaginal birth; those in whom sublingual administration of misoprostol was not possible; those in whom the pregnancy was not viable according to local gestational viability age limits; those who declined, or were too ill or distressed, to give consent; and those not entitled to give informed consent, such as minors were excluded.
Interventions	400 mcg of misoprostol immediately after delivery, in addition to standard active management of the third stage of labour, as currently practiced in the collaborating centres (parenteral oxytocin in Uganda and South Africa, and oxytocin or ergometrine in Nigeria) versus placebo immediately after delivery, in addition to standard active management of the third stage of labour, as currently practiced in the collaborating centres.
Outcomes	The primary outcome was the incidence of 500 mL or more of measured blood loss within 1 hour after the trial medication was administered. Secondary outcomes were the mean measured blood loss 1 hour after the trial medication was administered, a measured blood loss of 1000 mL or more, adverse effects such as shivering (mild and moderate/severe) and pyrexia, manual removal of the placenta, laparotomy, hysterectomy, and maternal morbidity and mortality.
Notes	Active management of third stage labour. Blood collection was started as soon as possible after delivery. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low- profile, plastic bedpan was positioned below the woman's perineum in a position to collect all subsequent blood loss, for a period of 1 hour, measured by a standard clock. The blood collected in the bedpan and any spilled blood, which was collected from the non-absorbent sheet and any blood-soaked small gauze swabs, were transferred to a measuring jar and the volume was measured. Alternatively, the blood was collected into a plastic sheet placed below the woman immediately after delivery.

Africa 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random allocation sequence was generated by using computer-generated random numbers and was stratified by country in blocks of 6-8."
Allocation concealment (selection bias)	Low risk	"The packs were identical in shape, color, weight, and feel, and contained either 2 tablets of 200 mcg of misoprostol or 2 matching placebo tablets."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 people were lost to follow-up due to data not recorded.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were similar in terms of baseline characteristics, except for a 2.8-year difference in mean age.

Australia 1999

Methods	Random allocation from a table of random numbers with sequentially numbered, sealed, opaque envelopes. Block randomisation was utilized. The study was not blinded.
Participants	930 women with vaginal delivery in 4 centres in Australia, China, and Papua New Guinea. Exclusion criteria: coagulation disorders, asthma, severe renal disease, epilepsy, elective caesarean section, severe hypertension.
Interventions	Misoprostol 400 mcg orally vs IM injection of either oxytocin (10 IU) (1 centre) or ergometrine-oxytocin (5 IU oxytocin + 0.5 mg ergometrine) (3 centres).
Outcomes	Blood loss, duration of third stage, use of additional uterotonics, blood transfusion, side-effects, haemoglobin level. Measurement of blood loss: by combining estimated (assessment by clinician) and measured (measuring volume with calibrated measuring jug, and weighing of linen). It is unclear if some centres used 1 or the other method.
Notes	Management of third stage: no mention of third stage management technique. 31/455 (7%) were excluded after randomisation in the misoprostol group, and 36/475 (8%) were excluded after randomisation in the oxytocin/ergometrine-oxytocin group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was by random number list in blocks of 20 with a separate randomization for each center."
Allocation concealment (selection bias)	Low risk	"Sequentially numbered sealed security (opaque) envelopes containing the appropriate drug label were provided for each center."

Australia 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	"Not blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	94 patients were excluded prior to randomisation and 31 patients (6.8%) from the misoprostol arm and 36 patients (7.6%) from the control arm have been excluded after randomisation. The main reasons for exclusion prior to randomisation and following randomisation were the need for caesarean sections and the development of hypertension.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	High risk	This trial was stopped after recruitment of 863/1862 women following the unsatisfactory results of an interim analysis. Patient characteristics prior to treatment showed no differences between the groups.

Bangladesh 2007

Methods	Randomised controlled trial.
Participants	400 labouring women (nulliparous/multiparous) in vertex presentation with no known risk for excessive third stage blood loss. No exclusion criteria were reported.
Interventions	Oral 400 mg misoprostol versus IM 10 IU oxytocin just after cord clamping.
Outcomes	Incidence of postpartum haemorrhage, estimation of average blood loss, the length of the third stage labour, manual removal of placenta, additional oxytocics, blood transfusion and side-effects.
Notes	Active management of third stage labour. Blood loss was estimated on approximate bases by the delivering physician after collecting blood within a plastic bowl.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not clear on how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Not clear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions have been reported.

Bangladesh 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	At randomisation, the 2 groups were well-balanced and comparable for demographic and labour characteristics.

Belgium 1999

Methods	Random allocation from a computer-generated list of study numbers. Randomisation in blocks. Identical numbered study boxes were used. Outcome assessments were blinded.
Participants	213 women with vaginal delivery in Leuven, Belgium. Exclusion criteria: caesarean section, hypertensive disorders, gestational age < 32 weeks, intrauterine death, uterine malformations, allergy to prostaglandins or alkaloids, inflammatory bowel disease, coronary disease, vascular disease, sepsis.
Interventions	Misoprostol 600 mcg orally vs methylergometrine 200 mcg IV. Both oral and IV placebos were used.
Outcomes	Blood loss, need for additional uterotonics, side-effects. Blood loss was estimated.
Notes	Management of third stage: uterine massage, cord traction, manual removal of placenta after 30-60 minutes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study number was taken from a computer-generated list and randomization was in blocks."
Allocation concealment (selection bias)	Low risk	"The study boxes and capsules were indistinguishable in the two groups and both groups receives the full package of active management of the third stage equally."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 5 women (5%) from the misoprostol group and 8 women (7.4%) from the control group were excluded after randomisation due to having a caesarean section.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The demographic characteristics and labour variables are comparable in both groups.

Canada 2002

Methods	Random allocation from a central centre statistician using block randomisation for each participating centre. Consecutively-numbered opaque, sealed packets for allocation concealment. No blinding of treatment or outcome assessments.
Participants	223 women with vaginal delivery from 3 hospitals in Toronto, Canada. Exclusion criteria: parity > 6, gestational age < 32 weeks, clotting disorder, anticoagulant therapy, history of postpartum haemorrhage, previous caesarean delivery.
Interventions	Misoprostol 400 mcg rectally after delivery vs oxytocin 5 IU IV or IM, or 10 IU IM given after delivery (sometimes given after placenta delivered).
Outcomes	Blood loss was captured by measuring change in measured haemoglobin. Other outcomes were duration of third stage, need for additional uterotonics, manual removal of placenta, blood transfusion, side-effects.
Notes	No description of third stage management. 13 women excluded after randomisation secondary to having a caesarean section. 2 women lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The coordinating centre statistician developed blocked randomization tables for each participating centre."
Allocation concealment (selection bias)	Low risk	"consecutively numbered opaque, sealed packets that contained the group allocation and datasheets."
Blinding (performance bias and detection bias) All outcomes	High risk	"the allocation was revealed to the caregivers and the women."
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 women were excluded after randomisation due to having caesarean sections. 2 women were lost to follow-up early in the trial. Analysis of 223 women was on intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	There were no significant differences between the 2 groups.

Canada 2005

Methods	Randomised double blind, no further details. Unclear if outcome assessments were blinded.
Participants	622 women with vaginal delivery at a university hospital in Halifax, Nova Scotia, Canada. Women with multiple pregnancy, placenta previa, abruptio placentae, coagulation abnormalities, caesarean delivery and asthma were excluded.
Interventions	Misoprostol 400 mcg orally after delivery of anterior shoulder vs oxytocin 5 IU IV.
Outcomes	Blood loss measured by haematocrit drop greater than 10%, haemoglobin drop greater than 30%, additional uterotonics, blood loss greater than 1000 mL and 500 mL.

Canada 2005 *(Continued)*

Notes	Third stage management was 'active'. No mention of postrandomisation exclusion or loss to follow-up. The authors attribute the high numbers of additional uterotonic use to most women having IV lines during labour and the threshold for bolus oxytocin administration being low.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of how the sequence generation was created.
Allocation concealment (selection bias)	Unclear risk	No mention of how the concealment occurred.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of postrandomisation exclusion or loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The baseline variables among 2 groups are comparable.

China 2003a

Methods	Randomised controlled trial.
Participants	156 women in labour who gave birth without complications via the birth canal and had no coagulation disorders or contraindications regarding the use of misoprostol.
Interventions	Oral 200 mcg dose of misoprostol immediately after delivery and another 200 mcg after 60 minutes versus no medication (a total of 400 mcg).
Outcomes	Haemorrhage occurrence rate, amount 2 hours after delivery and side-effects.
Notes	No mention of active management of third stage labour. Blood loss was measured based on volume and weight.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias)	Unclear risk	Unclear on blinding.

China 2003a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or postrandomisation exclusions.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	2 groups were comparable.

China 2003b

Methods	Randomised controlled trial.
Participants	137 women with risk factors for postpartum haemorrhage such as placenta previa, polyhydramnios, macrosomia, twin pregnancy and pregnancy-induced hypertension. Control group had 28 women who had caesarean sections. No exclusion criteria specified.
Interventions	400 mcg oral misoprostol versus 20 IU IM oxytocin immediately after the delivery of the baby.
Outcomes	Amount of bleeding after delivery, blood pressure and pulse before and after taking the medication, side-effects.
Notes	AMSTL not mentioned and not applicable to caesarean section patients in the control group. Volume was measured with a blood collection drape until 2 hours after delivery, then poured into a scaled bottle to measure the volume. For caesarean patients, the volume of blood was directly measured in the suction bottle (after putting it aside all the visible amniotic fluid above the cleared blood was discarded and not counted). The weighing method for bleeding 2 hours after delivery used the dressings before and after which were weighed separately. The estimation method used surgical single contaminated blood stain range of 10 cm X 10 cm equals 5 mL blood estimation. The 3 methods mentioned above were added up to be the total amount of blood lost 2 hours after delivery. For 24 hours after delivery a paper pad was used to absorb vaginal bleeding, and then the weighing method was used to calculate the blood loss. Then finally added up the total amount of bleeding 24 hours after delivery.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not clear on how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear on the blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were mentioned.

China 2003b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	General comparison of the 2 groups showed that there was no significant difference in age and gestational week, however, there are 28 caesarean sections in the control group only.

China 2004a

Methods	Open, randomised trial. Randomisation generated by a random-number table. Unclear if outcome assessments were blinded.
Participants	60 low-risk women delivering vaginally in Hong Kong, China.
Interventions	Misoprostol 600 mcg sublingually vs syntometrine IV.
Outcomes	Blood loss, side-effects. Blood loss was both estimated visually and measured using alkaline hematin technique.
Notes	Third stage management was 'active' using early cord clamping and cord traction.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random number-generated table."
Allocation concealment (selection bias)	High risk	Inadequate concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial. Unclear if outcome assessments are blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of postrandomisation exclusion or loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review have been reported.
Other bias	Low risk	Demographic and labour characteristics of the 2 groups are comparable.

China 2007

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	355 women having a singleton pregnancy beyond 34 weeks of gestation, low risk for postpartum haemorrhage and a vaginal delivery. Women were considered low risk for postpartum haemorrhage if the index pregnancy was not complicated by presence of fibroids, polyhydramnios, fetal microsomia or any significant history of antepartum haemorrhage.

China 2007 *(Continued)*

	Exclusion criteria included presence of contraindications for the use of either misoprostol or syntometrine, such as pre-eclampsia, cardiac disease and asthma, and the presence of conditions requiring prophylactic oxytocin after delivery such as multiparity (parity >= 4) or presence of uterine fibroids.
Interventions	400 mcg oral misoprostol versus 2 mL of syntometrine).
Outcomes	Change in Hb levels before and 48 hr after delivery Blood loss, duration of 3rd stage labour, use of additional oxytocics, use of blood transfusion, manual removal of placenta and side-effects (nausea, vomiting, headache, diarrhoea, shivering, pyrexia)
Notes	Active management of third stage of labour. Blood loss was assessed by clinical estimation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"table of computer generated random numbers."
Allocation concealment (selection bias)	Low risk	"All women were asked to swallow the tablets directly from the opaque cup without looking at them."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded, placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 women were excluded from the analysis because of missing postdelivery haemoglobin level, all of them had postpartum blood loss of < 500 mL. Results from 355 women were analyzed on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	Baseline characteristics between the 2 groups are similar.

Colombia 2002

Methods	Method of random allocation not stated. No placebo use or blinding of outcome assessments
Participants	75 women with vaginal delivery in Colombia. Exclusion criteria: asthma, coagulopathy, twins, stillbirth, lacerations, and "amniotic fluid in the blood collection".
Interventions	Misoprostol 50 mcg sublingually after cord clamp vs oxytocin 16 m IU per minute intravenously after cord clamp vs methylergometrine 0.2 mg after placenta delivery.
Outcomes	Blood loss, side-effects, cost. Method of collection or estimation of blood loss not stated.
Notes	Management of third stage: no mention of third stage management technique. No reported postrandomisation exclusions or loss to follow-up. Analysis was based on the total population of 75 women.

Risk of bias

Colombia 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random allocation not stated.
Allocation concealment (selection bias)	Unclear risk	No mention of how the concealment occurred.
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo use or blinding of outcome assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up and postrandomisation exclusions have been reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The characteristics of the 2 groups have been comparable.

Egypt 1993

Methods	Random allocation from a table of random numbers. No mention of blinding or placebo use.
Participants	150 low-risk women after vaginal delivery in Assiut, Egypt. Excluded: labour < 2 hours, prolonged labour (> 24 hours), magnesium sulphate therapy during labour, history of postpartum haemorrhage, chorioamnionitis, multiple pregnancy, antepartum haemorrhage and episiotomy.
Interventions	Carboprost trometamol* 0.250 mg IM vs methylergometrine maleate 0.2 mg IV.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: immediate blood loss was collected in trays and measured. Also, pads were used to collect blood for 4 hours and weighed.
Notes	Management of third stage: reported as active but only uterotonic use is mentioned. No mention of exclusions or missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a table of random numbers."
Allocation concealment (selection bias)	High risk	Inadequate concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding or placebo use.
Incomplete outcome data (attrition bias)	Low risk	No mention of exclusions or missing data.

Egypt 1993 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	There were no significant differences between the 2 groups in age, parity and duration of gestation.

Egypt 1997

Methods	Randomisation using table of random numbers. No mention of blinding or placebo use.
Participants	132 high-risk women after vaginal delivery in Assiut, Egypt. 'High-risk' risk factors included: previous history of postpartum haemorrhage, high parity, uterine overdistention due to multiple pregnancy, polyhydramnios or fetal macrosomia, prolonged labour, placental abnormalities or chorioamnionitis. Exclusion criteria: organic heart disease, bronchial asthma, epilepsy, renal disease, caesarean section, episiotomy.
Interventions	Carboprost trometamol* 250 mcg IM vs methylergonovine maleate 0.4 mg IV, vs oxytocin 10 IU IV.
Outcomes	Blood loss, duration of third stage. Measurement of blood loss - blood collected in trays and measured. Sterile pads were weighed.
Notes	Management of third stage: reported only as active. No report of exclusion after randomisation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"using a table of random numbers."
Allocation concealment (selection bias)	Unclear risk	No mention of how the concealment occurred.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding or placebo use.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No report of exclusion after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review have been reported.
Other bias	Low risk	"There were no statistically significant differences between the three groups in any of the variables mentioned except age."

Egypt 2009

Methods	Double blind, randomised, placebo-controlled trial.
Participants	514 women with spontaneous normal delivery of a live, singleton neonate, and absence of any contraindications for misoprostol or oxytocin use were included. The women were excluded if they delivered by caesarean, had a history of antepartum haemorrhage or bleeding tendency, were diagnosed with hypertensive disorder with pregnancy or had the need for anticoagulants.
Interventions	800 mcg rectal misoprostol versus 5 IU of oxytocin in 5 mL lactated Ringer.
Outcomes	The primary outcome was the number of patients estimated to have postpartum haemorrhage. Secondary outcomes were a haematocrit drop of 10% or more 24 hours postpartum; haemoglobin concentration 24 hours postpartum; changes in systolic and diastolic blood pressure; duration of the third stage of labour; need for manual removal of the placenta and/or blood transfusion; additional uterotonics, and nausea, shivering and fever (≥ 38 C) assessed 1 hour postpartum as the adverse effects of misoprostol.
Notes	Active management of third stage of labour. Estimation of blood loss was not done on a quantitative basis; diagnosis of blood loss greater than 500 mL and the decision to apply further measures to control postpartum blood loss were based on a subjective estimation of blood loss by the obstetrician.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated random allocation system."
Allocation concealment (selection bias)	Low risk	"sealed, opaque, consecutively numbered and coded envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. The randomisation code of data sheets was not broken until completion of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusions reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	2 groups were comparable at baseline.

France 2001

Methods	Randomly drawn envelopes containing the treatment codes. Placebos were not used.
Participants	602 women after vaginal delivery in France. Exclusion criteria: preterm birth (< 32 weeks), antepartum haemorrhage, intrauterine fetal death, uterine scar, caesarean section, multiple pregnancy, pre-eclampsia.

France 2001 *(Continued)*

Interventions	Misoprostol 600 mcg orally vs oxytocin 2.5 IU IV given after cord clamp, vs no uterotonic.
Outcomes	Blood loss, duration of third stage, side-effects. Blood loss was measured.
Notes	Management of the third stage: active with immediate cord clamping.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly drawn envelopes."
Allocation concealment (selection bias)	Low risk	Used opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes have been reported.
Other bias	Low risk	The characteristics of all the groups are comparable.

Gambia 2005

Methods	Randomisation generated by computer, allocation concealment by sealed, opaque envelopes. Power calculation made. Outcome assessments were blinded.
Participants	1229 women delivering vaginally at home by trained birth attendants in rural Gambia.
Interventions	Misoprostol 600 mcg orally vs oral ergometrine 2 mg.
Outcomes	Blood loss, postpartum haemoglobin. Blood loss was measured by collection of blood, pads and linen and weighing until 1 hour after delivery.
Notes	Management of the third stage: controlled cord traction, delayed cord clamping (after cessation of pulsation), early suckling of the breast. No loss to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer randomization codes were generated in blocks of 10."

Gambia 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	"each sequentially numbered opaque sealed treatment packet."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusion after randomisation was reported.
Selective reporting (reporting bias)	Low risk	All of the primary outcomes of the review which can be collected in the community setting were reported.
Other bias	Low risk	"The two groups were similar with regard to baseline characteristics and other factors potentially associated with the primary outcomes, except for men Hb level at last ANC visit."

Ghana 2000

Methods	Randomised, double-blind, controlled trial. Randomisation sequence generated by computer. Allocation by sequentially numbered, opaque packets containing active and placebo medications. The packets and misoprostol solution were prepared by a pharmacist not involved in the trial. Power calculation was based on a difference of drop in haemoglobin concentration (> 0.1 g/dL).
Participants	401 women delivering vaginally at the Korle Bu teaching hospital and its clinics in Accra, Ghana. Women were excluded if they were at risk of postpartum haemorrhage (grand multiparae, multiple gestation, gestation < 32 weeks, gestational hypertension with haemolysis-elevated liver enzymes-low platelets syndrome, hydramnios, previous postpartum haemorrhage, coagulation abnormalities, precipitous labour, chorioamnionitis and oxytocin induction or augmentation of labour.
Interventions	Misoprostol 400 mcg in powdered form orally (in 50 mL of water) and 1 mL IM injection of normal saline (placebo) vs powdered lactose placebo orally (in 50 mL of water) and 1 mL IM injection of 10 IU oxytocin.
Outcomes	Primary outcome: drop in haemoglobin concentration; side-effects. Blood loss measurement: clinical estimation.
Notes	Management of third stage: active with cord traction. The authors mention that they report the data as intention to treat although outcome data are missing for 9/401 women.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using computer generated random numbers."
Allocation concealment (selection bias)	Low risk	"sequentially numbered opaque packet."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo controlled trial.

Ghana 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The outcome data is missing in 9 patients out of 401 women. The analysis was intention-to-treat.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	"There were no significant differences between the two groups with regards to maternal and neonatal demographics."

Ghana 2006

Methods	Random-number scheme generated by computer. Allocation concealment by opening the next sequentially-numbered, sealed, opaque envelope. The study was not blinded. Power calculation is reported.
Participants	450 women delivering vaginally at Holy Family hospital, Techiman, Ghana. Women at both high and low risk for postpartum haemorrhage were included.
Interventions	Misoprostol 800 mcg orally vs oxytocin 10 IU IM.
Outcomes	Primary outcome: change in haemoglobin concentration, other measures of blood loss, side-effects. Blood loss was estimated.
Notes	Management of the third stage: 'active', no further details. No loss to follow-up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random, computer-generated assignment."
Allocation concealment (selection bias)	Low risk	"sequentially numbered, opaque, sealed envelope."
Blinding (performance bias and detection bias) All outcomes	High risk	The study was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was intent-to-treat. No loss to follow-up and exclusion after randomisation was reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	"There was no difference between the groups regarding baseline characteristics or risk factors for postpartum haemorrhage."

Ghana 2007

Methods	Randomised controlled trial.

Ghana 2007 *(Continued)*

Participants	440 women who had advanced labour and delivered vaginally at the 2 district hospitals in the Brong Ahafo region of Ghana were included. Exclusion criteria included any known contraindication to prostaglandin administration (hypersensitivity or medical conditions, including asthma or epilepsy). Women at perceived high risk for postpartum haemorrhage were not excluded, but the factors that increased the risk were recorded on the data sheet. They were as follows: grand multiparity (greater than para 5), multiple gestation, previous postpartum haemorrhage, precipitous labour (less than 3 hours), coagulation abnormality, chorioamnionitis, polyhydramnios, previous caesarean section, and oxytocin induction or augmentation of labour.
Interventions	Rectal misoprostol 800 mcg versus IM 10IU oxytocin with the delivery of the anterior shoulder.
Outcomes	Primary outcome was the change in haemoglobin from before delivery to after delivery. Other outcomes were estimated blood loss, additional uterotonic use, clinical diagnosis of postpartum haemorrhage, blood transfusion and side-effects (nausea, vomiting, shivering and temperature > 37.5 C).
Notes	Active management of the third stage of labour. A subjective estimate of blood loss was recorded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only mentions a "random assignment", not clear on how the sequence generation was done.
Allocation concealment (selection bias)	Low risk	"The next sequentially numbered, opaque, sealed envelope containing a standard data sheet with a random assignment to either the control group (intramuscular oxytocin) or the treatment group (rectal misoprostol) was opened."
Blinding (performance bias and detection bias) All outcomes	High risk	It was not mentioned in the text, however, the different administration methods of the 2 drugs and no use of placebo suggests that there was no blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 women from the oxytocin group and 6 women from the misoprostol group were excluded from the analysis as hey did not have both pre and post delivery Hb concentration essays recorded.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	There was no significant difference between the groups regarding baseline characteristics or risk factors for postpartum haemorrhage.

Guinea-Bissau 2005

Methods	Random-number list used for randomisation scheme. Allocation concealment by sealed, opaque, consecutively-numbered envelopes. Outcome assessments were blinded.
Participants	661 women delivering at a primary care centre in Guinea-Bissau.
Interventions	Misoprostol 600 mcg sublingual vs identical placebo.
Outcomes	Blood loss, side-effects. Blood loss was measured by collecting blood in swabs and absorbent drape and then weighing them.

Guinea-Bissau 2005 *(Continued)*

Notes	Management of the third stage: active with early cord clamping and controlled cord traction. The midwives were trained in these procedures before the start of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a list of random numbers."
Allocation concealment (selection bias)	Low risk	"opaque envelopes were consecutively numbered and filled."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up and exclusion after randomisation have been reported. All the women enrolled were included in the analysis.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	Baseline characteristics were comparable between the 2 groups.

Holland 1991

Methods	Random allocation was by allocating identical numbered boxes containing trial medications. Method of generation of numbers was not stated. Outcome assessments were not blinded. Saline injections were used as placebo.
Participants	74 low-risk women with spontaneous labour and vaginal delivery in Nijmegen and Bergen op Zoom, Holland.
Interventions	Sulprostone** 0.5 mg IM vs oxytocin 5 IU IM vs saline.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood and clots collected in trays, swabs and linen weighed for the first hour after delivery.
Notes	Management of third stage: 'conservatively', cord clamped within 1 minute, women asked to push after signs of separation, no cord traction or fundal pressure. 3/77 excluded (2 because of induction of labour, 1 vacuum delivery). There were more multiparous women with fewer episiotomies in the sulprostone group despite randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization was within each block of 10."
Allocation concealment (selection bias)	Low risk	"allocating identical numbered boxes containing trial medications."

Holland 1991 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded, placebo controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women were excluded due to induction of labour and vacuum extraction.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	High risk	There were more multiparous women with fewer episiotomies in the sulprostone group. To adjust for these factors, the authors used a linear regression model. The trial was stopped after 2 years for organisational reasons.

Holland 1995

Methods	Random allocation to pharmacy coded identical boxes containing trial medications. Outcome assessments were blinded. Placebo use.
Participants	69 women with a history of previous postpartum blood loss of more than 1000 mL were eligible for this trial conducted in Leiden, Holland. Exclusion criteria: coagulation disorders, anticoagulant treatment, fibroids, multiple pregnancy, hypertension and induction of labour were excluded.
Interventions	Sulprostone** 0.5 mg IM at delivery of anterior shoulder + placebo after delivery of placenta vs oxytocin 5 IU IM at delivery of anterior shoulder + methylergometrine 0.2 mg IM after delivery of placenta.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood and clots were collected in trays and linen weighed.
Notes	Management of third stage: fundal pressure while holding lower segment of the uterus after signs of placental detachment. 12/81 (15%) excluded after randomisation and before the intervention. No further exclusions after participation in the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"pharmacy coded boxes."
Allocation concealment (selection bias)	Low risk	Random allocation to pharmacy coded identical boxes containing trial medications.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12/81 (15%) excluded after randomisation and before the intervention. No further exclusions after participation in the trial.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.

Holland 1995 *(Continued)*

Other bias	Unclear risk	No mention of the comparability between groups.

Hong Kong 2001

Methods	Random allocation was by sealed, consecutively-numbered, opaque envelopes. Random allocation scheme was generated by computer. Outcome assessments were not blinded. Power calculation was done.
Participants	2058 women with singleton pregnancies and vaginal delivery in 3 hospitals in Hong Kong participated in the trial. Women with pre-eclampsia, cardiac disease and asthma, conditions requiring prophylactic oxytocin infusion after delivery (uterine fibroids, grand multiparity) were excluded.
Interventions	Misoprostol 600 mcg oral after delivery of the baby, vs oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder.
Outcomes	Blood loss, duration of third stage, delayed haemorrhage, maternal haemoglobin after delivery, side-effects. Shivering was assessed using a visual analogue scale. Blood loss was estimated.
Notes	Management of third stage: controlled cord traction after signs of placental separation. No loss to follow-up or postrandomisation exclusions were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"table of computer-generated blocks of random numbers."
Allocation concealment (selection bias)	Low risk	"sealed consecutively numbered opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessments were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	"There was no significant difference the two groups in terms of their demographic characteristics both within and among the three individual analysis."

India 1988c

Methods	Random allocation by serially numbered, sealed envelopes. There was no placebo use or blinding of outcome assessments.
Participants	300 women in 3 centres in India. No mention of risk status.

India 1988c *(Continued)*

	No note of exclusion criteria.
Interventions	PGF2alpha 0.125 mg IM vs methylergometrine 0.2 mg IV.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: blood was collected in trays for 4 hours postpartum and measured.
Notes	Management of third stage: no mention of the third stage management technique.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated."
Allocation concealment (selection bias)	Low risk	Random allocation by serially numbered, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of any loss to follow-up or exclusions after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	"The age, parity and the incidence of episiotomy were not significantly different between the two groups."

India 2001b

Methods	Randomised trial. No further details. Unclear if outcome assessments were blinded.
Participants	120 women with at least 1 risk factor for atonic haemorrhage at Jawaharial Institute of Medical Education and Research Hospital in Pondicherry, India.
Interventions	Group A: methylergometrine 0.2 mg IV. Group B: oxytocin 10 IU in 10 mL saline into the umbilical cord. Group C: carboprost 0.250 mg IM.
Outcomes	Blood loss, side-effects. Blood loss measurement not mentioned.
Notes	Management of third stage: 'active' with controlled cord traction following signs of separation. No loss to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of sequence generation.

India 2001b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusion after randomisation was mentioned.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	No mention of comparability of the groups.

India 2004b

Methods	Random allocation by sealed, consecutively-numbered envelopes. Unclear if outcome assessments were blinded.
Participants	120 low-risk women at a rural health centre in New Delhi, India.
Interventions	Misoprostol 400 mcg sublingually vs 0.2 mg methylergometrine IV.
Outcomes	Blood loss, side-effects. Blood loss was measured collecting all blood and weighing the linen and swabs.
Notes	Management of the third stage: active with cord traction.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"using a random number table."
Allocation concealment (selection bias)	Low risk	"sequentially numbered sealed opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 2 maternal groups were similar in maternal and neonatal demographics.

India 2005a

Methods	Random allocation, no further details. Unclear if outcome assessments were blinded.
Participants	200 primiparous women with singleton births at Lok Nayak Hospital, New Delhi, India.
Interventions	Misoprostol 600 mcg orally immediately after delivery vs 0.2 mg methylergometrine IV at delivery of anterior shoulder.
Outcomes	Blood loss, side-effects. Blood loss measurement method not mentioned.
Notes	Management of the third stage: early cord clamping but no mention of placental delivery. No mention of missing data or loss to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"1:1 ratio by random number sequence."
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	The information on the comparability of 2 groups were not provided.

India 2006a

Methods	Randomisation by computer-generated random-number list, allocation concealment by opening sealed opaque envelopes. Unclear if outcome assessments were blinded.
Participants	100 women undergoing caesarean section at the All India Institute of Medical Sciences, New Delhi, India. Women with risk factors for postpartum haemorrhage were not eligible.
Interventions	Misoprostol 400 mcg sublingually vs 20 IU oxytocin in 1 litre lactated Ringer's solution at 125 mL/h. All women had spinal anaesthesia.
Outcomes	Blood loss, side-effects. Blood loss measurement: volume of blood in the suction bottle + weighing of blood-soaked linen.
Notes	Management of the third stage: not applicable.

Risk of bias

Bias	Authors' judgement	Support for judgement

India 2006a *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer generated random number."
Allocation concealment (selection bias)	Low risk	"sealed opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	Open-labeled. Unclear if outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals following randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	"There were no significant differences in demographic data in relation to age, parity, gestation, history of previous cesarean section and neonatal birth weight."

India 2006b

Methods	Randomisation achieved by computer-generated numbers. No details regarding allocation concealment available.
Participants	2023 women delivering at the Christian Medical College Hospital, Vellore, India. Women with cardiac disease, bronchial asthma, rhesus factor incompatibility, pregnancy-induced or pregnancy-aggravated hypertension and caesarean delivery were excluded.
Interventions	Misoprostol 400 mcg orally vs oxytocin 10 IU IM versus ergometrine 0.2 mg IV.
Outcomes	Blood loss, haemoglobin levels, side-effects. Blood loss measurement: large plastic bag placed under the buttocks following drainage of amniotic fluid. The blood was then transferred to a measuring jar.
Notes	Management of the third stage: active management.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.

India 2006b *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	Baseline characteristics were similar in all the groups.

India 2006c

Methods	Computer-generated, random-number schedule with a random block list. Random allocation by giving the next of a series of non-distinguishable envelopes containing active or placebo tablets. Identical placebos were used. Outcome assessments were blinded.
Participants	1620 women delivering at home or primary care centre in 4 primary health centre areas of Belgaum District, Karnataka State, India. Women were delivered by ANMs who were trained in the trial procedures and the intervention. 2 sets of midwives were involved in the study. 18 at the beginning and 12 leaving and replaced by 7 new ANMs.
Interventions	Misoprostol 600 mcg orally vs identical placebos.
Outcomes	Blood loss, side-effects. Blood loss measurement: A calibrated blood collection drape placed under the buttocks following delivery. Blood loss was measured after 1 hour and 2 hours.
Notes	Management of the third stage: the ANMs practised expectant management of the third stage of labour apart from the uterotonic in the intervention arm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generation randomization list with a random block size."
Allocation concealment (selection bias)	Low risk	"non-distinguishable envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	"The two groups did not differ across any characteristics."

India 2006d

Methods	Randomised study, no further details presented. Unclear if outcome assessments were blinded.

India 2006d *(Continued)*

Participants	120 low-risk women delivering at the Comprehensive Rural Health Services Project, a rural health centre affiliated with the All India Institute of Medical Sciences, New Delhi, India. Women who received oxytocin during labour, caesarean section delivery, multiple pregnancy and Hb < 8 g/dL were excluded.
Interventions	Misoprostol 400 mcg rectally vs PG-F2alpha 125 mcg IM.
Outcomes	Blood loss. Blood loss measurement: by clinical estimation.
Notes	Management of the third stage: not mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear on how the adequate sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if blinding occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of loss to follow-up or exclusion after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review have been reported.
Other bias	Low risk	"The two treatment groups were similar with respect to demographic and labour characteristics."

India 2006f

Methods	Randomised, placebo-controlled study.
Participants	200 women in spontaneous labour. No exclusion criteria were reported.
Interventions	600 mcg rectal misoprostol versus 10 IU IM oxytocin.
Outcomes	Estimated blood loss (mL), blood loss ≥ 500 mL, change in Hb (g/dL), length of third stage of labour (min), need for additional oxytocic drugs, need for manual removal of placenta and side-effects (shivering, nausea, temperature ≥ 38 C)
Notes	Active management of third stage of labour. Blood loss was measured by using calibrated drapes (BRASSS-V drape) and using preweighted gauzes to clean the perineal tears and episiotomy.

Risk of bias

India 2006f *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated random tables."
Allocation concealment (selection bias)	Low risk	"sealed envelope with a code number was opened when vaginal delivery was imminent."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. The code was not broken until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Low risk	All of the outcomes were reported.
Other bias	Low risk	The 2 groups were similar with regards to baseline characteristics.

India 2006g

Methods	Randomised controlled trial.
Participants	200 women with singleton pregnancy, spontaneous onset of labour at term and vertex presentation admitted in active phase of labour were included. Women with hypertension, cardiac disease, renal disease, gastrointestinal disorders, respiratory disease, endocrinal problems, coagulation disorder, and sensitivity to prostaglandin or methergin were excluded.
Interventions	125 mcg IM PGF2 versus 0.2 mg methergin IV at the time of the anterior shoulder delivery.
Outcomes	Duration of third stage, blood loss, need for additional drugs, retained placenta and side-effects (nausea and vomiting).
Notes	Active management of third stage of labour. Blood loss was estimated by blood and blood clots collected in the kidney tray.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number tables."
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear on if the blinding occurred.

India 2006g *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up and exclusions after randomisation were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were well matched in the baseline.

India 2007

Methods	Randomised controlled trial.
Participants	100 women aged 18-32 years of age, gravida 1-3 with singleton pregnancy and vertex presentation delivered normally. Women with heart disease, renal or hepatic disorder, previous caesarean section delivery and severe hypertension.
Interventions	Intramuscular 125 mcg carboprost tromethamine at the delivery of the anterior shoulder versus IM 0.2 mg methylergometrine after expulsion of the placenta.
Outcomes	Postpartum haemorrhage (more than 500 mL), amount of blood loss (mL), duration of the third stage of labour (minutes), requiring blood transfusion and other uterotonics and side-effects (high blood pressure, nausea, vomiting, diarrhoea, pyrexia).
Notes	It is not clear whether all the components of AMTSL other than the uterotonics have been used in this study. The blood loss has been estimated by weighing the blood clots and vaginal pads before and after use following delivery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if the blinding was done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	The authors mention that the groups were comparable in terms of gravida, but no other baseline characteristics are mentioned.

India 2008a

Methods	Randomised controlled trial (2 arms of misoprostol and 1 arm of methylergometrine).
Participants	300 women with term gestation and spontaneous onset of labour (low-risk, as identified by the authors) Exclusion criteria included grand multiparity (parity > 5), multiple gestation, pregnancy-induced hypertension, antepartum haemorrhage, labour induction or augmentation, caesarean delivery (past/present), haemoglobin concentration of < 8 gm/dL or other obstetric problems and known hypersensitivity to prostaglandins.
Interventions	With the delivery of the anterior shoulder of the baby, women in group I received 100 mcg (1 tablet) of sublingual misoprostol, while the women in group II received 200 mcg (2 tablets) versus group III received a 200-mcg IV injection of methylergometrine with the delivery of the anterior shoulder of the baby.
Outcomes	The need for additional oxytocic drugs (If the blood exceeded 100 mL, an additional oxytocic was administered), blood loss ≥ 500 mL, change in haemoglobin levels and side-effects (shivering, recorded temperature > 38 C, nausea, vomiting, headache, giddiness).
Notes	Unclear whether all the components of active management of labour was performed other than the uterotonics. Blood loss was estimated by measuring blood and blood clots collected in sponges.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using random number tables."
Allocation concealment (selection bias)	Unclear risk	Not clear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear if the blinding occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or postrandomisation exclusions were mentioned.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 3 groups were similar in maternal and neonatal demographic profile and haemoglobin concentration at admission.

India 2008b

Methods	Randomised controlled trial.
Participants	215 parturients who were at term(≥ 37 to < 41 weeks of gestation), with singleton pregnancy in cephalic presentation and vertex as presenting part, having haemoglobin concentration of at least 10g/dL.

India 2008b *(Continued)*

	Parturients with active renal or hepatic disease, bronchial asthma, parity > 4 and bleeding disorders were excluded.
Interventions	Intramuscular carboprost tromethamine (0.5 mL containing125 mcg) versus intravenous methyl ergometrine (0.5 mL containing 200 mcg), both at the time of the delivery of the anterior shoulder.
Outcomes	Duration of third stage of labour, measured blood loss, side-effects (hypertension and diarrhoea).
Notes	Active management of third stage labour. Amount of blood loss was quantified by noting the increment in weight of standardized tampons, which were placed high up in the vagina immediately after placental delivery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation, using odd numbers for the control group and even numbers for the intervention group.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Partial blinding. The patient was blinded to the kind of intervention but the clinician and outcome assessor knew. This could not be hidden as the clinician could tell which oxytocic was being given from the mode of administration-ie intravenous for methyl ergometrine and intramuscular for carboprost
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or postrandomisation exclusions are reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	Both groups were similar with regard to age distribution, parity and gestational age.

India 2009b

Methods	Randomised, double-blind, placebo-controlled trial (2 arms of misoprostol and 1 arm of oxytocin).
Participants	300 women with healthy singleton pregnancies in spontaneous or induced labour at term were included. Exclusion criteria included known hypersensitivity/contraindication to prostaglandins, intrauterine fetal demise, antepartum haemorrhage, multiple pregnancy, malpresentation, cardiac disease, Rhesus-negative mother, hypertensive disorders, and severe anaemia (haemoglobin < 7 g/dL).
Interventions	400 mcg sublingual misoprostol, 600 mcg sublingual misoprostol versus 5 IU IV oxytocin.
Outcomes	Blood loss during the 3rd and 4th stage of labour, duration of 3rd stage of labour, need for additional oxytocics, need for blood transfusion and adverse effects of the drugs.
Notes	Active management of third stage of labour

India 2009b *(Continued)*

	1 hour after delivery, the preweighted, blood-soaked linen-saver sheet and preweighted sanitary pads were weighted to assess maternal blood loss.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	Baseline demographic and clinical characteristics of patients were similar among the groups.

India 2009d

Methods	Randomised controlled trial.
Participants	200 pregnant women at ≥ 32 weeks of gestation with either spontaneous or induced labour (what authors identified as low-risk) were included. Exclusion criteria included grandmultipara (≥ 5), multiple gestation, < 32 weeks of gestation, HELLP syndrome, hydramnios, known blood coagulation disorders, history of asthma or drug allergy, heart disease, severe renal disease, epilepsy, hypertension and haemoglobin concentration < 8 g%.
Interventions	400 mcg sublingual misoprostol versus 0.2 mg IM methylergometrine
Outcomes	Primary outcome measures were amount of blood loss in third stage of labour, postpartum haemorrhage (blood loss greater than 500 mL). Secondary outcome measures were change in haemoglobin concentration, need for additional oxytocic and side-effects (nausea, temperature ≥ 38 C, shivering, pain in the abdomen and diarrhoea).
Notes	Active management of third stage of labour. Blood loss was estimated by measuring blood collected in the BRASS-V drape, up to 1 hour after delivery of the baby, and blood soaked in gauze pieces. Blood loss in gauze pieces was calculated by subtracting weight of dry gauze from the weight of blood-soaked gauze pieces.

Risk of bias

Bias	Authors' judgement	Support for judgement

India 2009d *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated random number."
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusion postrandomisation were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	Demographic variables were equally distributed in the groups.

India 2010

Methods	Randomised controlled trial.
Participants	200 women with singleton pregnancies, spontaneous onset of labour at term and vertex position admitted in active phase of labour were included. Exclusion criteria included hypertension, cardiac disease, renal disease, gastrointestinal disorders, respiratory disease, endocrinal problems, coagulation disorder and sensitivity to prostaglandins.
Interventions	IM 125 mcg PGF2α versus IV 0.2 mg of methergin at the time of the delivery of the anterior shoulder.
Outcomes	The interval between injection and expulsion of the placenta, amount of blood loss, third stage complications, side-effects and need for second injection of additional drug.
Notes	Active management of third stage of labour Blood loss was estimated by blood and blood clots collected in the kidney tray and adding the difference in the weight of the drapes before use and after delivery.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"using random tables."
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear on the blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.

India 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were well matched in terms of gravidity, parity and age.

Iran 2009

Methods	Open-label randomised controlled trial.
Participants	100 term pregnant women between 37 and 40 weeks of pregnancy who were candidates for caesarean and underwent general anaesthesia were included. Exclusion criteria included an additional risk for postcaesarean haemorrhage, including: multiple gestation; prolonged labour of more than 12 hours; 2 or more previous caesarean sections; a history of uterine rupture and anaemia-Hb (8 mg/dL). Also women who had a history of heart, renal or liver disorders or had a coagulopathy were excluded.
Interventions	Immediately after delivery, 2 misoprostol tablets (200 mcg) dissolved in 5 cc of distilled water (for better distribution and absorption) and taken sublingually (vs 20 units of oxytocin in 1 litre Ringer lactate at the rate of 10 cc/min was used until full contraction of the uterus).
Outcomes	The need for additional oxytocin in surgery, the volume of infusion, need for blood transfusion, drug side-effects (such as tachycardia, decrease in blood pressure, fever, shivering, headache and metallic taste) or any other significant complications were recorded.
Notes	AMTSL not applicable, as this study includes women who had caesarean section only. The blood loss was measured in the suction bottle so that amniotic fluid was first suctioned and measured and then subtracted from the total volume of the suction bottle. The amount of blood on the patients' drapes and pads was measured by weighing them and then subtracting their known dry weight and this value was added to the amount of blood in the suction bottle.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	High risk	This was an open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusions were mentioned.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	"There were no significant differences in demographic data between the 2 groups in relation to age, weight, gestational age and parity."

Jamaica 2009

Methods	Open-label randomised controlled trial.
Participants	140 women delivering at the labour ward at the hospital during the 6-month period were included. Exclusion criteria included previous postpartum haemorrhage, hypertensive disorders, previous caesarean section, intrauterine death in current pregnancy, sepsis/pyrexia ≥ 38 C), antepartum haemorrhage, symptomatic anaemia or haemoglobin below 8 gr/dL.
Interventions	Rectally administered 400 mcg misoprostol versus IM syntometrine in the AMTSL.
Outcomes	Main outcome parameter was measured blood loss up to 1 hour postdelivery. Secondary outcome measures included the proportion of participants with postpartum haemorrhage, the proportion of women who need additional uterotonic agents and incidence of adverse events (shivering, nausea, vomiting).
Notes	Active management of third stage labour. Blood loss was measured by the use of a modified plastic collection drape.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated block randomisation."
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	High risk	Open label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	"The clinical characteristics of the sample showed no difference in the variables measured between the two treatment groups."

Mexico 2009

Methods	Randomis double-blind study.
Participants	200 patients requiring caesarean section with single or multiple pregnancy and not presenting placenta previa, blood dyscrasia or myomatosis. Patients with obstetrical haemorrhage caused by uterine lacerations and those who did not want to participate in the study were excluded.

Mexico 2009 *(Continued)*

Interventions	Misoprostol (800 mcg) intravaginally versus placebo (Manogen-sorbitol with aerosol) Both groups received oxytocin after the birth of the baby.
Outcomes	Hb and Hct levels before and after labour and the difference and side-effects (pain, fever, shivers, nausea, vomiting, average systolic and diastolic blood pressure before and after caesarean section) were measured.
Notes	AMTSL not applicable, as the study includes caesarean sections. Measurement of blood loss was not mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. The tablets were placed in 200 separate envelopes and assigned a number that was chosen randomly. The content of the envelopes were not revealed until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up and postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Unclear risk	Not clear on the comparability of the groups at the baseline.

Mozambique 2001

Methods	Randomised double-blind trial. Generation of allocation sequence unclear. Double placebos prepared by a pharmacist independent of the trial on a daily basis and provided to the investigators upon request. Outcome assessments were blinded.
Participants	663 women with uncomplicated vaginal delivery between 30 and 42 weeks of gestation at Central Hospital of Maputo, Mozambique. Women undergoing induction or augmentation of labour were excluded.
Interventions	Misoprostol 400 mcg dissolved in 5 mL saline and administered rectally as a micro-enema + 1 mL saline placebo IM versus oxytocin 10 IU administered IM + 5 mL saline micro-enema (placebo).
Outcomes	Blood loss, side-effects. Blood loss measured by a metal collector placed under the buttocks after delivery until the woman was moved from the delivery room.
Notes	Management of third stage not described. 26/350 (7.4%) in the misoprostol group and 11/350 (3.1%) in the oxytocin group were excluded after randomisation because of emergency caesarean section or incomplete data collection.

Risk of bias

Mozambique 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear on how the adequate sequence generation was done.
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. Outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 women in the misoprostol group and 11 women in the oxytocin group were excluded after randomisation due to having emergency caesarean section or incomplete data collection.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were similar in baseline characteristics.

Nigeria 2003

Methods	Randomised double-blind trial with identical looking double placebos. Randomisation schedule generated using random-number tables. Allocation concealment achieved by using sealed opaque packets containing both active and the corresponding placebo medication.
Participants	496 low-risk women having vaginal births in 2 hospitals in Delta State, Nigeria. Women undergoing caesarean section and who had other risk factors for haemorrhage were excluded.
Interventions	Misoprostol 600 mcg in powder form dissolved in 50 mL water per os vs oxytocin 10 IU IM at delivery of anterior shoulder.
Outcomes	Blood loss, postdelivery haemoglobin, side-effects. Blood loss estimated by the clinicians.
Notes	Management of third stage: controlled cord traction, no other details. No loss to follow-up or postrandomisation exclusions reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number-generated tables."
Allocation concealment (selection bias)	Low risk	"opaque sealed packets containing a card indicating group allocation."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up or postrandomisation exclusions reported.

Nigeria 2003 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	There were no significant differences between 2 groups.

Nigeria 2007

Methods	Single-blinded randomised controlled study.
Participants	864 women with singleton, low-risk pregnancies with anticipated spontaneous vertex delivery in a secondary health centre located in a semi-urban area of Ibadan, capitol city of Oyo State. Exclusion criteria included the presence of contraindications to the use of either misoprostol and methylergometrine, such as pre-eclampsia and other hypertensive diseases in pregnancy, pre-existing cardiac disease, severe anaemia, history of asthma, renal or hepatic disorders, allergy to prostaglandins, and the presence of conditions requiring prophylactic oxytocin infusion after delivery such as grand multiparity, multiple pregnancy, polyhydramnios, previous history of postpartum haemorrhage and uterine fibroid.
Interventions	400 mcg of oral misoprostol versus 500 mcg of IM methylergometrine at the delivery of the anterior shoulder.
Outcomes	Total estimated blood loss (mL), postpartum haemorrhage (blood loss > 500 mL), duration of third stage of labour (min), duration of third stage of labour > 15 min, postdelivery packed cell volume (PCV) (%), differences in PCV (%), percentage changes in PCV (%), percentage PCV change > 10%, manual placental removal, additional oxytocics and side-effects (fever, shivering, nausea, vomiting, headache).
Notes	Active management of third stage labour. Blood loss was estimated by a combination of careful measurement of blood collected in a receptacle after the delivery of the baby, visual estimation of blood loss and extrapolation of blood loss using weight difference of the total perineal pad used up to 24 hours in the postpartum period.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent statistician generated sets of four random letters, which were in boxes, and each box contained four separate random allocations which was equivalent to an opaque sealed envelope stratified in a block for four."
Allocation concealment (selection bias)	Low risk	Adequate, see above.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Single-blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.

Nigeria 2007 *(Continued)*

Other bias	Low risk	None of the baseline variables are statistically significant between 2 groups.

Nigeria 2011

Methods	Double-blind, randomised, placebo-controlled trial.
Participants	1345 pregnant multiparous women who deliver vaginally in 6 different hospitals in Nigeria were included. Only multiparous women were recruited because they were more likely to proceed to normal delivery. Exclusion criteria included any severe allergic condition or severe asthma, age below 18 years, temperature above 38 C, or abortion of the pregnancy.
Interventions	This is a trial where misoprostol is given in addition to the traditional oxytocics. In addition to 10-IU oxytocin or 0.25 mg/0.5 mg ergometrine immediately after delivery of the child, 2 tablets of 200 mcg misoprostol (400 mcg dose) were provided versus only below traditional treatment and 2 placebo tablets.
Outcomes	Primary: blood loss of at least 500 mL within 1 hour of administration of the trial medication. Secondary: total severe postpartum blood loss of at least 1000 mL within 1 hour of drug administration, average blood loss after drug administration, need for additional oxytocin or ergometrine, maternal morbidity, maternal mortality, and adverse effects. Adverse-effect measures were self-reported moderate/severe shivering and pyrexia (body temperature at least 38 C) within 1 hour of taking the trial drug. The occurrence of nausea, vomiting, and diarrhoea after administration of the trial drug was also assessed.
Notes	All centres had a policy of active management of the third stage of labour. Blood collection was initiated as soon as possible after administration of the trial medication. A low-profile plastic fracture bedpan was placed below the woman's perineum to collect all subsequent blood loss for a period of 1 hour. Blood collected in the bedpan and all blood-soaked small gauze swabs were emptied into a plastic measuring jar and the volume was measured.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Treatment was allocated in blocks of 6-8 women by the research nurse, who used a computer-generated randomization sequence."
Allocation concealment (selection bias)	Low risk	"The trial drugs were concealed in sealed, sequentially numbered opaque envelopes and were identical in shape, color, size and design."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.

Nigeria 2011 *(Continued)*

Other bias	Low risk	"The baseline characteristics in the two arms of the study were similar with regard to age, proportion of primiparous women, proportion of labours induced with misoprostol, type of routine uterotonic administered, and birth weight of the infant."

Pakistan 2011

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	1119 pregnant women in general good health, residing in 1 of the 46 study villages and planning to deliver at home with a study TBA were eligible for inclusion. Women were not eligible if presenting with pregnancy complications such as hypertension, non-cephalic presentation, polyhydramnios, previous caesarean section, suspected multiple pregnancy, suspected stillbirth, antepartum haemorrhage, and Hb < 8 g/dL.
Interventions	600 mcg oral misoprostol versus placebo. The use of a placebo was considered ethical because the standard care for home births with TBAs in the study area is to give no prophylactic uterotonic at delivery.
Outcomes	The primary outcomes were postpartum haemorrhage (defined as measured blood loss >= 500 mL) and drop in Hb > 2 g/dL. Secondary outcomes included intermediate and severe postpartum haemorrhage (blood loss 750 and 1000 mL), mean blood loss and postpartum Hb < 9 and < 11 g/dL.
Notes	Providers were asked to document how the third stage was managed for each participant. The TBAs are trained in management of the third stage of labour, including performing uterine massage, cord traction, delayed cutting of the cord, and immediate suckling at the breast. To collect postpartum blood loss, women were positioned on a perineal sheet and bedpan for a minimum of 1 hour or until active bleeding stopped whichever occurred last. Study TBAs were provided with a 1-hour timer to track that blood was collected for 1 hour and were asked to estimate the time in minutes between delivery of the baby and of the placenta. Blood collected in the bedpan was transferred to a measuring jar, which was then closed, and the used perineal sheet and cotton roll were placed in a sealed plastic bag. The closed measuring jar and sealed plastic bag were then placed inside a plastic cooler which was tightly closed and stored in a secure place in the woman's home until the LHV/CHN arrived for weighing, 1-2 days after delivery.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer- generated random code in blocks of 6 was maintained by Gynuity Health Projects in New York and not revealed until data collection and cleaning were completed."
Allocation concealment (selection bias)	Low risk	"Study medication was packed in numbered colour-coded boxes to identify the randomization sequence. Study TBAs were provided with specially designed colour-coded drug boxes to ensure that the sequence was maintained."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias)	Low risk	3 patients (1 in the misoprostol group and 2 in the placebo group) could not be followed up.

Pakistan 2011 *(Continued)*

All outcomes		Blood loss data was not available for 19 patients in the misoprostol group and 25 patients in the placebo group. Hb measures were not available pre and post delivery for 5 patients in the misoprostol group and 12 patients in the placebo group.
Selective reporting (reporting bias)	Low risk	All of the primary outcomes of the review which can be collected in the community setting were reported.
Other bias	Low risk	2 groups were comparable.

Singapore 1995

Methods	Random allocation by a random-number table. Blinding of some outcome assessments.
Participants	115 women with spontaneous labour and delivery in Singapore. Exclusion criteria: multiple pregnancy, any antenatal complications.
Interventions	Carboprost trometamol* 125 mcg IM vs ergometrine-oxytocin 0.5 mg IM.
Outcomes	Blood loss, need for additional uterotonics, transfusion, haemoglobin levels, side-effects. Measurement of blood loss: blood and clots in the first 2 hours after delivery mopped with absorbent paper, sanitary pads collected for the next 22 hours, and then measured.
Notes	Management of third stage: controlled cord traction after placenta separation. 3/115 (2.6%) women were excluded after randomisation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number table."
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if blinding occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women were excluded as the births occurred before the blood loss measurement was set up.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	"The parity, gestation, mode of delivery and the mean duration of first and second stage of labor were similar in the two groups."

South Africa 1998a

Methods	Random allocation by computer-generated, random sequence for sealed opaque envelopes. No placebo use. Outcome assessments were not blinded.
Participants	491 women at low risk for postpartum haemorrhage at Natalspruit Hospital, Johannesburg, South Africa. Exclusion criteria: not noted.
Interventions	Misoprostol 400 mcg rectally vs ergometrine-oxytocin 1 ampoule IM.
Outcomes	Blood loss, duration of third stage, side-effects. Measurement of blood loss: by estimation.
Notes	Third stage management was active.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	"sealed opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear if blinding occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was minimal for primary outcomes (2-3%) with the exception of postpartum haemoglobin which was measured in 67% and 65% of women in the misoprostol and ergometrine-oxytocin groups respectively. A small number of women (unspecified) allocated to ergometrine-oxytocin were excluded because of high blood pressure discovered after randomisation. However, results were similar to the whole group when all hypertensives were excluded in a subgroup analysis.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	Baseline variables were comparable between 2 groups except systolic BP during labour.

South Africa 1998b

Methods	Random allocation by computer-generated random sequence. Double-blinded, placebo-controlled trial. Tablets kept in numbered, sealed, opaque containers. Non-identical placebo tablets.
Participants	500 women after delivery at Coronation Hospital, Johannesburg, South Africa. No mention of risk status. Exclusion criteria: oxytocin infusion in progress at the time of delivery, hypertension, diabetes, previous caesarean section delivery.
Interventions	Misoprostol 400 mcg orally vs placebo.
Outcomes	Blood loss greater than or equal to 1000 mL within first hour of birth, use of additional uterotonics, side-effects, third stage 30 minutes or longer, manual removal of the placenta, blood transfusion.

South Africa 1998b *(Continued)*

	Measurement of blood loss: blood and clots collected in bedpans and volume assessed. Linen weighed.
Notes	Management of third stage: placenta removed by cord traction once firm uterine contraction diagnosed by palpation. No withdrawals after randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	"numbered, opaque test tubes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after the randomisation. Intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The groups were well-matched.

South Africa 1998c

Methods	Random allocation by computer-generated random numbers. Tablets kept in numbered, sealed, opaque containers. Non-identical placebo tablets. Outcome assessments were blinded.
Participants	550 low-risk women after delivery at Coronation Hospital Johannesburg, South Africa. Exclusion criteria: not noted.
Interventions	Misoprostol 400 mcg rectally vs placebo.
Outcomes	Blood loss greater than or equal to 1000 mL, use of additional uterotonics, spontaneous delivery of the placenta, third stage longer than or equal to 30 minutes, side-effects. Measurement of blood loss: blood collected in bedpan until 1 hour after delivery. Linens weighed.
Notes	Management of third stage: placenta delivered either by cord traction or spontaneous expulsion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	"sealed, opaque containers."

South Africa 1998c *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Non-identical placebo. The blinding of the midwife administering the tablets was not possible, as identical placebo tablets were not available. Outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions after randomisation: records for 4 allocations (all in placebo group), could not be traced.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The 2 groups were well-matched.

South Africa 1998d

Methods	Random allocation according to a computer-generated random sequence. Serially numbered, opaque test tubes. Outcome assessments were blinded.
Participants	600 women after delivery at Coronation Hospital, Johannesburg, South Africa. No mention of whether they are high or low risk. No mention of exclusion criteria.
Interventions	Misoprostol 600 mcg orally vs misoprostol 400 mcg orally vs placebo.
Outcomes	Shivering, pyrexia. Blood loss was measured using a flat bed pan.
Notes	Management of third stage: placenta removed by cord traction after firm contraction of uterus.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	"Serially numbered, opaque test tubes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded according to the authors' other published work.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes of the review have been reported.
Other bias	Unclear risk	Unclear if the baseline characteristics are comparable.

South Africa 2001

Methods	Random allocation according to a computer-generated random sequence. Serially numbered, opaque test tubes. Outcome assessments were blinded.
Participants	600 women after delivery at Coronation Hospital, Johannesburg, South Africa. Exclusion criteria: no mention of exclusion criteria.
Interventions	Misoprostol 600 mcg oral vs placebo.
Outcomes	Shivering, pyrexia. Measurement of blood loss: blood in bed pan measured, linen and sanitary towels weighed.
Notes	Management of third stage: placenta removed by cord traction after firm contraction of uterus. No exclusions after randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	"Serially numbered, opaque test tubes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals after randomisation and all outcomes were analysed in the allocated group.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were well-matched.

Switzerland 1999

Methods	Random allocation using random-number tables. Trial was double blinded.
Participants	65 low-risk women with vaginal births at Basel University Hospital, Basel, Switzerland. Exclusion criteria: multiple pregnancy, pre-eclampsia, previous postpartum haemorrhage or antepartum haemorrhage, caesarean delivery.
Interventions	Misoprostol 600 mcg orally vs placebo.
Outcomes	Blood loss, length of third stage, use of additional uterotonics, side-effects, haematocrit values. Measurement of blood loss: estimation by delivery physicians.
Notes	Management of third stage: early cord clamping and cord traction.

Risk of bias

Bias	Authors' judgement	Support for judgement

Switzerland 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	"random number-generated tables."
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	2 groups were comparable in the baseline.

Switzerland 2006

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	56 pregnant women at low risk for postpartum haemorrhage who underwent indicated or elected caesarean section after the 37th week of pregnancy at the Basel Women's University Hospital in Switzerland. Indications for caesarean section were breech presentation, malposition, IUGR, placenta previa marginalis, twin pregnancy, previous caesarean section, maternal disease and failure of labour to progress. Exclusion criteria included emergency caesarean section within 30 minutes of admission, fetal distress, fetal malformations, preeclampsia or HELLP, hypersensitivity to prostaglandins, coagulopathy, severe systemic disorders, and American Society of Anesthesiologists physical status of 3 or greater, severe asthma, prior myomectomy, and fever (> 38.5 C).
Interventions	800 mcg of oral misoprostol versus 20 IU of oxytocin in saline solution.
Outcomes	Outcomes are estimated blood loss (mL), calculated blood loss (mL), Hb level 24 hours postoperatively, g/dL, Hb level 48 hours postoperatively, g/dL, hospital stay (days) and side-effects (shivering, headache, nausea, flush, diarrhoea).
Notes	Active management is not applicable, as the study is limited to caesarean sections. When the membranes had ruptured before the section, the amount of intraoperative and postoperative blood loss was calculated by determining the difference in weight of cloths and pads used to absorb blood during surgery and postoperatively in the intermediate care unit. When the membranes had not ruptured preoperatively, the amount of blood loss was assessed by collecting the blood in suction bottles and subtracting the estimated amniotic fluid volume. It should be noted that all participants received a 5 IU bolus of oxytocin intravenously and afterwards were randomised to receive either of the above medications immediately after cord clamping. This regimen was imposed by the institutional ethics committee as a consequence of the Cochrane Library Review.

Risk of bias

Bias	Authors' judgement	Support for judgement

Switzerland 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	"The hospital pharmacy performed 1:1 computer-generated randomization that assigned the participants to their group."
Allocation concealment (selection bias)	Low risk	"The pharmacy also provided the study drugs and placebos in unidentifiable form.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients in the oxytocin group were excluded from statistical analysis because of errors in drug administration.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The demographic and obstetric characteristics are similar between the 2 groups.

Tibet 2009

Methods	Double-blind, double placebo, randomised 2-arm trial.
Participants	967 pregnant women 18 years of age or older with a viable intrauterine singleton pregnancy, ≥ 28 weeks' gestation at 3 obstetric units in Lhasa, TAR, PRC, were considered eligible for study participation.
Interventions	Traditional dose of ZB11 at full dilation versus oral 600 mcg misoprostol immediately after delivery.
Outcomes	Primary outcomes are postpartum haemorrhage (MBL >= 500 mL), administration of open label uterotonics within the 1 hour observation period after delivery, or maternal death. Secondary outcomes included: MBL >= 500 to 999 mL, MBL >= 1000 mL, mean and median MBL during the first hour postpartum, and side-effects.
Notes	Active management of third stage of labour. Postpartum blood loss was measured using a closed-end blood collection drape (BRASSS-V drape blood collection receptacle) for 1 hour after delivery of the baby.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer generated randomization list with a random block size for each hospital."
Allocation concealment (selection bias)	Low risk	"Sealed opaque study medication envelopes were distributed to the hospitals by research study staff."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.

Tibet 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	4 out of 480 ZB11 patients and 3 out of 487 misoprostol group patients have been excluded due to developing eclampsia, vomiting and unable to take medication.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The 2 groups did not differ in any characteristic at the baseline.

Tunisia 2009

Methods	Randomised controlled trial.
Participants	250 single low-risk pregnant women undergoing caesarean section at gestational age > 32 weeks' gestation, under regional anaesthesia at the Department of Obstetrics Sousse, Tunisia. Exclusion criteria included patients with placenta previa, abruptio placentae, multiple gestation, preterm delivery (less than 32weeks), fetal death in utero, a caesarean under general anaesthesia, anaemia (Hb <8 g /dL), haemostasis disorders(congenital or anticoagulant therapy), HELLP syndrome, a history of postpartum haemorrhage, previous uterine rupture, women with more than 2 caesareans, prolonged labour (over 12 hours) and maternal fever(temperature ? 38 ? C).
Interventions	This study uses misoprostol on top of conventional oxytocics for prevention for 200 mcg sublingual misoprostol with 20 IU intravenous oxytocin (10 UI intravenous direct and 10 IU diluted in an infusion of 500 cc of Ringer lactate) versus only 20 IU intravenous oxytocin within 30 minutes after clamping umbilical cord.
Outcomes	The primary outcome: the fall of the haematocrit (difference between preoperative haematocrit value and the measured 48 hours after caesarean section). The secondary outcomes were the fall of the haemoglobin (difference between preoperative haemoglobin value and the measured 48 hours after caesarean section), blood loss estimated by direct method, the need for additional doses of oxytocin and the occurrence of adverse events related to administration of misoprostol.
Notes	AMTSL is not applicable as the study is limited to women with caesarean sections. Blood loss was estimated by the direct method (the sum of the volume of intraoperative blood draws in and the amount of blood found in gauze and surgical drapes).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by computer and the result is marked on a notice placed in an opaque envelope and sealed. Just before surgery the responsible of the progress of the study will proceed to the opening of the envelope and thus the patient was assigned to one of two groups."
Allocation concealment (selection bias)	Low risk	Adequate. See above.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear on blinding.

Tunisia 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusion after randomisation were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	Demographic, maternal and obstetric characteristics were similar in both groups.

Turkey 2002

Methods	Randomisation based on computer-generated random numbers. Sealed, consecutively-numbered, opaque envelopes were used. Identical placebos were used except for the misoprostol tablets which were similar in size and colour but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments.
Participants	1633 women with vaginal births in Ankara, Turkey. Exclusion criteria: Gestational age < 32 weeks, caesarean delivery, hypersensitivity to prostaglandins.
Interventions	Women randomised into 4 groups, all received corresponding placebos. Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg rectally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol. Group 2: misoprostol 400 mcg rectally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus 1 mL methylergometrine IM.
Outcomes	Blood loss, transfusion, change in Hb, need for additional uterotonics, length of the third stage, subsequent evacuation of uterus, frequency of delayed haemorrhage, side-effects. Clinical estimation of blood loss was done.
Notes	Active management of third stage with early cord clamping, traction, and uterine massage. Concurrent study at this institution with similar design but evaluating oral misoprostol also published and is included in this meta-analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"table of computer generated blocks of random numbers."
Allocation concealment (selection bias)	Low risk	"sealed, consecutively numbered opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebos were used except for the misoprostol tablets which were similar in size and colour but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 exclusions after randomisation secondary to lack of Hb measurements. These were spread out among the 4 groups.

Turkey 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	There were no significant differences among the groups.

Turkey 2003

Methods	Randomisation based on computer-generated random numbers. Sealed, consecutively numbered, opaque envelopes were used. Identical placebos were used except for the misoprostol tablets which were similar in size and colour but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments.
Participants	1800 women with vaginal births in Ankara, Turkey. Exclusion criteria: Gestational age < 32 weeks, caesarean delivery, hypersensitivity to prostaglandins.
Interventions	Women randomised into 4 groups, all received corresponding placebos. Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol. Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus 1 mL methylergometrine IM.
Outcomes	Blood loss, transfusion, change in Hb, need for additional uterotonics, length of the third stage, subsequent evacuation of uterus, frequency of delayed haemorrhage, side-effects. Clinical estimation of blood loss was done.
Notes	Active management of third stage with early cord clamping, traction, and uterine massage. 226 (12.6%) exclusions after randomisation secondary to lack of haemoglobin measurements. Concurrent study at this institution with similar design but evaluating oral misoprostol also published and is included in this meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-based random allocation."
Allocation concealment (selection bias)	Low risk	"sealed, consecutively numbered opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebos were used except for the misoprostol tablets which were similar in size and colour but not in shape. There was blinding of outcome assessments. Midwives administered the misoprostol tablets, but residents that were blinded to the intervention, did the outcome assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	226 (12.6%) exclusions after randomisation secondary to having caesarean sections and lack of haemoglobin measurements.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	The groups were comparable.

Turkey 2010

Methods	Randomised controlled study.
Participants	200 term singleton pregnancies undergoing spontaneous vaginal and elective caesarean section at the University Hospital in Eskisehir, Turkey. Exclusion criteria included known sensitivity to prostaglandins, excessive postpartum haemorrhage with haemodynamic instability that necessitated blood transfusion. Assisted vaginal delivery, use of epidural anaesthesia and cases with labour induction.
Interventions	Controlled release PGE2 vaginal insert (Dinoprostone) with a constant delivery of 0.3 mg/hr for 12 hours versus IV oxytocin infusion in balanced solution (10 IU for vaginal, 20 IU for caesarean delivery).
Outcomes	Main outcome measures: amount of bleeding, need for additional oxytocins, haemoglobin and haematocrit level changes during the postpartum period and drug related side-effects such as nausea, vomiting, shivering, pyrexia and diarrhoea and postpartum vaginal or endometrial infections. Some of these results have been reported by subgroup only (caesarean section, vaginal delivery).
Notes	Active management of third stage of labour for the vaginal births. In cases undergoing caesarean section, 20 IU intravenous oxytocin infusion was given after the delivery of the placenta. Estimated amount of postpartum blood was assessed via a gravimetric method by counting the blood-filled pads within 24 hours of postpartum. Dry weight of the pads was assessed prior to delivery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not clear how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or postrandomisation exclusions were reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported and some of them have only been reported within the subgroups (vaginal/caesarean section).
Other bias	Low risk	Demographic characteristics did not differ between the 2 groups.

United Kingdom 1994

Methods	Method of random allocation not stated. Sealed opaque envelopes used for allocation concealment. Interventions prepared by someone not involved in the study, outside the intervention area (operating theatre). Outcome assessments were blinded.
Participants	60 low-risk women undergoing elective caesarean section in an academic hospital in Oxford, UK.

United Kingdom 1994 *(Continued)*

	Exclusion criteria: hypertensive disease, asthma, heart disease.
Interventions	Prostaglandin group: 15-methyl prostaglandin F2alpha, 125 mcg intramyometrial + placebo. Oxytocin group: 5 IU oxytocin IV bolus injection followed by 15 IU in 500 mL of Ringer's lactate solution + placebo. Both interventions were started after delivery of the baby but before delivery of the placenta.
Outcomes	Blood loss, use of additional uterotonics, blood transfusion, side-effects, change in haemoglobin (subset of patients). Measurement of blood loss: clinical estimation.
Notes	Management of third stage: not applicable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear if the sequence generation was adequate.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes used for allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. Outcome assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or postrandomisation exclusions reported.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The groups were comparable.

United Kingdom 2000

Methods	Random allocation by sealed, opaque, consecutively-numbered envelopes. No blinding of outcome assessments.
Participants	1000 women delivering vaginally, in London, UK. Women with a history of asthma, planned caesarean section and water birth were excluded.
Interventions	Misoprostol group: 500 mcg misoprostol orally after baby delivered and cord clamped. Uterotonic group: this group was given uterotonics at delivery of anterior shoulder. The choice of uterotonics varied according to the hospital policy for different groups of women. Women at high risk of haemorrhage received ergometrine (2%), those with hypertension received oxytocin (18%). All others received ergometrine-oxytocin (80%).
Outcomes	Blood loss, side-effects. Measurement of blood loss: clinical estimation by the midwives.
Notes	Management of third stage: 'active': cord traction with signs of separation, oxytocics at anterior shoulder delivery.

United Kingdom 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated block randomization."
Allocation concealment (selection bias)	Low risk	"opaque, sequentially numbered sealed envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of postrandomisation exclusions or protocol violations.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	Both groups were comparable at entry to the trial.

United Kingdom 2001b

Methods	Random allocation schedule generated by computer. Allocation made by opening sealed opaque envelopes which contained the names of the groups. No mention of consecutive numbering and opening. The obstetrician, surgical assistant, scrub nurse and recovery midwives were blinded to the group while anaesthetist was not. Double, non-identical placebos were used.
Participants	40 women undergoing elective or emergency caesarean section in a university hospital in London, United Kingdom. Women with 2 or more caesarean sections or a history of previous ruptured uterus were excluded. Other eligibility criteria are not mentioned.
Interventions	Misoprostol 500 mcg orally + 2 mL IV normal saline bolus vs 10 IU oxytocin bolus + 2 placebo tablets.
Outcomes	Blood loss (clinical estimation), change in Hb levels, shivering (assessed in the recovery room), temperature within 1 hour.
Notes	Management of third stage: 'active' during caesarean section.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Allocation made by opening sealed opaque envelopes which contained the names of the groups. No mention of consecutive numbering and opening.
Blinding (performance bias and detection bias) All outcomes	Low risk	The obstetrician, surgical assistant, scrub nurse and recovery midwives were blinded to the group while anaesthetist was not. Double, non-identical placebos were used.

United Kingdom 2001b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals after caesarean section.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The groups were comparable.

United Kingdom 2001c

Methods	Open-label, assessor-blind, randomised controlled trial.
Participants	Pregnant women over 16 years of age and delivering infants after 24 completed weeks of gestation at the Northwick Park Hospital, a district general hospital in the UK. Exclusion criteria included a known sensitivity to either prostaglandins, ergotrates or oxytocin, had a history of asthma, glaucoma, raised intraocular pressure or were known to have cardiac, pulmonary, renal or hepatic disease, hypertension, sepsis or obliterative vascular disorders. Women were excluded if they were currently taking anticoagulant treatment or participating in other clinical trials.
Interventions	1 mL IM (250 mcg) of carboprost versus 1 mL of syntometrine (0.5 mg of ergometrine plus 5 units of syntocinon) intramuscularly at the time of presentation of the anterior shoulder.
Outcomes	Main outcome measure was the occurrence of primary postpartum haemorrhage (500-1000 mL). Other measures include maternal haemoglobin and haematocrit measured 3 days later, mode and timing of delivery of the placenta and maternal blood pressure after delivery of the placenta and 1 hour later. side-effects (diarrhoea, nausea, vomiting) were also measured.
Notes	Active management of third stage of labour. Blood loss was measured as accurately as possible, taking into consideration the liquor amnii and soiling of the surgical drapes.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not clear on how the random sequence was generated.
Allocation concealment (selection bias)	Low risk	"The randomization slips were contained in envelopes which were opened by a person not involved in the postpartum assessments who resealed the envelope and drew 1 ml of the appropriate medication into a syringe."
Blinding (performance bias and detection bias) All outcomes	Low risk	The study is open-labelled, however, the outcome assessments are blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman in the carboprost group was excluded from the analysis because she did not receive the medication.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.

United Kingdom 2001c *(Continued)*

Other bias	High risk	This study has been suspended during the interim analysis due to higher percentage of GI adverse events, especially diarrhoea seen in the Carboprost group. The groups were comparable at the baseline.

United Kingdom 2003

Methods	Random allocation prepared by independent statistician using computer-generated random numbers with blocked randomisation. Sequentially numbered, sealed, opaque, envelopes used. No placebos used. No blinding of outcome assessments.
Participants	275 women with vaginal delivery in London, UK. Exclusion criteria: < 37 weeks' gestation, < 18 yrs old, multiple gestation, induced labour, asthma, cardiac, renal or hepatic disorder. Study was reported in conjunction with a misoprostol pharmacokinetics trial.
Interventions	Misoprostol 600 mcg orally vs 600 mcg rectally vs 400 mcg rectally.
Outcomes	Side-effects, clinical estimation of blood loss, duration of third stage, manual removal of placenta.
Notes	"Usual" management of third stage with cord traction. Blood loss estimated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random numbers."
Allocation concealment (selection bias)	Low risk	"sequentially numbered, sealed, opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	The study was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or postrandomisation exclusions.
Selective reporting (reporting bias)	Low risk	Not all of the primary outcomes of the review were reported, however, this study was conducted to analyze the side-effects of different doses.
Other bias	Low risk	There was a borderline statistically significant difference between the 2 groups with regard to the maximum plasma concentration. Otherwise the groups were comparable.

USA 1990

Methods	Method of random allocation not stated. Double-blinded trial.
Participants	46 women at low risk for postpartum haemorrhage undergoing delivery by caesarean section in Arkansas, USA.

USA 1990 *(Continued)*

	Exclusion criteria: hypertension, asthma, pre-eclampsia, chorioamnionitis, multiple gestation or were receiving tocolytic agents.
Interventions	Carboprost tromethamine* 0.125 mg intramyometrial vs oxytocin 20 IU intramyometrial. Both groups received 20 IU of oxytocin in 1 litre saline after delivery.
Outcomes	Haematocrit change after delivery, blood loss not measured.
Notes	Management of third stage: not applicable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear on how the adequate sequence generation was done.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were comparable.

USA 2001

Methods	Random allocation sequence concealed until enrolment. Packs containing both active and placebo were made available after random allocation. It is not clear if the placebos are identical. No mention of blind outcome assessments.
Participants	400 women in active labour or undergoing induction of labour in Los Angeles, USA were enrolled. Women with multiple gestation, known coagulation disorders, contraindication to prostaglandin or oxytocin use, known initial haemoglobin below 7.0 mg/dL and an indication for caesarean section were excluded.
Interventions	Misoprostol 400 mcg rectally + placebo (2 mL saline) vs oxytocin 20 IU + placebo (lactose tablets). Oxytocin (and its placebo) was administered as IV infusion in 1 L of Ringer's lactate solution.
Outcomes	Blood loss (estimated and measured by weighing linen etc.), haematocrit, side-effects.
Notes	Management of the third stage not mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement

USA 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	"random number sequence."
Allocation concealment (selection bias)	Unclear risk	Unclear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if the blinding was not broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions after randomisation: 75/400 (18.75%), 73 had caesarean section during labour, 1 had Hb < 7.0 mg/dL and 1 was discharged home before delivery.
Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	2 groups were comparable.

USA 2004

Methods	Random allocation sequence generated by using a table of random numbers. Active and placebo (similar but not identical) were placed in opaque, numbered vials. Power calculation was made. Outcome assessments were not blinded.
Participants	756 women with anticipated vaginal delivery at a maternity hospital in Florida, USA.
Interventions	Misoprostol 200 mcg buccal vs placebo. All women received intravenous infusion of 20 IU oxytocin in 1 litre of saline at 10 mL/min for 30 minutes (i.e. received approximately 6 IU oxytocin IV).
Outcomes	Blood loss, haemoglobin measurements, side-effects. Blood loss was estimated by the attending physician.
Notes	Management of the third stage: active management with early cord clamping. controlled cord traction and oxytocin after delivery of the placenta.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number table."
Allocation concealment (selection bias)	Unclear risk	Not clear on how the allocation concealment was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled. It should be noted that the outcome assessors are not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	756/848 eligible women were randomised. 15 patients in the misoprostol group and 19 patients in the placebo group were excluded due to having caesarean section, refusing to participate and nursing or physician error. Analysis was intention to treat.

USA 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not all of the primary outcomes of the review were reported.
Other bias	Low risk	There were no differences between the groups.

USA 2005

Methods	Randomised, placebo-controlled. No mention of random-number generation scheme. Allocation concealment by pharmacy-assigned numbers to opaque vials containing either misoprostol tablets or oxytocin ampoules. Outcome assessments were blinded.
Participants	352 women undergoing caesarean section in Orlando, Florida, USA.
Interventions	Misoprostol 200 mcg buccal vs placebo at cord clamping. All women received 20 IU IV oxytocin in 1000 mL saline.
Outcomes	Blood loss, additional uterotonics. Blood loss was estimated following 'standard' procedures.
Notes	No loss to follow-up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of random-number generation scheme.
Allocation concealment (selection bias)	Low risk	Allocation concealment by pharmacy-assigned numbers to opaque vials containing either misoprostol tablets or oxytocin ampoules.
Blinding (performance bias and detection bias) All outcomes	Low risk	"At no time before the data analysis were the assignments available to anyone but the pharmacy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review have been reported.
Other bias	Low risk	2 groups were comparable.

WHO 1999

Methods	Random allocation sequence, generated centrally. Sealed and numbered identical treatment packs taken consecutively from a dispenser. Double-blinded, placebo controlled pilot trial.
Participants	597 women after delivery in Khon Kaen, Thailand and Johannesburg, South Africa. Risk status not stated.

WHO 1999 *(Continued)*

	Exclusion criteria: asthma, other severe chronic allergic condition, if delivery considered an abortion, planned caesarean section, not willing or able to give informed consent.
Interventions	Misoprostol 600 mcg orally vs misoprostol 400 mcg orally vs oxytocin 10 IU IV.
Outcomes	Shivering, pyrexia, side-effects, blood loss from delivery to transferal of mother to postnatal care. Measurement of blood loss: collected blood poured in standard measuring jar. Linen not weighed. Small gauze swabs soaked with blood put into measuring jar and included in measurement.
Notes	Management of third stage: uterotonics, clamping and cutting of cord immediately after delivery, fundal or suprapubic pressure with cord traction after signs of placental separation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence, generated centrally.
Allocation concealment (selection bias)	Low risk	Sealed and numbered identical treatment packs taken consecutively from a dispenser.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded using double placebos.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion after randomisation: 8 women in the oxytocin group did not comply with treatment (6 had an emergency caesarean section, 1 was HIV positive and mistakenly excluded, 1 whose ampoule was not located). 1 woman in the 600 mcg group was excluded because her tablets could not be located, and 1 woman in the 400 mcg group was excluded because of an emergency caesarean section.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The groups were comparable at the trial entry and at delivery except for low birthweight, which was higher in the misoprostol 600 mch group.

WHO 2001

Methods	Random allocation sequence, generated centrally. Sequentially-numbered, identical treatment packs drawn from a treatment pack dispenser. Double blinding achieved by use of double placebos.
Participants	18,530 women expecting vaginal delivery in 9 countries. Countries were Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam. Exclusion criteria: pyrexia (> 38 degrees C) on admission to labour ward, severe asthma, bleeding disorders, elective caesarean section, no consent.
Interventions	Misoprostol 600 mcg orally + placebo IV/IM, vs oxytocin 10 IU IV/IM + placebo tablets.
Outcomes	Blood loss, shivering, pyrexia, nausea, vomiting, diarrhoea, need for transfusion, manual removal of placenta, exploration under general anaesthesia, hysterectomy, admission to ICU, maternal deaths.

WHO 2001 *(Continued)*

	Measurement of blood loss: collected blood poured in standard measuring jar. Small gauze swabs soaked with blood put into measuring jar and included in measurement. Linen weighed in some centres.
Notes	Management of third stage: uterotonics, clamping and cutting of cord immediately after delivery, fundal or suprapubic pressure with cord traction after signs of placental separation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence, generated centrally.
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, identical treatment packs drawn from a treatment pack dispenser.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding achieved by use of double placebos.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50/9264 (0.54%) excluded after randomisation in the misoprostol group, 37 because of an emergency caesarean section, and 13 for loss to follow-up. 38/9226 (0.41%) excluded after randomisation in the oxytocin group, 34 for emergency caesarean section and 4 lost to follow-up.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The 2 groups were comparable.

Zimbabwe 2001

Methods	Random allocation sequence generated by computer, allocation by numbered, sealed, opaque envelopes. Placebos used but were not identical. It is not mentioned whether outcome assessments were blinded or not.
Participants	500 low-risk women delivering at Harare Maternity Hospital, Zimbabwe were included. Women with a history of postpartum haemorrhage, disseminated intravascular coagulation, antepartum haemorrhage, coagulation disorders, operative delivery, multiple pregnancy, history of asthma and known allergies to misoprostol or oxytocin were excluded.
Interventions	Misoprostol 400 mcg orally + 1 mL saline (placebo) vs oxytocin 10 IU IM + 2 placebo tablets.
Outcomes	Blood loss, side-effects. Measurement of blood loss: blood volume in jug + weighing of soiled linen.
Notes	Management of the third stage not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence generated by computer.

Zimbabwe 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Numbered, sealed, opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear if the blinding was protected throughout the study or if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions after randomisation: 1 women excluded because of undiagnosed twin delivery.
Selective reporting (reporting bias)	Low risk	Primary outcomes of the review were reported.
Other bias	Low risk	The groups were comparable.

* (15(S) 15 methyl PGF2alpha)
** Synthetic PGE2 derivative (16-phenoxy-17,18,19,20-tetranor-PGE2-methylsulphonamide)
ANM: auxiliary nurse midwives
BP: blood pressure
GI: gastrointestinal
Hb: haemoglobin
Hct: haematocrit
ICU: intensive care unit
IM: intramuscular(ly)
IU: international unit(s)
IUGR: intrauterine growth restriction
IV: intravenous(ly)
MBL: measured blood loss
PCV: packed cell volume
PPH: postpartum haemorrhage
vs: versus
wks: weeks

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Australia 2009	This study was comparing 3 different regimens for third stage management after second-trimester intravaginal misoprostol termination.
Austria 1983	No clinically relevant outcomes reported. Healthy women delivering at term who had a normal duration of labour (< 12 hours) and without the use of oxytocics before delivery were recruited. Immediately following the separation of the placenta, a twin catheter was introduced into the cavity for intrauterine pressure measurement which was recorded on the cardiotocograph. The women were randomised to receive methergin (methylergometrine) 0.2 mg, or oxytocin 2 IU, or sulprostone 0.5 mg or saline, all administered intramuscularly. Sulprostone had the quickest onset of action and strongest increase in uterine contractility whereas methergin had the longest duration of action on uterine contractility.
Canada 2004	Not a randomised controlled trial. A nested study within a randomised controlled trial to look at peripheral blood flow and temperature changes in women receiving misoprostol or oxytocin.
China 1997	This trial was reported as randomised but no details of the method of randomisation were given. The 2 study groups were not balanced (260 versus 100), and they were further randomised into subgroups.

Study	Reason for exclusion
China 1998	Randomised controlled trial of misoprostol versus oxytocin in caesarean section births only. Data are not presented in a form that can be extracted for the meta-analysis.
China 1998b	This trial randomised 80 women to 1 mg carboprost methylate intravaginally versus sublingually vs ergometrine IV. The data were not in a form suitable for extraction for this meta-analysis.
China 2000	This trial randomised 102 women to receive 200 mcg rectal misoprostol versus Pitocin, however, there were not enough information in the article for the assessment of the methodology.
China 2001	This trial randomised 348 women into 4 groups of misoprostol 200, 400, and 600 micrograms orally, and oxytocin 20 units intramuscularly. Data were presented only in means, and were not presented in a form suitable for extraction and inclusion in this meta-analysis.
China 2002	This study only includes women with pregnancy-induced hypertension syndrome.
China 2003c	This study included only women with failure of induction and was excluded because there was very little information on the methodology and the outcomes were not reported properly.
China 2003d	This study was excluded because there was no information provided on the paper in regards to the methodology of the study (randomisation, allocation concealment, blinding, etc).
China 2004b	Randomised, double blind trial of 298 low-risk women delivering vaginally in Hong Kong, China. Oral misoprostol vs IV oxytocin. The trial is excluded because the number of women in each group are not described and the report is available as an abstract. The authors have not responded to the request for additional information and clarification. There was no statistically significant difference in blood loss > 500 and 1000 mL. Additional oxytocics were used in 25.2 vs 7.5% in the misoprostol and oxytocin groups respectively.
China 2004c	Data are not in a usable format. Randomised controlled trial comparing misoprostol 400 mcg + syntometrine vs syntometrine. The author contacted but no response.
Egypt 1999	140 women were allocated to receive either 2 different doses of rectal misoprostol or 5 units of oxytocin and 0.2 mg ergometrine intramuscularly. There is no indication of any randomised comparison between the groups.
Hungary 1979	The reason for exclusion is that the data are not presented in a usable form. The study is a randomised comparison of 1 mg intramyometrial prostaglandin F2alpha (47 women), 0.2 mg intravenous ergometrine (50) and no treatment (43). Prostaglandin F2alpha reduced the blood loss in the third stage of labour significantly when compared with ergometrine and no treatment.
India 1988a	60 women were allocated to 125 microgram PGF2alpha intramuscularly or no uterotonic. There is no indication of any randomised comparison between the 2 groups.
India 1988b	Multicentre study carried out in 4 centres. Of these, 2 employed a random allocation scheme and 2 used a sequential scheme. The reason for exclusion is that the results are presented together and it is not possible to extract data for those utilising random allocation.
India 2000a	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again.
India 2000b	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again.

Study	Reason for exclusion
India 2000c	There are no data that can be extracted to evaluate the validity of the methods used and the outcome data in this study from the conference abstract. When the study is published in full it will be evaluated again.
India 2001a	This study is reported as randomised double blind but there is no mention of placebos. There is also a discrepancy in the results between the text and the tables. 200 women were assigned either misoprostol orally 400 mcg or methylergometrine.
India 2005b	The study is reported as a randomised controlled trial comparing carboprost with methylergometrine but the results are analyzed by risk subgroups only and they are imbalanced between the 2 random allocation groups.
India 2006e	This is a randomised trial (cluster) of an educational intervention to implement active management of the third stage of labour using misoprostol. The control group received standard practice which was 'no special training' and no use of misoprostol.
India 2006h	This study did not have sufficient information on the risk of bias and exclusion criteria. We have contacted the authors but have not received any response.
India 2009a	The study was reported in an abstract with not enough information on the methodology and outcomes. No contact information provided for the authors.
India 2009c	This study had a very high risk of bias on evaluation, therefore we have excluded the study.
Indonesia 2002	Data to evaluate the validity of the methods used are not available in this published abstract. When the study is published in full it will be evaluated again. This study involves 196 women undergoing full term vaginal delivery. 98 women were randomly allocated to 600 micrograms of oral misoprostol or 10 IU of oxytocin intramuscularly immediately after the baby was born. The length of the third stage of labour was 8.122 minutes for the misoprostol group and 8.388 minutes for the oxytocin group. Third stage blood loss for the misoprostol and oxytocin group was respectively 144.286 mL and 131.020 mL. Shivering occurred in 13.3% in the misoprostol group and 2.0% in the oxytocin group.
Israel 1992	This is a randomised controlled trial comparing intraumbilical PGF2alpha with saline injection. Although a prostaglandin was used for the management of the third stage of labour the mechanism of action may not be comparable to other routes of administration. This paper will be considered for inclusion in another review on the management of the third stage (intraumbilical uterotonics).
Italy 1988	Data from this trial were published in an abstract. It is excluded because no full publication of the trial data could be located.
Japan 1976	There does not seem to be a randomised comparison between study groups. 4 prostaglandin groups were studied: a. systemic: a.1. intramuscular (gluteal), a.2. continuous intravenous drip infusion, b. local: b.1. transabdominal intramyometrial injection, b.2. transvaginal intramyometrial injection. These groups were compared to ergot alkaloids. Number of participants are also not balanced (46 in prostaglandin vs 13 in ergot group).
Korea 2007	The study was reported in an abstract with not enough information on the methodology and outcomes. No contact information provided for the authors.
Singapore 1990	The outcome examined in this trial was serum prostaglandin levels.
Singapore 2001	This trial has 57 women randomly assigned to receive oral misoprostol 200, 400, 500, 600, or 800 micrograms or ergometrine-oxytocin. Uterine activity was the main outcome, but side-effects were also reported. The data are incomplete and not in a suitable form for extraction.

Study	Reason for exclusion
South Africa 1999	Data from this trial were published in an abstract. It is excluded because no further publication of complete trial data was located. This trial evaluates treatment of primary postpartum haemorrhage.
Thailand 2000	The study was reported in an abstract with not enough information on the methodology and outcomes. No contact information provided for the authors.
Turkey 2005	Randomised, placebo-controlled trial comparing 400 mcg rectal vs 400 mcg vaginal misoprostol vs placebo after delivery of the placenta. Women with haemorrhage were excluded from the analysis after randomisation. Authors contacted for clarification.
United Kingdom 2001a	Randomised controlled trial of 400 mcg oral misoprostol versus 10 IU IV oxytocin. Primary outcome was 'intraoperative blood loss', which is not 1 of the outcomes for this review.
USA 1983	75 women were randomised to 3e groups of different doses of prostaglandin F2alpha (62.5, 125, 250 microgram intramuscularly). Then another 15 women were sequentially allocated to the same treatment groups, in groups of 5. The randomised and non-randomised groups have been reported together in the paper to increase the sample size. It is not possible to extract data on the randomised women alone.
USA 1999	Data from this trial were published in an abstract. It is excluded because no further publication of the completed trial data was located and the data presented in the abstract are incomplete.
Yemen 2009	The study is not a randomised controlled trial. It used a "convenience sample" which was then divided into 2 groups by a "quasi-random" allocation.

IU: international unit
IV: intravenous
vs: versus

Characteristics of ongoing studies *[ordered by study ID]*

Kalahroudi 2010

Trial name or title	Comparison of the effect of rectal misoprostol and syntometrine in prevention of postpartum haemorrhage.
Methods	Randomised double blind clinical trial to investigate the effect of rectal misoprostol and syntometrine in prevention of postpartum haemorrhage.
Participants	200 pregnant women referred to the Shabihkhany Hospital in Kashan for vaginal delivery.
Interventions	The first group received 1 mL syntometrine IM and the second group received 600 mgr misoprostol rectal after placental expulsion.
Outcomes	All patients were assessed 0.5 and 1 hour after delivery for uterine tonicity, pulse rate and blood pressure. 24 hours after delivery haemoglobin was checked for estimation of postpartum haemorrhage. Need for uterotonic drugs and rate of adverse effects were also compared between the intervention groups.
Starting date	2010-04-21
Contact information	Masoumeh Abedzadeh Kalahroudi Midwifery Faculty, Kashan University of Medical Sciences, Ravand Road, kashan

Kalahroudi 2010 *(Continued)*

	Isfahan Iran, Islamic Republic Of 00983615550021 abedzadeh@kaums.ac.ir
Notes	As of June 14, 2011 recruitment has been completed.

Moradi 2010

Trial name or title	Comparison of misoprostol and oxytocin in reduction of postpartum haemorrhage.
Methods	A randomised controlled trial (not blinded).
Participants	300 pregnant women with these inclusion criteria: pregnant women with singleton pregnancy, cephalic, spontaneous and induced delivery, term pregnancy.
Interventions	To compare the effect of 400 µg of oral misoprostol with 10 IU of intravenous oxytocin in preventing postpartum haemorrhage.
Outcomes	Haemoglobin and haematocrit were measured in admission and 24 hours after delivery in order to compare drugs in reduction of postpartum haemorrhage.
Starting date	2009-12-22
Contact information	Simindokht Moradi Kosar Hospital Qazvin Iran, Islamic Republic Of 00982813666770 simindokht56@yahoo.com
Notes	As of June 14, 2011 recruitment has been complete.

IM: intramuscular

DATA AND ANALYSES

Comparison 1. Oral misoprostol versus no uterotonic/placebo (subgroups by dose)

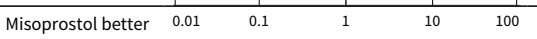
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	3	3965	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.24, 8.81]
1.1 600 mcg	3	3965	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.24, 8.81]
2 Maternal death or severe morbidity	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.36, 3.80]
2.1 600 mcg	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.36, 3.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Severe postpartum haemorrhage (>= 1000 ml)	7		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 600 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Postpartum haemorrhage (>= 500 ml)	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 600 mcg	5		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 400 mcg	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Blood loss (ml)	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 600 mcg	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 400 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Use of additional uterotonics	5	3585	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.08]
6.1 600 mcg	4	2685	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.13]
6.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.61, 1.26]
7 Blood transfusion	4	3519	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.94]
7.1 600 mcg	3	2619	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.94]
7.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.52]
8 Manual removal of placenta	3	1900	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.27, 2.63]
8.1 600 mcg	2	1000	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.30, 5.93]
8.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.06, 2.89]
9 Duration of third stage (minutes)	1	65	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.64, 1.64]
9.1 600 mcg	1	65	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.64, 1.64]
9.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Third stage >= 30 minutes	3	1899	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.90, 4.44]
10.1 600 mcg	2	999	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.61, 5.34]
10.2 400 mcg	2	900	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.70, 7.26]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11 Any side-effect	1	500	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.35, 3.20]
11.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 400 mcg	1	500	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.35, 3.20]
12 Nausea	4	3741	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.64]
12.1 600 mcg	4	3343	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.58]
12.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.20]
13 Vomiting	5	4147	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.52, 1.25]
13.1 600 mcg	5	3749	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.25]
13.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.88]
14 Headache	3	2512	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.65, 3.32]
14.1 600 mcg	3	2114	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.54, 3.03]
14.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 103.49]
15 Abdominal pain	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 600 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Diarrhoea	4	3741	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.42, 2.92]
16.1 600 mcg	4	3343	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.42, 2.92]
16.2 400 mcg	1	398	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Any shivering	8	6332	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [2.66, 3.31]
17.1 600 mcg	7	5434	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [2.68, 3.39]
17.2 400 mcg	2	898	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [1.90, 3.63]
18 Pyrexia (>= 38 degrees C)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 600 mcg	5	4140	Risk Ratio (M-H, Fixed, 95% CI)	5.39 [3.78, 7.69]
18.2 400 mcg	1	400	Risk Ratio (M-H, Fixed, 95% CI)	5.6 [2.21, 14.21]

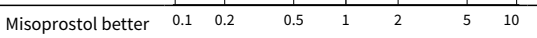
Analysis 1.1. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 1 Maternal death.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 600 mcg					
Gambia 2005	2/630	0/599		25.42%	4.75[0.23,98.83]
India 2006c	0/812	1/808		74.58%	0.33[0.01,8.13]
Pakistan 2011	0/533	0/583			Not estimable
Subtotal (95% CI)	**1975**	**1990**		**100%**	**1.46[0.24,8.81]**
Total events: 2 (Misoprostol), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.41, df=1(P=0.24); I^2=28.86%					
Test for overall effect: Z=0.41(P=0.68)					
Total (95% CI)	**1975**	**1990**		**100%**	**1.46[0.24,8.81]**
Total events: 2 (Misoprostol), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.41, df=1(P=0.24); I^2=28.86%					
Test for overall effect: Z=0.41(P=0.68)					



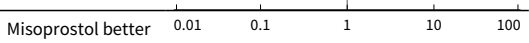
Analysis 1.2. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 2 Maternal death or severe morbidity.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 600 mcg					
Gambia 2005	4/629	3/599		60.52%	1.27[0.29,5.65]
India 2006c	2/812	2/808		39.48%	1[0.14,7.05]
Subtotal (95% CI)	**1441**	**1407**		**100%**	**1.16[0.36,3.8]**
Total events: 6 (Misoprostol), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					
Total (95% CI)	**1441**	**1407**		**100%**	**1.16[0.36,3.8]**
Total events: 6 (Misoprostol), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					

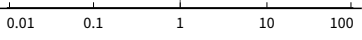


Analysis 1.3. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 3 Severe postpartum haemorrhage (>= 1000 ml).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.3.1 600 mcg				
India 2006c	2/812	10/808		0.2[0.04,0.91]
Gambia 2005	2/629	4/599		0.48[0.09,2.59]
Pakistan 2011	10/514	19/558		0.57[0.27,1.22]
South Africa 2001	27/300	29/299		0.93[0.56,1.53]

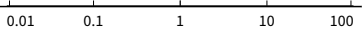


Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
France 2001	16/186	13/220		1.46[0.72,2.95]
South Africa 1998d	17/200	6/200		2.83[1.14,7.04]
1.3.2 400 mcg				
South Africa 1998b	15/250	23/250		0.65[0.35,1.22]
South Africa 1998d	16/200	6/200		2.67[1.07,6.68]



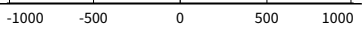
Analysis 1.4. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 4 Postpartum haemorrhage (>= 500 ml).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.4.1 600 mcg				
France 2001	52/186	60/220		1.03[0.75,1.41]
Gambia 2005	69/629	72/599		0.91[0.67,1.25]
India 2006c	52/812	97/808		0.53[0.39,0.74]
Pakistan 2011	85/514	122/558		0.76[0.59,0.97]
Switzerland 1999	2/31	5/34		0.44[0.09,2.1]
1.4.2 400 mcg				



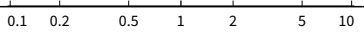
Analysis 1.5. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 5 Blood loss (ml).

Study or subgroup	Misoprostol N	Misoprostol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.5.1 600 mcg						
Gambia 2005	630	281 (175)	599	292 (178)		-11[-30.75,8.75]
India 2006c	811	214.3 (144.6)	808	262.3 (203.2)		-48[-65.19,-30.81]
Pakistan 2011	514	337 (226)	528	366 (262)		-29[-58.68,0.68]
Switzerland 1999	31	345 (10.5)	34	417 (151)		-72[-122.9,-21.1]
1.5.2 400 mcg						
China 2003a	80	212 (76)	76	243 (87)		-31[-56.69,-5.31]



Analysis 1.6. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 6 Use of additional uterotonics.

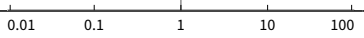
Study or subgroup	Misoprostol better n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 600 mcg					
India 2006c	3/812	6/808		3.97%	0.5[0.12,1.98]
South Africa 1998d	32/200	23/200		15.19%	1.39[0.85,2.29]
South Africa 2001	42/300	54/300		35.66%	0.78[0.54,1.13]
Switzerland 1999	5/31	13/34		8.19%	0.42[0.17,1.05]
Subtotal (95% CI)	**1343**	**1342**		**63.02%**	**0.86[0.66,1.13]**
Total events: 82 (Misoprostol better), 96 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.82, df=3(P=0.08); I^2=55.99%					
Test for overall effect: Z=1.07(P=0.28)					
1.6.2 400 mcg					
South Africa 1998b	21/250	33/250		21.79%	0.64[0.38,1.07]
South Africa 1998d	28/200	23/200		15.19%	1.22[0.73,2.04]
Subtotal (95% CI)	**450**	**450**		**36.98%**	**0.88[0.61,1.26]**
Total events: 49 (Misoprostol better), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.03, df=1(P=0.08); I^2=66.96%					
Test for overall effect: Z=0.73(P=0.47)					
Total (95% CI)	**1793**	**1792**		**100%**	**0.87[0.7,1.08]**
Total events: 131 (Misoprostol better), 152 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.85, df=5(P=0.08); I^2=49.24%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%					



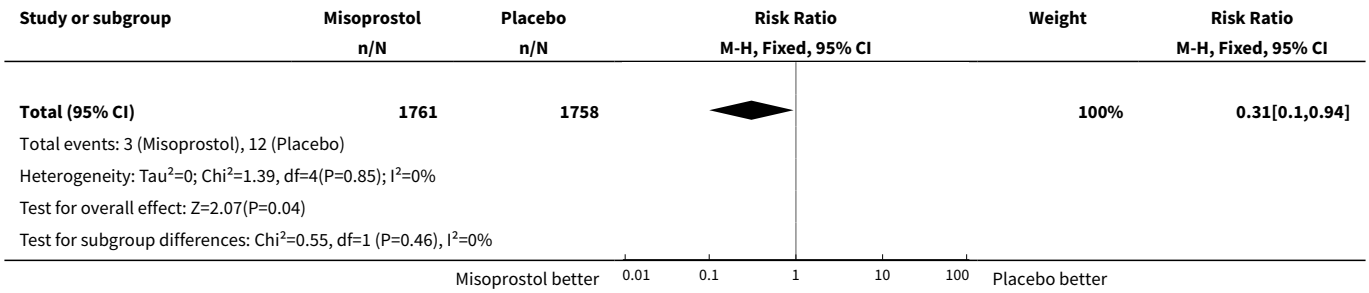
Misoprostol better — Placebo better

Analysis 1.7. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 7 Blood transfusion.

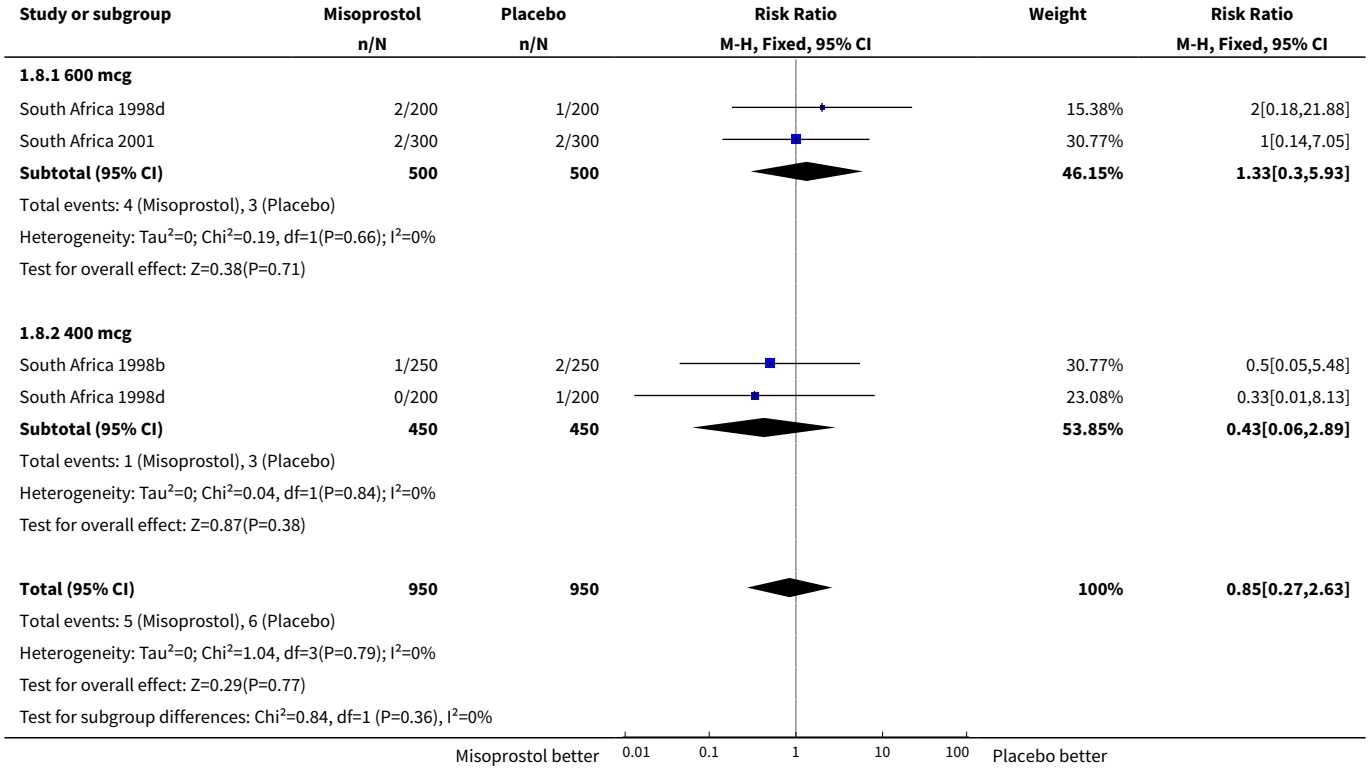
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 600 mcg					
India 2006c	1/812	7/808		53.92%	0.14[0.02,1.15]
South Africa 1998d	0/200	1/200		11.53%	0.33[0.01,8.13]
South Africa 2001	1/299	2/300		15.34%	0.5[0.05,5.5]
Subtotal (95% CI)	**1311**	**1308**		**80.79%**	**0.24[0.06,0.94]**
Total events: 2 (Misoprostol), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=2(P=0.72); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
1.7.2 400 mcg					
South Africa 1998b	1/250	1/250		7.68%	1[0.06,15.9]
South Africa 1998d	0/200	1/200		11.53%	0.33[0.01,8.13]
Subtotal (95% CI)	**450**	**450**		**19.21%**	**0.6[0.08,4.52]**
Total events: 1 (Misoprostol), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=1(P=0.61); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					



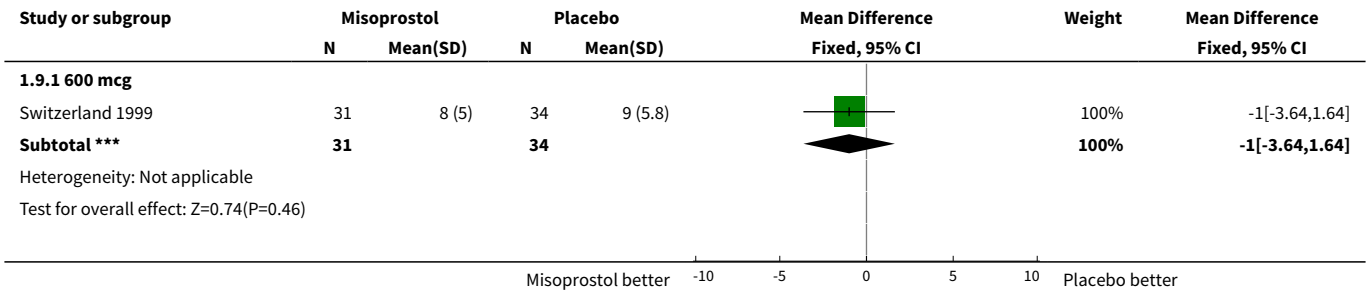
Misoprostol better — Placebo better

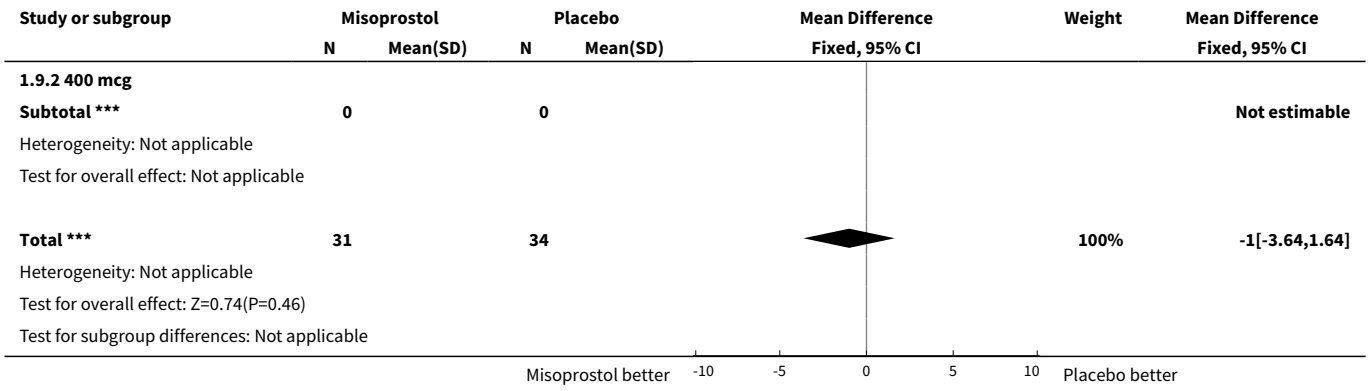


Analysis 1.8. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 8 Manual removal of placenta.

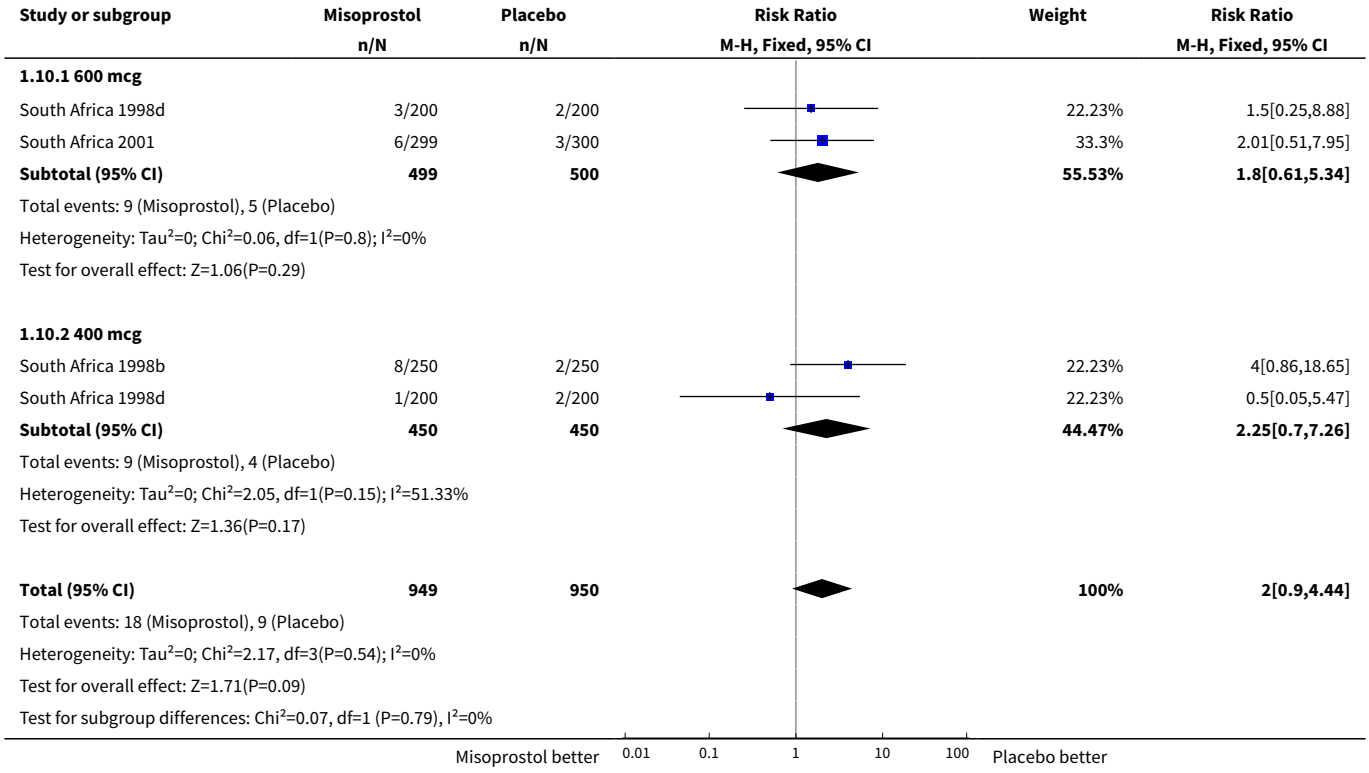


Analysis 1.9. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 9 Duration of third stage (minutes).

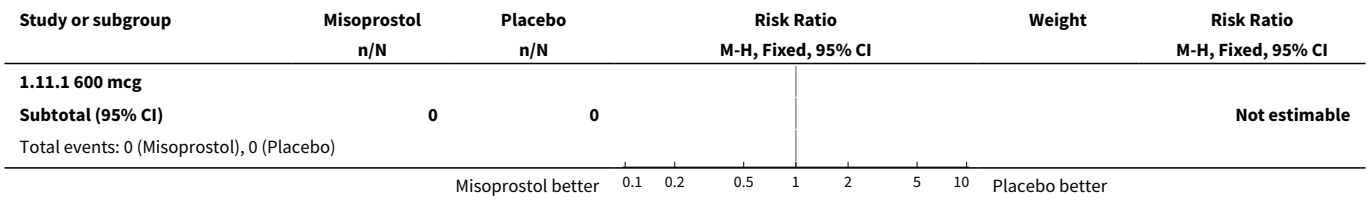


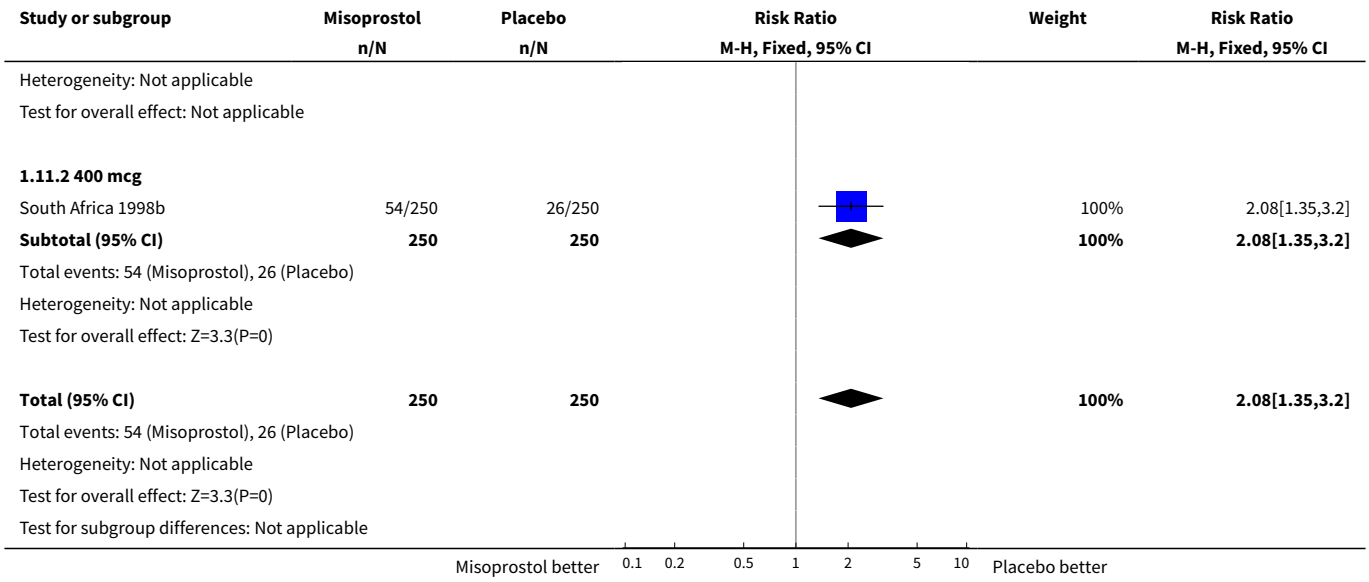


Analysis 1.10. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 10 Third stage >= 30 minutes.

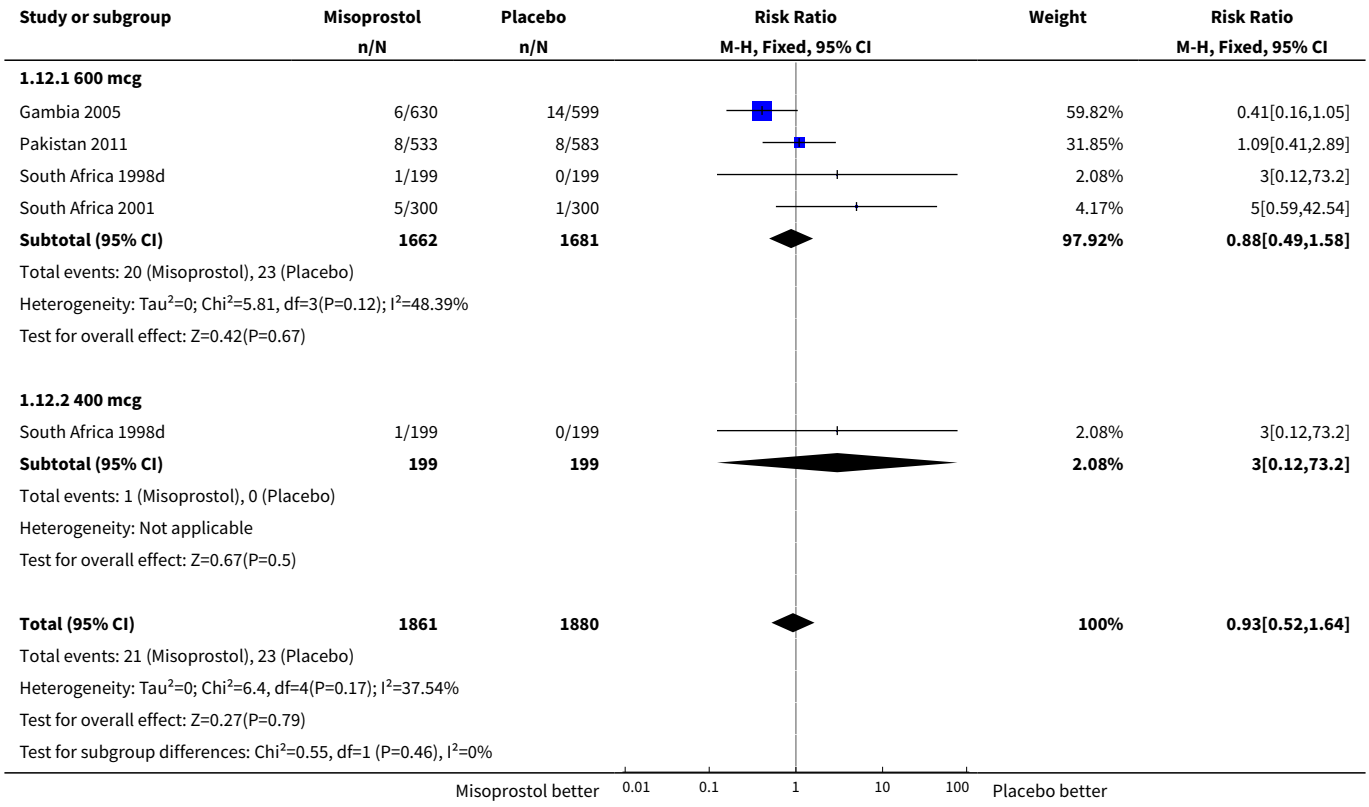


Analysis 1.11. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 11 Any side-effect.



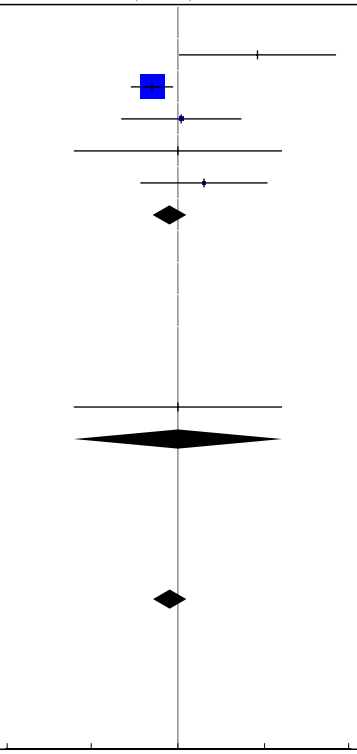


Analysis 1.12. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 12 Nausea.



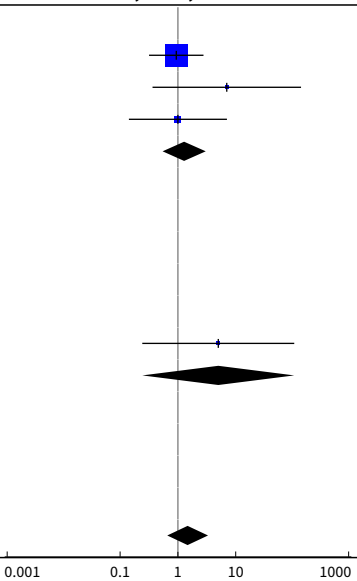
Analysis 1.13. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 13 Vomiting.

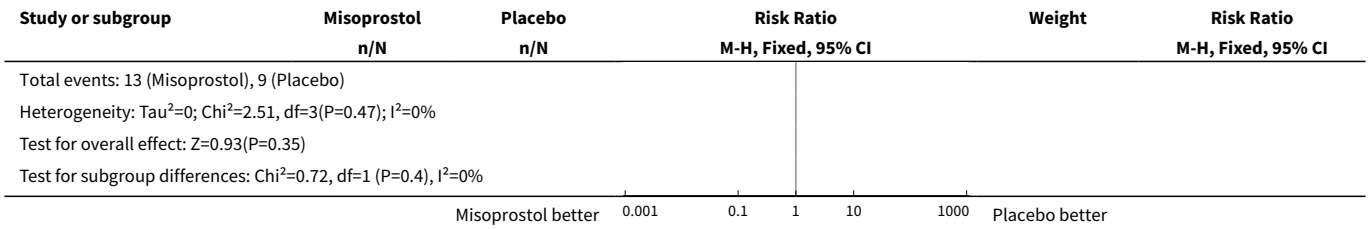
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 600 mcg					
France 2001	7/186	1/220		2.15%	8.28[1.03,66.68]
Gambia 2005	18/630	34/599		81.75%	0.5[0.29,0.88]
Pakistan 2011	3/533	3/583		6.72%	1.09[0.22,5.4]
South Africa 1998d	1/199	1/199		2.35%	1[0.06,15.88]
South Africa 2001	4/300	2/300		4.69%	2[0.37,10.84]
Subtotal (95% CI)	**1848**	**1901**		**97.65%**	**0.8[0.51,1.25]**
Total events: 33 (Misoprostol), 41 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.74, df=4(P=0.07); I^2=54.26%					
Test for overall effect: Z=0.99(P=0.32)					
1.13.2 400 mcg					
South Africa 1998d	1/199	1/199		2.35%	1[0.06,15.88]
Subtotal (95% CI)	**199**	**199**		**2.35%**	**1[0.06,15.88]**
Total events: 1 (Misoprostol), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**2047**	**2100**		**100%**	**0.8[0.52,1.25]**
Total events: 34 (Misoprostol), 42 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.79, df=5(P=0.12); I^2=43.12%					
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



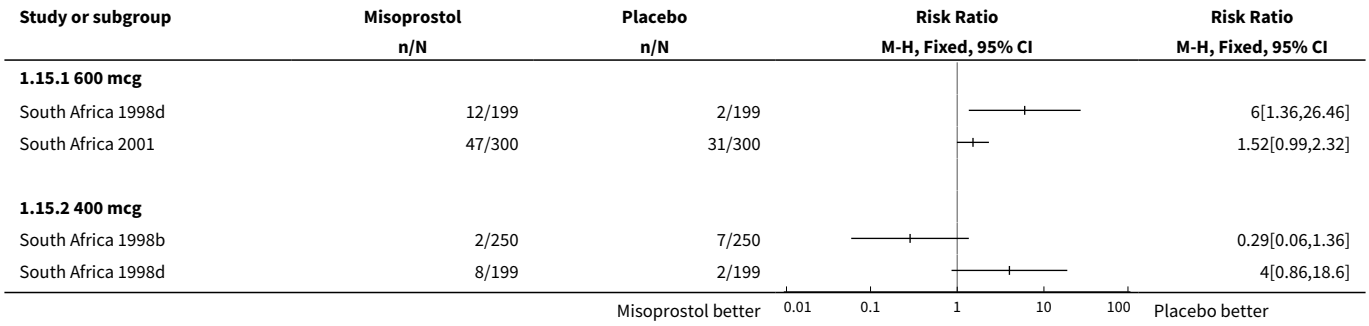
Analysis 1.14. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 14 Headache.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 600 mcg					
Pakistan 2011	6/533	7/583		69.03%	0.94[0.32,2.77]
South Africa 1998d	3/199	0/199		5.16%	7[0.36,134.64]
South Africa 2001	2/300	2/300		20.65%	1[0.14,7.05]
Subtotal (95% CI)	**1032**	**1082**		**94.84%**	**1.28[0.54,3.03]**
Total events: 11 (Misoprostol), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.65, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					
1.14.2 400 mcg					
South Africa 1998d	2/199	0/199		5.16%	5[0.24,103.49]
Subtotal (95% CI)	**199**	**199**		**5.16%**	**5[0.24,103.49]**
Total events: 2 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
Total (95% CI)	**1231**	**1281**		**100%**	**1.47[0.65,3.32]**

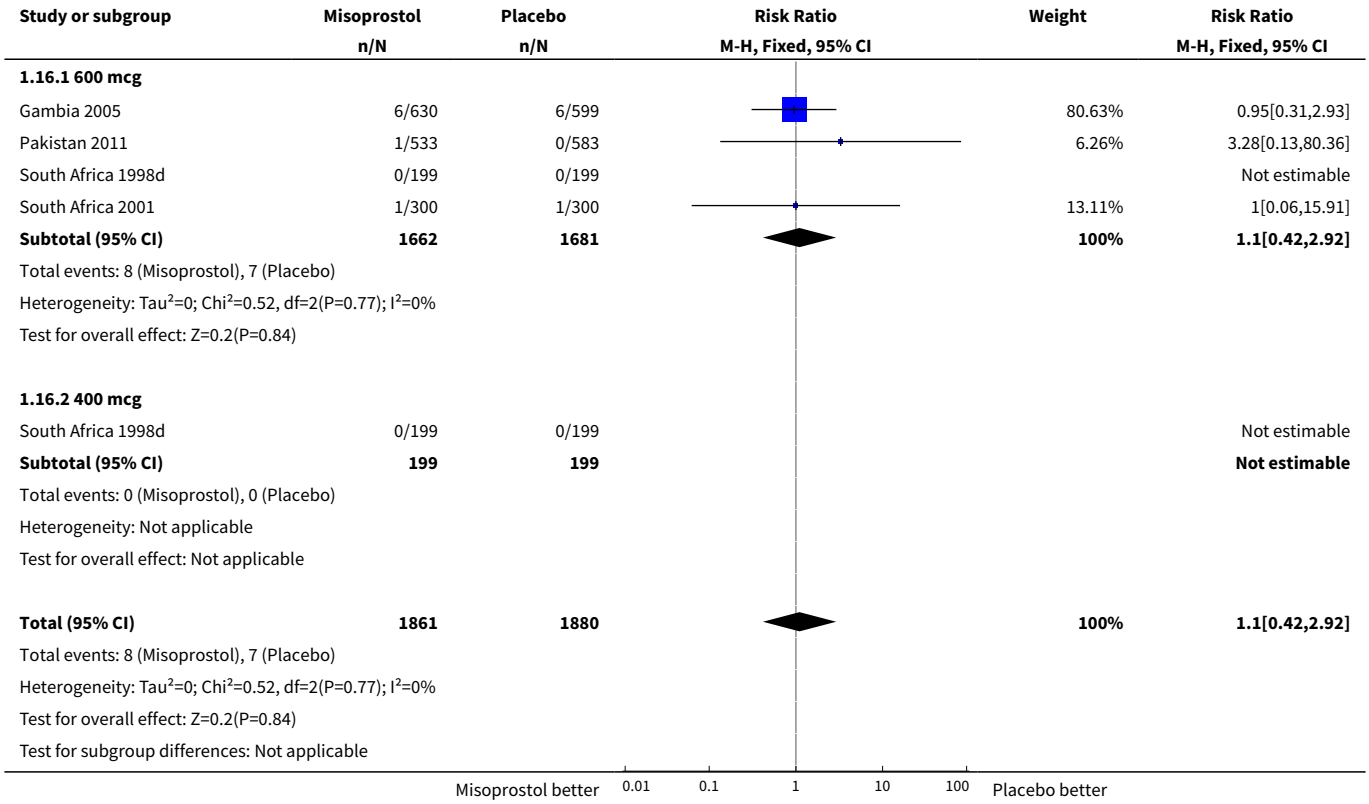




Analysis 1.15. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 15 Abdominal pain.

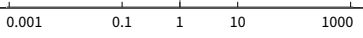


Analysis 1.16. Comparison 1 Oral misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 16 Diarrhoea.



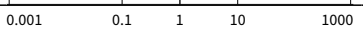
Analysis 1.17. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 17 Any shivering.

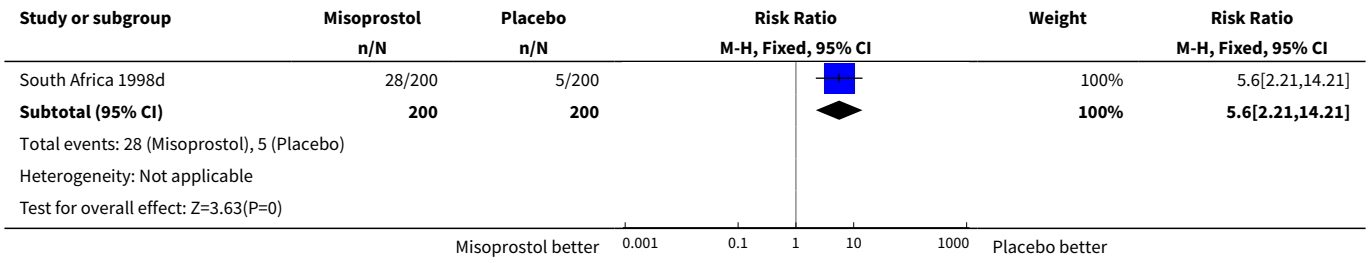
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 600 mcg					
France 2001	5/186	0/220		0.13%	13[0.72,233.56]
Gambia 2005	202/630	70/599		21.02%	2.74[2.14,3.52]
India 2006c	424/812	140/808		41.1%	3.01[2.56,3.55]
Pakistan 2011	50/533	23/583		6.43%	2.38[1.47,3.84]
South Africa 1998d	81/199	30/199		8.78%	2.7[1.87,3.91]
South Africa 2001	133/300	33/300		9.66%	4.03[2.85,5.7]
Switzerland 1999	7/31	1/34		0.28%	7.68[1,58.92]
Subtotal (95% CI)	**2691**	**2743**		**87.41%**	**3.01[2.68,3.39]**
Total events: 902 (Misoprostol), 297 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.33, df=6(P=0.39); I^2=5.24%					
Test for overall effect: Z=18.55(P<0.0001)					
1.17.2 400 mcg					
South Africa 1998b	48/250	13/250		3.81%	3.69[2.05,6.64]
South Africa 1998d	65/199	30/199		8.78%	2.17[1.47,3.19]
Subtotal (95% CI)	**449**	**449**		**12.59%**	**2.63[1.9,3.63]**
Total events: 113 (Misoprostol), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=1(P=0.13); I^2=55.59%					
Test for overall effect: Z=5.88(P<0.0001)					
Total (95% CI)	**3140**	**3192**		**100%**	**2.96[2.66,3.31]**
Total events: 1015 (Misoprostol), 340 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.42, df=8(P=0.31); I^2=15.08%					
Test for overall effect: Z=19.44(P<0.0001)					
Test for subgroup differences: Chi^2=0.61, df=1 (P=0.43), I^2=0%					



Analysis 1.18. Comparison 1 Oral misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 18 Pyrexia (>= 38 degrees C).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 600 mcg					
France 2001	6/186	0/220		1.34%	15.36[0.87,270.93]
India 2006c	34/812	9/808		26.41%	3.76[1.81,7.79]
Pakistan 2011	4/533	7/583		19.57%	0.63[0.18,2.12]
South Africa 1998d	53/200	5/200		14.63%	10.6[4.33,25.96]
South Africa 2001	86/299	13/299		38.05%	6.62[3.78,11.59]
Subtotal (95% CI)	**2030**	**2110**		**100%**	**5.39[3.78,7.69]**
Total events: 183 (Misoprostol), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=16.08, df=4(P=0); I^2=75.12%					
Test for overall effect: Z=9.29(P<0.0001)					
1.18.2 400 mcg					





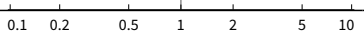
Comparison 2. Rectal misoprostol versus no uterotonic/placebo (subgroups by dose)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Severe postpartum haemor-rhage (>= 1000 mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 400 mcg	1	542	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.35, 1.37]
2 Use of additional uterotonics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.62]
3 Manual removal of placenta	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 74.40]
4 Third stage >= 30 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 400 mcg	1	540	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.56]
5 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.14]
6 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 400 mcg	1	546	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 74.40]
7 Any shivering	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 400 mcg	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.25]

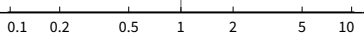
Analysis 2.1. Comparison 2 Rectal misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 1 Severe postpartum haemorrhage (>= 1000 mL).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.2 400 mcg					
South Africa 1998c	13/270	19/272		100%	0.69[0.35,1.37]
Subtotal (95% CI)	**270**	**272**		**100%**	**0.69[0.35,1.37]**
Total events: 13 (Misoprostol), 19 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
Test for subgroup differences: Not applicable					

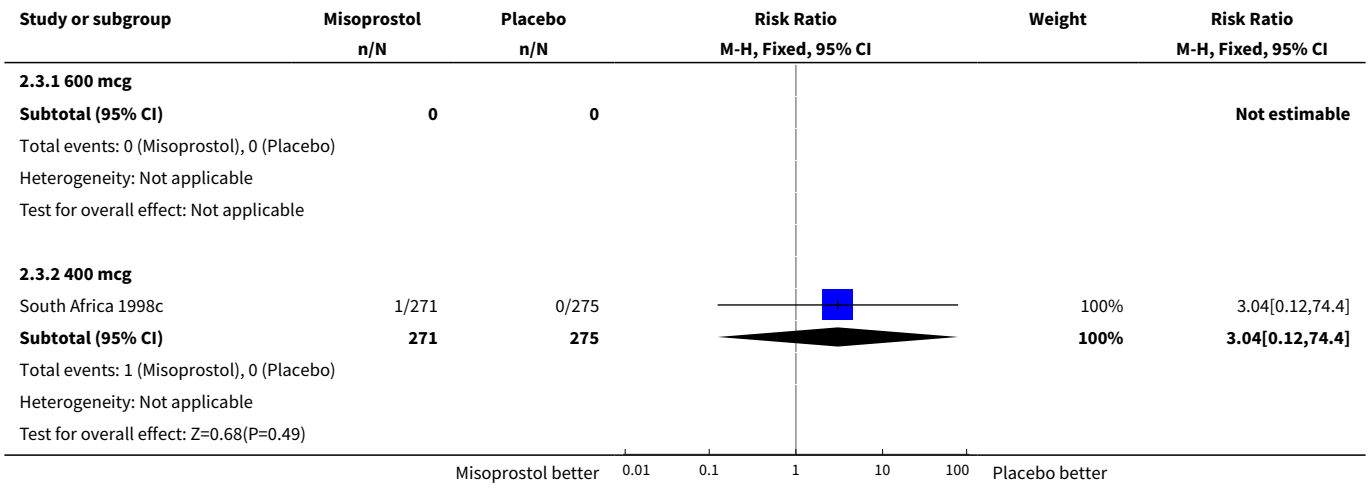


Analysis 2.2. Comparison 2 Rectal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 2 Use of additional uterotonics.

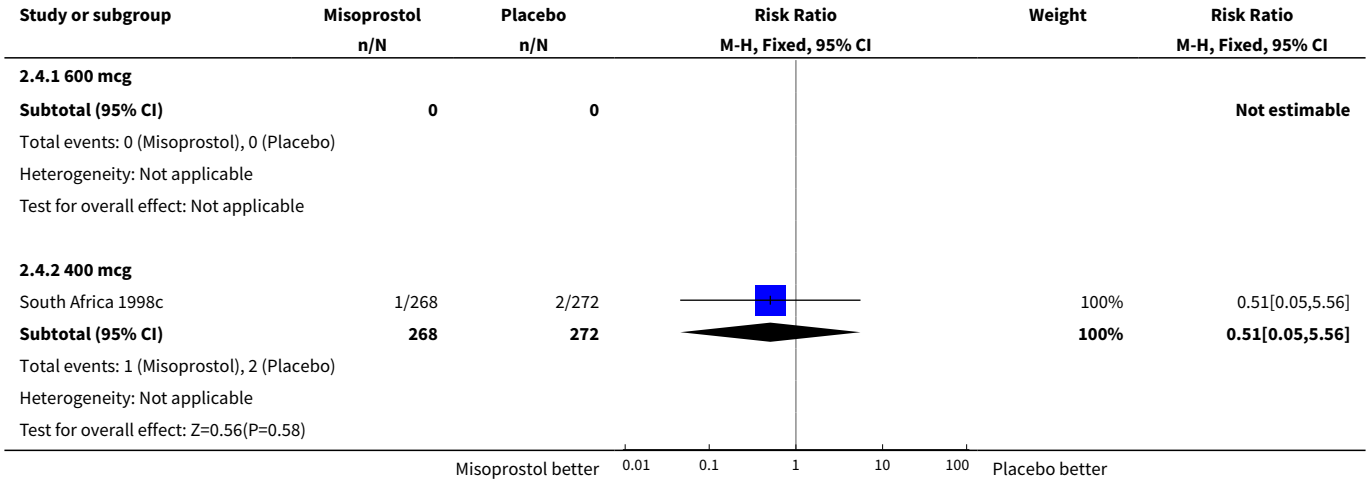
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.2.2 400 mcg					
South Africa 1998c	9/271	13/275		100%	0.7[0.31,1.62]
Subtotal (95% CI)	**271**	**275**		**100%**	**0.7[0.31,1.62]**
Total events: 9 (Misoprostol), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					



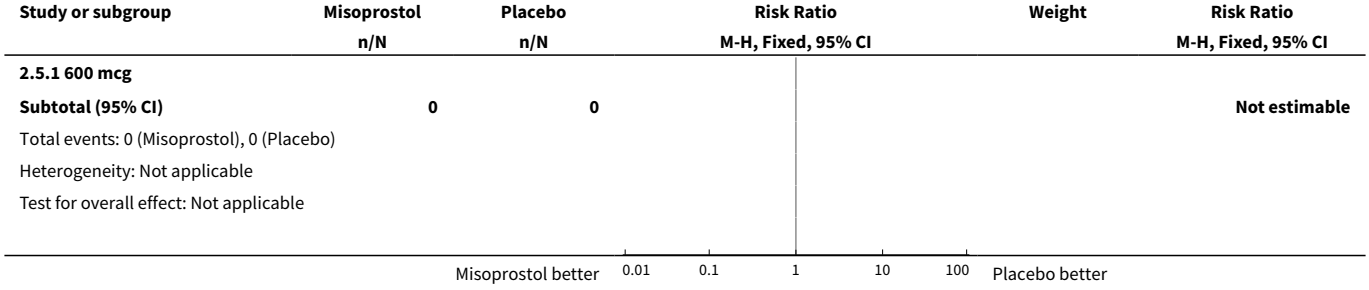
Analysis 2.3. Comparison 2 Rectal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 3 Manual removal of placenta.

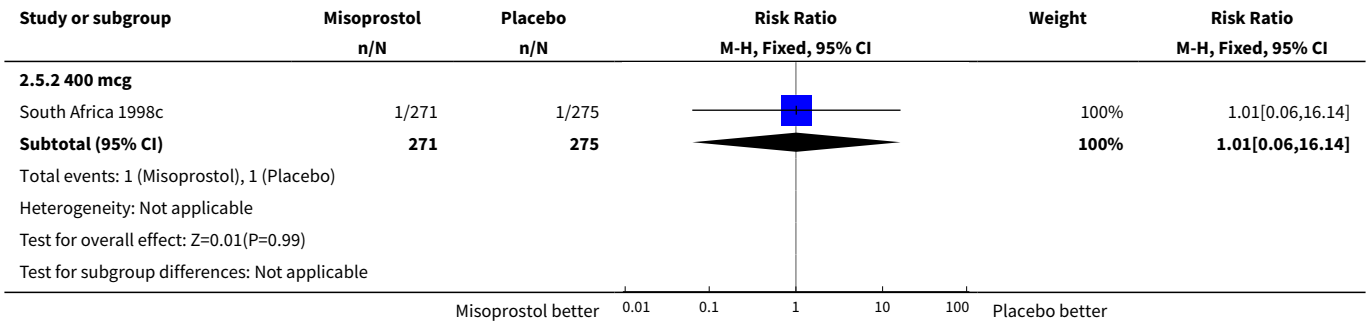


Analysis 2.4. Comparison 2 Rectal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 4 Third stage >= 30 minutes.

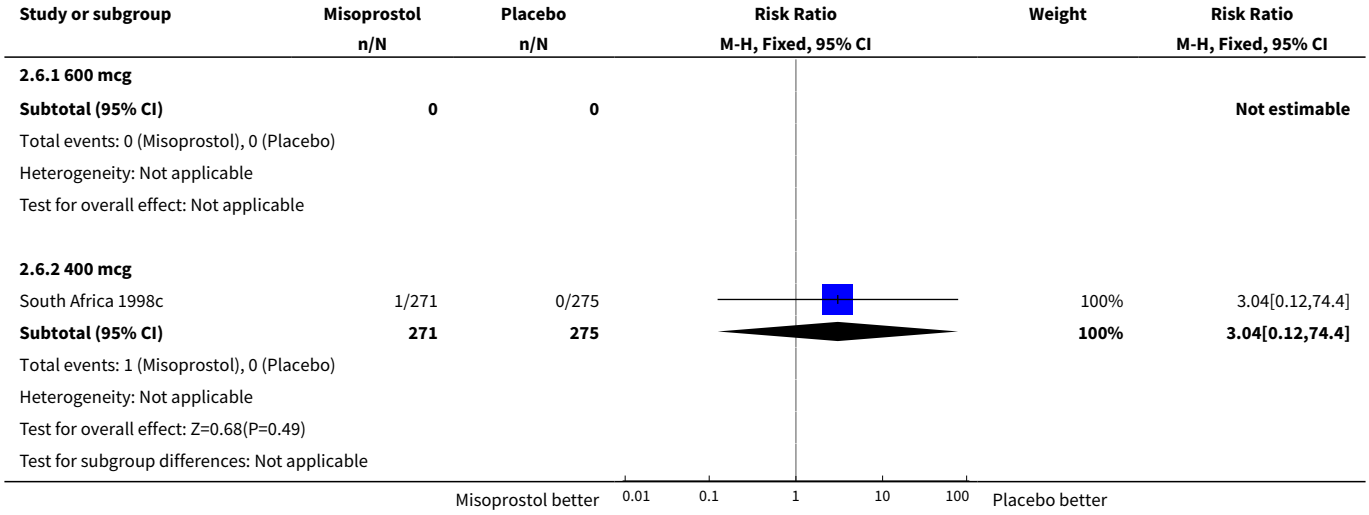


Analysis 2.5. Comparison 2 Rectal misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 5 Vomiting.

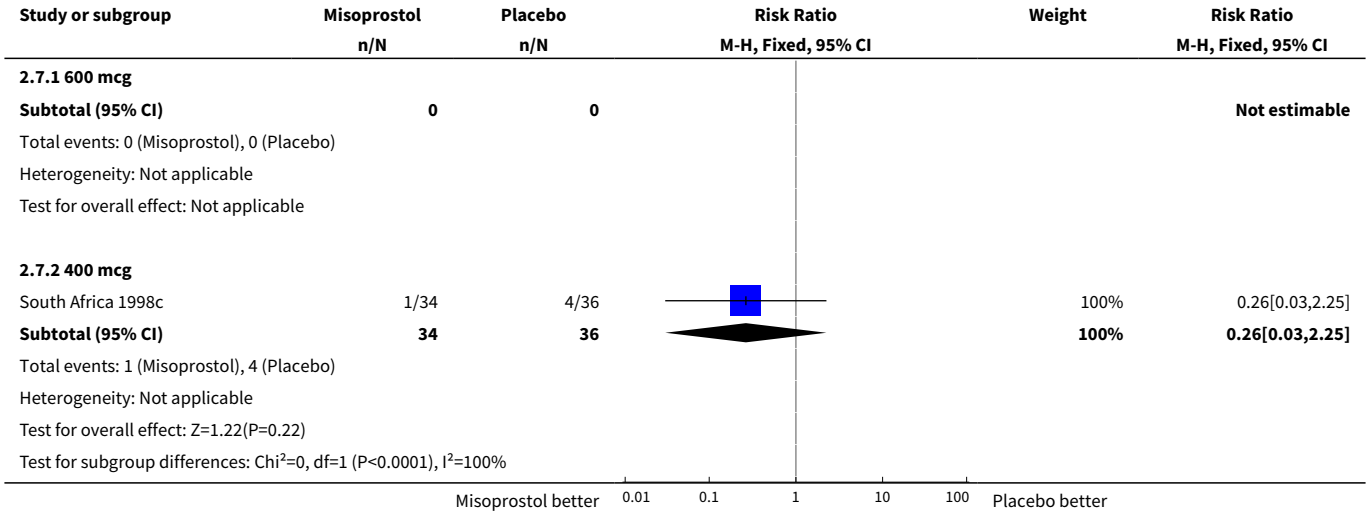




Analysis 2.6. Comparison 2 Rectal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 6 Abdominal pain.



Analysis 2.7. Comparison 2 Rectal misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 7 Any shivering.

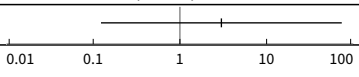


Comparison 3. Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Severe postpartum haemorrhage (>= 1000 mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.45, 0.98]
2.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Postpartum haemorrhage (>= 500 mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
3.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.09, 2.72]
4.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.79, 7.92]
5.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.79, 7.92]
6.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Any shivering	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.96, 3.01]
7.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Pyrexia (>= 38 degrees C)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [3.85, 13.12]
8.1 600 mcg	1	661	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [3.85, 13.12]
8.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

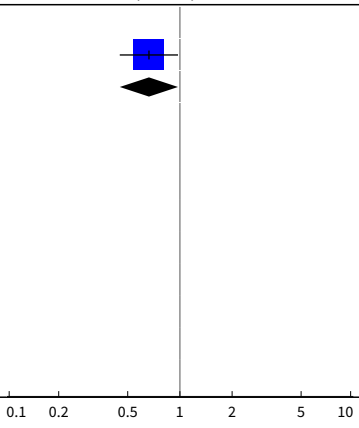
Analysis 3.1. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 1 Maternal death.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Guinea-Bissau 2005	1/330	0/331		0%	3.01[0.12,73.6]



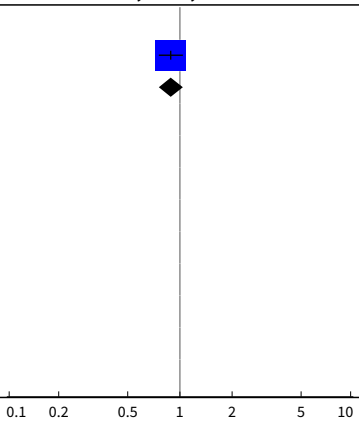
Analysis 3.2. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 2 Severe postpartum haemorrhage (>= 1000 mL).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 600 mcg					
Guinea-Bissau 2005	37/330	56/331		100%	0.66[0.45,0.98]
Subtotal (95% CI)	**330**	**331**		**100%**	**0.66[0.45,0.98]**
Total events: 37 (Misoprostol), 56 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
3.2.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



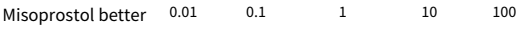
Analysis 3.3. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 3 Postpartum haemorrhage (>= 500 mL).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 600 mcg					
Guinea-Bissau 2005	150/330	170/331		100%	0.89[0.76,1.04]
Subtotal (95% CI)	**330**	**331**		**100%**	**0.89[0.76,1.04]**
Total events: 150 (Misoprostol), 170 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
3.3.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



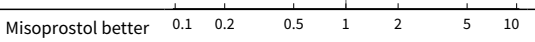
Analysis 3.4. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 4 Nausea.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 600 mcg					
Guinea-Bissau 2005	2/330	4/331		100%	0.5[0.09,2.72]
Subtotal (95% CI)	**330**	**331**		**100%**	**0.5[0.09,2.72]**
Total events: 2 (Misoprostol), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
3.4.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



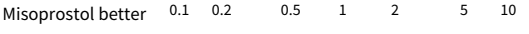
Analysis 3.5. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 5 Vomiting.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 600 mcg					
Guinea-Bissau 2005	10/330	4/331		100%	2.51[0.79,7.92]
Subtotal (95% CI)	**330**	**331**		**100%**	**2.51[0.79,7.92]**
Total events: 10 (Misoprostol), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.57(P=0.12)					
3.5.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 3.6. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 6 Diarrhoea.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 600 mcg					
Guinea-Bissau 2005	10/330	4/331		100%	2.51[0.79,7.92]
Subtotal (95% CI)	**330**	**331**		**100%**	**2.51[0.79,7.92]**
Total events: 10 (Misoprostol), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.57(P=0.12)					



Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Misoprostol better 0.1 0.2 0.5 1 2 5 10 Placebo better

Analysis 3.7. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 7 Any shivering.

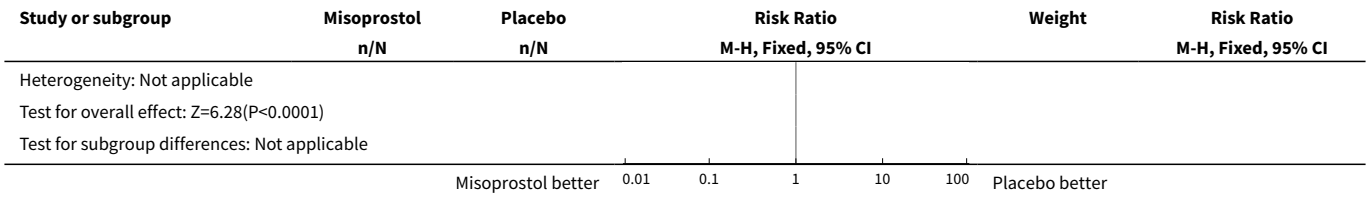
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 600 mcg					
Guinea-Bissau 2005	189/330	78/331		100%	2.43[1.96,3.01]
Subtotal (95% CI)	**330**	**331**		**100%**	**2.43[1.96,3.01]**
Total events: 189 (Misoprostol), 78 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.09(P<0.0001)					
3.7.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Misoprostol better 0.1 0.2 0.5 1 2 5 10 Placebo better

Analysis 3.8. Comparison 3 Sublingual misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 8 Pyrexia (>= 38 degrees C).

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 600 mcg					
Guinea-Bissau 2005	78/330	11/331		100%	7.11[3.85,13.12]
Subtotal (95% CI)	**330**	**331**		**100%**	**7.11[3.85,13.12]**
Total events: 78 (Misoprostol), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.28(P<0.0001)					
3.8.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**330**	**331**		**100%**	**7.11[3.85,13.12]**
Total events: 78 (Misoprostol), 11 (Placebo)					

Misoprostol better 0.01 0.1 1 10 100 Placebo better

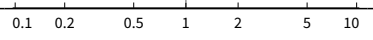


Comparison 4. Buccal misoprostol versus no uterotonic/placebo (subgroups by dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (>= 1000 mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 200 mcg	1	352	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.66, 1.94]
2 Use of additional uterotonics	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 200 mcg	2	1108	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.85]
3 Blood transfusion	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 400 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 200 mcg	2	1108	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.24, 1.89]
4 Blood loss (mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 400 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 200 mcg	1	352	Mean Difference (IV, Fixed, 95% CI)	24.0 [-16.36, 64.36]

Analysis 4.1. Comparison 4 Buccal misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 1 Severe postpartum haemorrhage (>= 1000 mL).

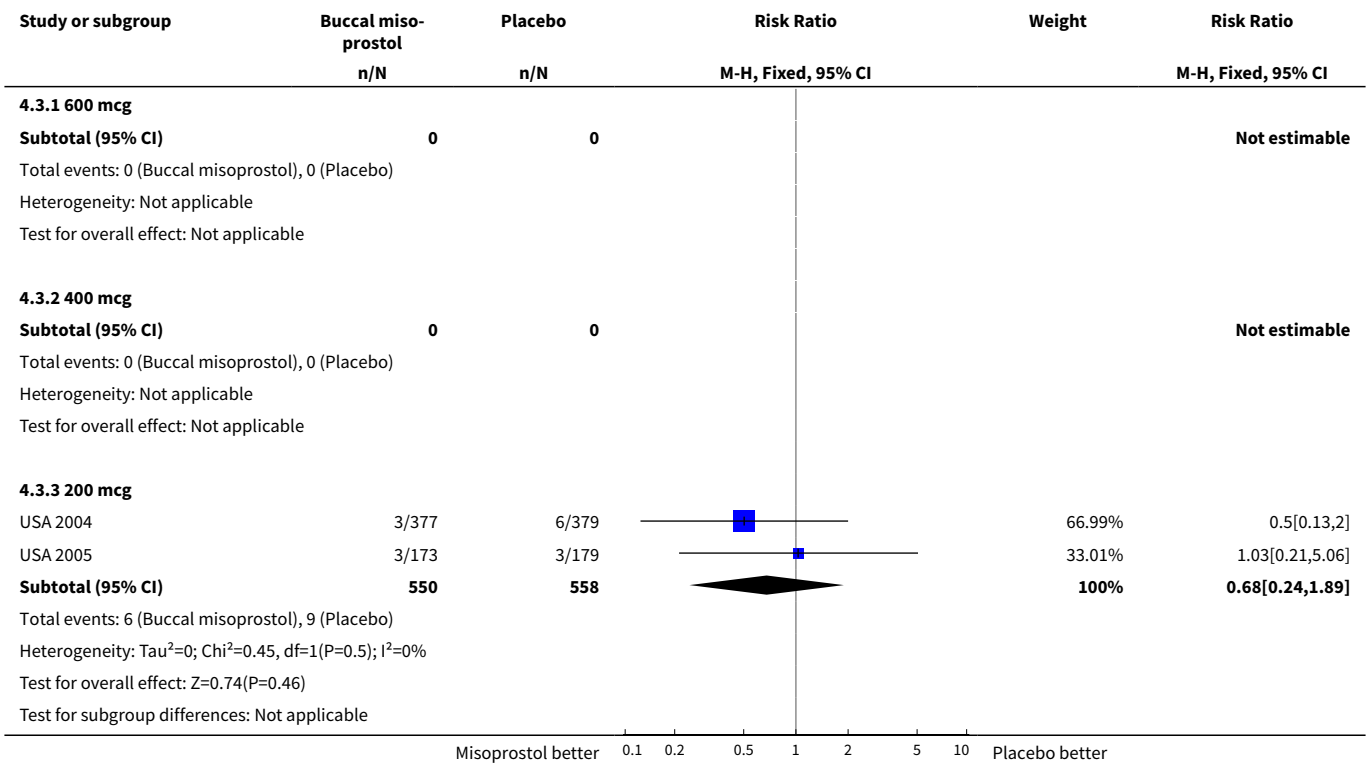
Study or subgroup	Buccal misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Buccal misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.1.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Buccal misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.1.3 200 mcg					
USA 2005	24/173	22/179		100%	1.13[0.66,1.94]
Subtotal (95% CI)	**173**	**179**		**100%**	**1.13[0.66,1.94]**
Total events: 24 (Buccal misoprostol), 22 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					



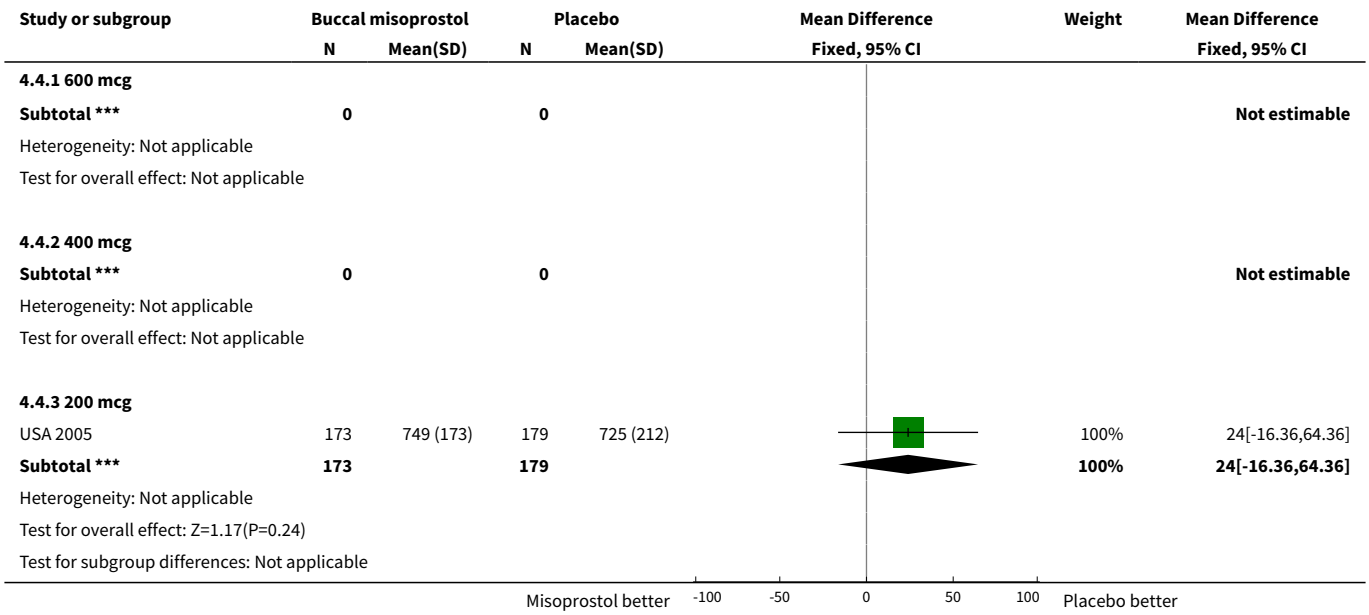
Analysis 4.2. Comparison 4 Buccal misoprostol versus no uterotonic/placebo (subgroups by dose), Outcome 2 Use of additional uterotonics.

Study or subgroup	Buccal misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Buccal misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.2 400 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Buccal misoprostol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.3 200 mcg					
USA 2004	10/377	13/379		14.79%	0.77[0.34,1.74]
USA 2005	45/173	76/179		85.21%	0.61[0.45,0.83]
Subtotal (95% CI)	**550**	**558**		**100%**	**0.64[0.48,0.85]**
Total events: 55 (Buccal misoprostol), 89 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=3.09(P=0)					

Analysis 4.3. Comparison 4 Buccal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 3 Blood transfusion.



Analysis 4.4. Comparison 4 Buccal misoprostol versus no uterotonic/ placebo (subgroups by dose), Outcome 4 Blood loss (mL).



Comparison 5. Oral misoprostol versus injectable uterotonics (subgroups by dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	4	20199	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.10]
1.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 600 mcg	2	18829	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.10]
1.3 400 mcg	2	920	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Severe postpartum haemorrhage (>= 1000 mL)	17	29797	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.16, 1.52]
2.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 600 mcg	6	21977	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.17, 1.58]
2.3 500 mcg	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.43, 1.98]
2.4 400 mcg	9	6330	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.89, 1.75]
3 Postpartum haemorrhage (>= 500 mL)	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.63]
3.2 600 mcg	7	22164	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.34, 1.52]
3.3 500 mcg	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.41]
3.4 400 mcg	8	5496	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.34]
4 Blood loss (mL)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 800 mcg	1	53	Mean Difference (IV, Fixed, 95% CI)	-29.0 [-158.67, 100.67]
4.2 600 mcg	3	20897	Mean Difference (IV, Fixed, 95% CI)	42.14 [35.44, 48.84]
4.3 400 mcg	7	4537	Mean Difference (IV, Fixed, 95% CI)	-7.54 [-16.16, 1.08]
5 Use of additional uterotonics	17		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 800 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 600 mcg	6		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 500 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 400 mcg	8		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Blood transfusion	15	28213	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.06]

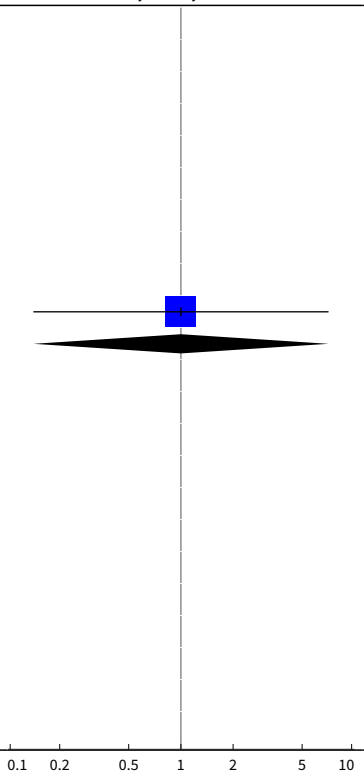
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 800 mcg	1	443	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.45]
6.2 600 mcg	5	21600	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.59, 1.02]
6.3 500 mcg	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.34, 1.95]
6.4 400 mcg	8	5130	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.91]
7 Postpartum haemoglobin	2	805	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.18, 0.28]
7.1 800 mcg	1	450	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.23, 0.43]
7.2 400 mcg	1	355	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.33, 0.33]
8 Haematocrit drop 10% or more	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.47, 2.52]
8.1 400 mcg	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.47, 2.52]
9 Haemoglobin drop 30 mg/L or more	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.88]
9.1 400 mcg	1	585	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.88]
10 Manual removal of placenta	15	26765	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.12]
10.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 600 mcg	6	21806	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.16]
10.3 500 mcg	1	1000	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.57]
10.4 400 mcg	8	3509	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.41]
11 Duration of third stage (minutes)	6	22690	Mean Difference (IV, Fixed, 95% CI)	0.44 [0.22, 0.66]
11.1 600 mcg	2	18811	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.21, 0.58]
11.2 400 mcg	5	3879	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.29, 0.82]
12 Third stage >= 30 minutes	8	5580	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.62, 1.42]
12.1 600 mcg	4	2954	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.53, 1.89]
12.2 500 mcg	1	1000	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.44, 1.95]
12.3 400 mcg	3	1626	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.36, 1.90]
13 Any side-effect	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 500 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 400 mcg	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.16, 1.77]
14 Nausea	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 800 mcg	2	498	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.10, 1.94]
14.2 600 mcg	6	21793	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.90, 1.41]
14.3 500 mcg	1	846	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.85]
14.4 400 mcg	6	3774	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
15 Vomiting	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 800 mcg	1	445	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.25]
15.2 600 mcg	7	22175	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.97, 1.58]
15.3 500 mcg	1	846	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.23]
15.4 400 mcg	8	5439	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.37, 0.86]
16 Diarrhoea	13	27011	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.34, 2.50]
16.1 800 mcg	1	439	Risk Ratio (M-H, Fixed, 95% CI)	10.85 [0.60, 195.06]
16.2 600 mcg	5	20326	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [1.60, 3.98]
16.3 500 mcg	1	846	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.19]
16.4 400 mcg	8	5400	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.67, 2.22]
17 Headache	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 800 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 600 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 500 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.4 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Any shivering	19		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 800 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 600 mcg	7		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 500 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

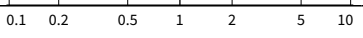
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.4 400 mcg	9		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Severe shivering	5	20823	Risk Ratio (M-H, Fixed, 95% CI)	7.24 [4.74, 11.08]
19.1 600 mcg	3	19038	Risk Ratio (M-H, Fixed, 95% CI)	7.28 [4.71, 11.24]
19.2 500 mcg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.52, 156.91]
19.3 400 mcg	2	1745	Risk Ratio (M-H, Fixed, 95% CI)	4.23 [0.20, 87.88]
20 Pyrexia (>= 38 degrees C)	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 600 mcg	7	22137	Risk Ratio (M-H, Fixed, 95% CI)	6.77 [5.55, 8.27]
20.2 500 mcg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 400 mcg	5	2642	Risk Ratio (M-H, Fixed, 95% CI)	6.68 [3.74, 11.93]

Analysis 5.1. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 1 Maternal death.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 800 mcg					
Ghana 2006	0/225	0/225			Not estimable
Subtotal (95% CI)	**225**	**225**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.1.2 600 mcg					
WHO 1999	0/199	0/100			Not estimable
WHO 2001	2/9264	2/9266		100%	1[0.14,7.1]
Subtotal (95% CI)	**9463**	**9366**		**100%**	**1[0.14,7.1]**
Total events: 2 (Misoprostol), 2 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0(P=1)					
5.1.3 400 mcg					
Canada 2005	0/311	0/311			Not estimable
WHO 1999	0/198	0/100			Not estimable
Subtotal (95% CI)	**509**	**411**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



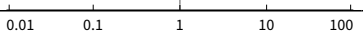
Study or subgroup	Misoprostol	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Total (95% CI)	**10197**	**10002**		**100%**	**1[0.14,7.1]**
Total events: 2 (Misoprostol), 2 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0(P=1)					
Test for subgroup differences: Not applicable					



Misoprostol better — Injectables better

Analysis 5.2. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 2 Severe postpartum haemorrhage (>= 1000 mL).

Study or subgroup	Misoprostol	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
5.2.1 800 mcg					
Ghana 2006	0/225	0/225			Not estimable
Subtotal (95% CI)	**225**	**225**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.2.2 600 mcg					
Belgium 1999	1/100	0/100		0.14%	3[0.12,72.77]
France 2001	16/186	12/196		3.22%	1.41[0.68,2.89]
Hong Kong 2001	5/1026	4/1032		1.1%	1.26[0.34,4.67]
Nigeria 2003	0/247	0/249			Not estimable
WHO 1999	8/199	13/200		3.57%	0.62[0.26,1.46]
WHO 2001	366/9214	263/9228		72.38%	1.39[1.19,1.63]
Subtotal (95% CI)	**10972**	**11005**		**80.4%**	**1.36[1.17,1.58]**
Total events: 396 (Misoprostol), 292 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=3.59, df=4(P=0.46); I^2=0%					
Test for overall effect: Z=4.07(P<0.0001)					
5.2.3 500 mcg					
United Kingdom 2000	9/501	10/499		2.76%	0.9[0.37,2.19]
United Kingdom 2001b	3/20	3/20		0.83%	1[0.23,4.37]
Subtotal (95% CI)	**521**	**519**		**3.59%**	**0.92[0.43,1.98]**
Total events: 12 (Misoprostol), 13 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					
5.2.4 400 mcg					
Australia 1999	13/424	7/439		1.89%	1.92[0.77,4.77]
Bangladesh 2007	5/210	3/190		0.87%	1.51[0.37,6.23]
Canada 2005	14/311	7/311		1.93%	2[0.82,4.89]
China 2007	2/178	1/177		0.28%	1.99[0.18,21.74]
Ghana 2000	0/202	0/196			Not estimable
India 2006b	1/730	10/1293		1.99%	0.18[0.02,1.38]
Turkey 2003	14/388	15/384		4.15%	0.92[0.45,1.89]
WHO 1999	14/198	13/200		3.56%	1.09[0.52,2.25]



Misoprostol better — Injectables better

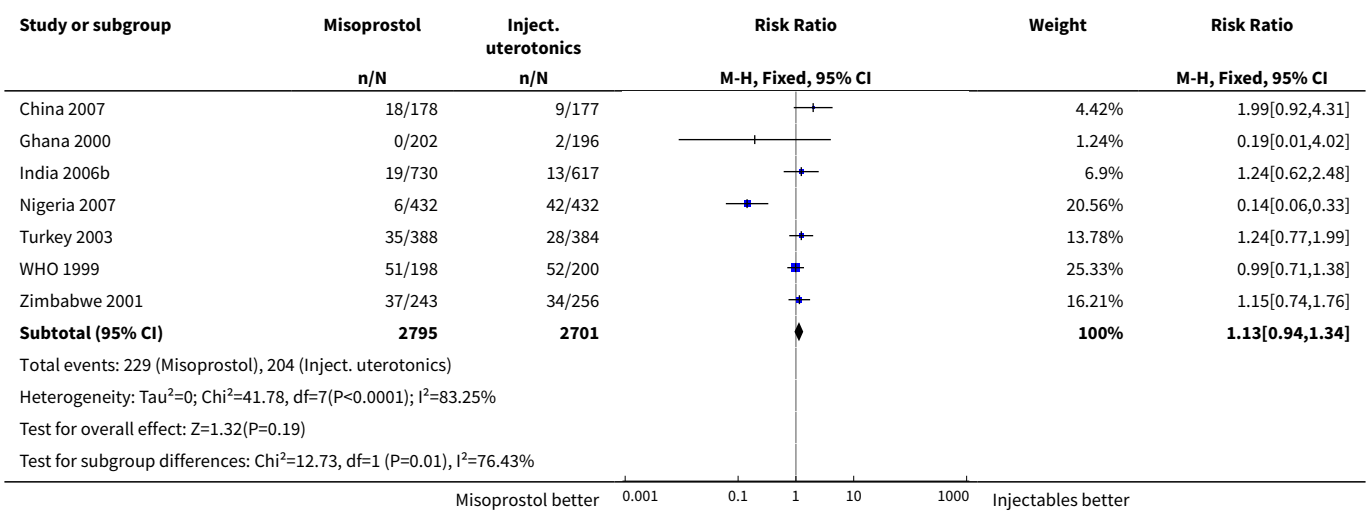
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zimbabwe 2001	9/243	5/256		1.34%	1.9[0.64,5.58]
Subtotal (95% CI)	**2884**	**3446**		**16.01%**	**1.25[0.89,1.75]**
Total events: 72 (Misoprostol), 61 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=7.02, df=7(P=0.43); I^2=0.32%					
Test for overall effect: Z=1.27(P=0.2)					
Total (95% CI)	**14602**	**15195**		**100%**	**1.33[1.16,1.52]**
Total events: 480 (Misoprostol), 366 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=11.56, df=14(P=0.64); I^2=0%					
Test for overall effect: Z=4.14(P<0.0001)					
Test for subgroup differences: Chi^2=1.12, df=1 (P=0.57), I^2=0%					

Misoprostol better 0.01 0.1 1 10 100 Injectables better

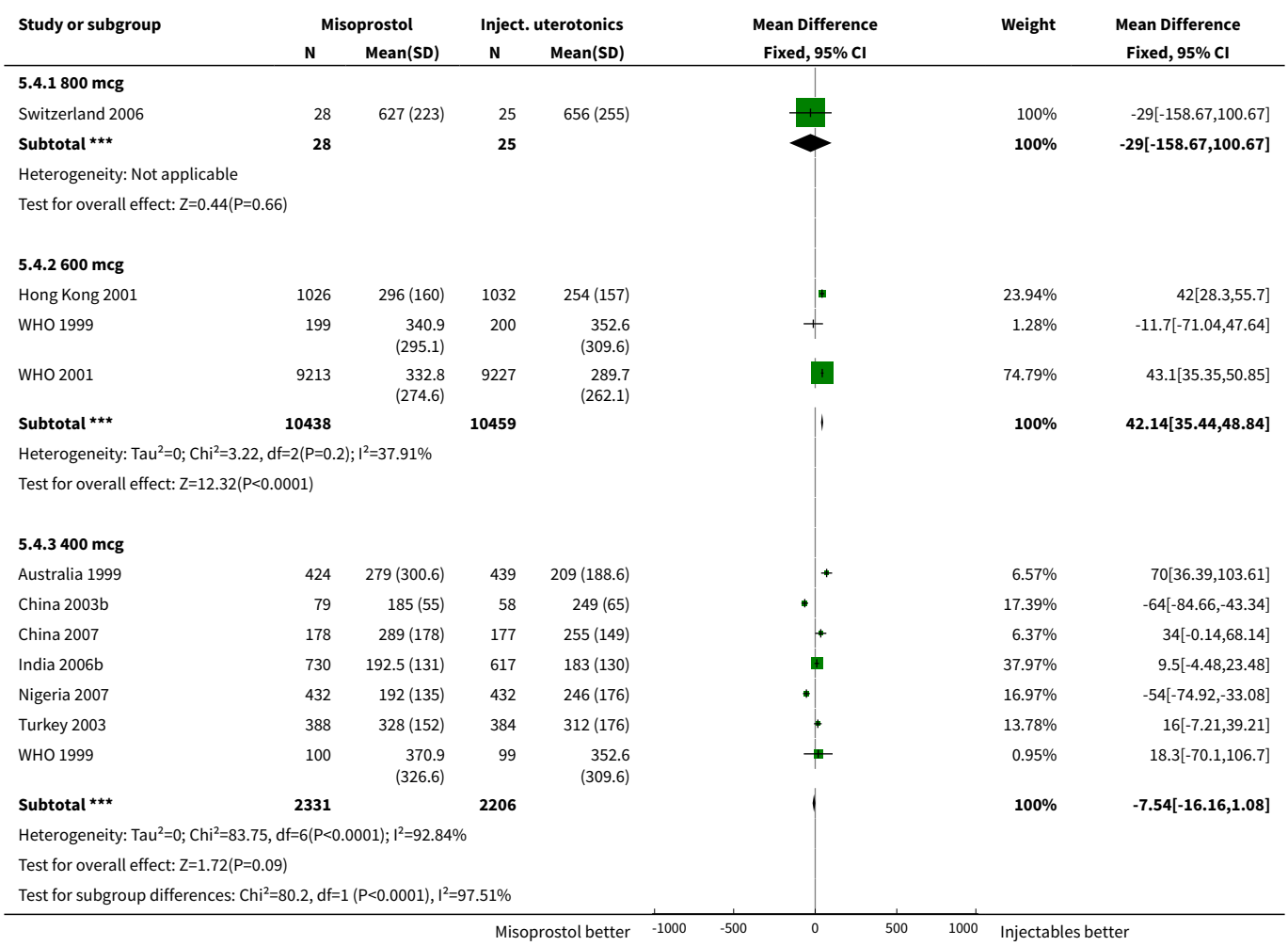
Analysis 5.3. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 3 Postpartum haemorrhage (>= 500 mL).

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 800 mcg					
Ghana 2006	0/225	5/225		100%	0.09[0.01,1.63]
Subtotal (95% CI)	**225**	**225**		**100%**	**0.09[0.01,1.63]**
Total events: 0 (Misoprostol), 5 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.63(P=0.1)					
5.3.2 600 mcg					
Belgium 1999	8/96	4/93		0.29%	1.94[0.6,6.22]
France 2001	52/186	29/196		2.04%	1.89[1.26,2.84]
Hong Kong 2001	60/1026	44/1032		3.17%	1.37[0.94,2]
India 2005a	8/100	6/100		0.43%	1.33[0.48,3.7]
Nigeria 2003	3/247	1/249		0.07%	3.02[0.32,28.88]
WHO 1999	45/199	52/200		3.75%	0.87[0.61,1.23]
WHO 2001	1793/9213	1248/9227		90.23%	1.44[1.35,1.54]
Subtotal (95% CI)	**11067**	**11097**		**100%**	**1.43[1.34,1.52]**
Total events: 1969 (Misoprostol), 1384 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=10.43, df=6(P=0.11); I^2=42.49%					
Test for overall effect: Z=11.05(P<0.0001)					
5.3.3 500 mcg					
United Kingdom 2000	62/501	56/499		76.75%	1.1[0.79,1.55]
United Kingdom 2001b	17/20	17/20		23.25%	1[0.77,1.3]
Subtotal (95% CI)	**521**	**519**		**100%**	**1.08[0.82,1.41]**
Total events: 79 (Misoprostol), 73 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
5.3.4 400 mcg					
Australia 1999	63/424	24/439		11.55%	2.72[1.73,4.27]

Misoprostol better 0.001 0.1 1 10 1000 Injectables better

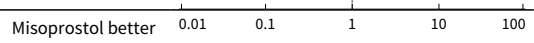


Analysis 5.4. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 4 Blood loss (mL).



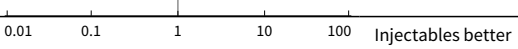
Analysis 5.5. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 5 Use of additional uterotonics.

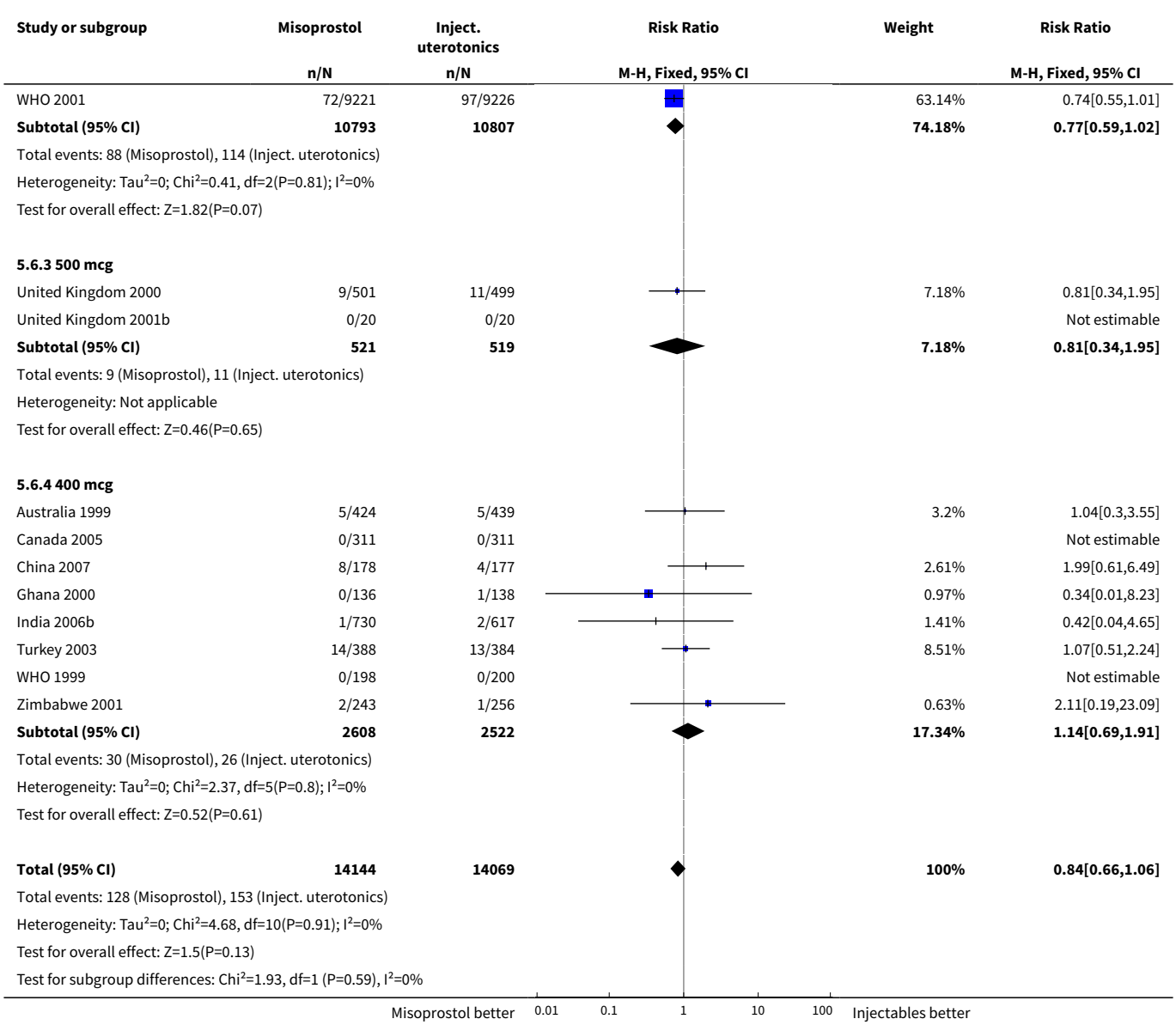
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.5.1 800 mcg				
Ghana 2006	16/225	21/225		0.76[0.41,1.42]
Switzerland 2006	0/28	0/25		Not estimable
5.5.2 600 mcg				
Belgium 1999	12/94	4/91		2.9[0.97,8.67]
Hong Kong 2001	232/1026	144/1032		1.62[1.34,1.96]
India 2005a	10/100	7/100		1.43[0.57,3.6]
Nigeria 2003	31/247	27/249		1.16[0.71,1.88]
WHO 1999	18/199	28/200		0.65[0.37,1.13]
WHO 2001	1398/9225	1002/9228		1.4[1.29,1.51]
5.5.3 500 mcg				
United Kingdom 2000	68/501	50/499		1.35[0.96,1.91]
United Kingdom 2001b	6/20	1/20		6[0.79,45.42]
5.5.4 400 mcg				
Australia 1999	95/424	34/439		2.89[2,4.18]
Canada 2005	159/311	126/311		1.26[1.06,1.5]
China 2007	41/178	24/177		1.7[1.07,2.69]
Ghana 2000	6/168	8/172		0.77[0.27,2.17]
India 2006b	63/730	38/617		1.4[0.95,2.07]
Nigeria 2007	33/432	80/432		0.41[0.28,0.6]
WHO 1999	23/198	28/200		0.83[0.5,1.39]
Zimbabwe 2001	13/243	7/256		1.96[0.79,4.82]



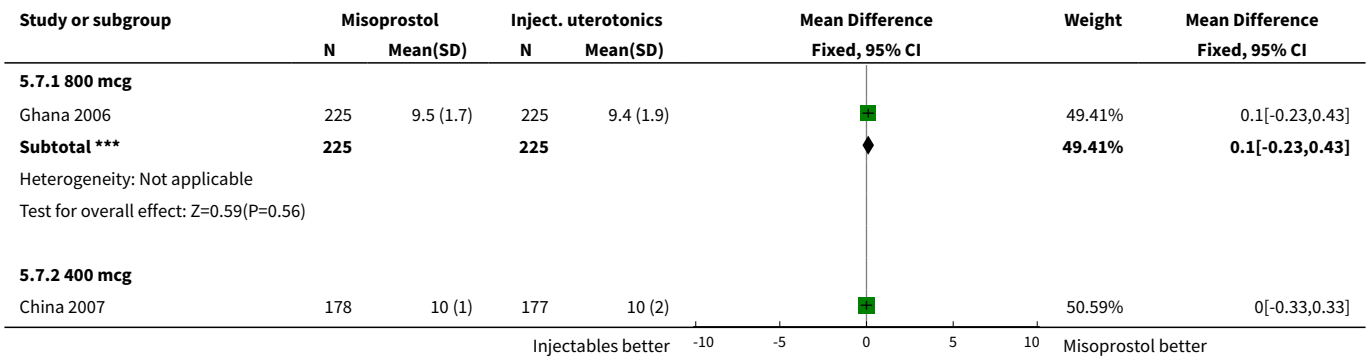
Analysis 5.6. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 6 Blood transfusion.

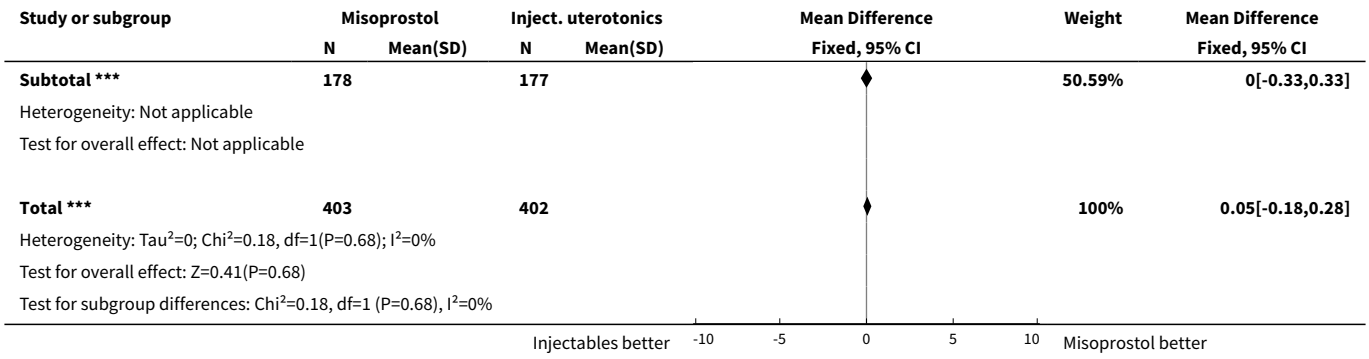
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 800 mcg					
Ghana 2006	1/222	2/221		1.31%	0.5[0.05,5.45]
Subtotal (95% CI)	**222**	**221**		**1.31%**	**0.5[0.05,5.45]**
Total events: 1 (Misoprostol), 2 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
5.6.2 600 mcg					
Belgium 1999	1/100	1/100		0.65%	1[0.06,15.77]
Hong Kong 2001	15/1026	16/1032		10.39%	0.94[0.47,1.9]
Nigeria 2003	0/247	0/249			Not estimable
WHO 1999	0/199	0/200			Not estimable



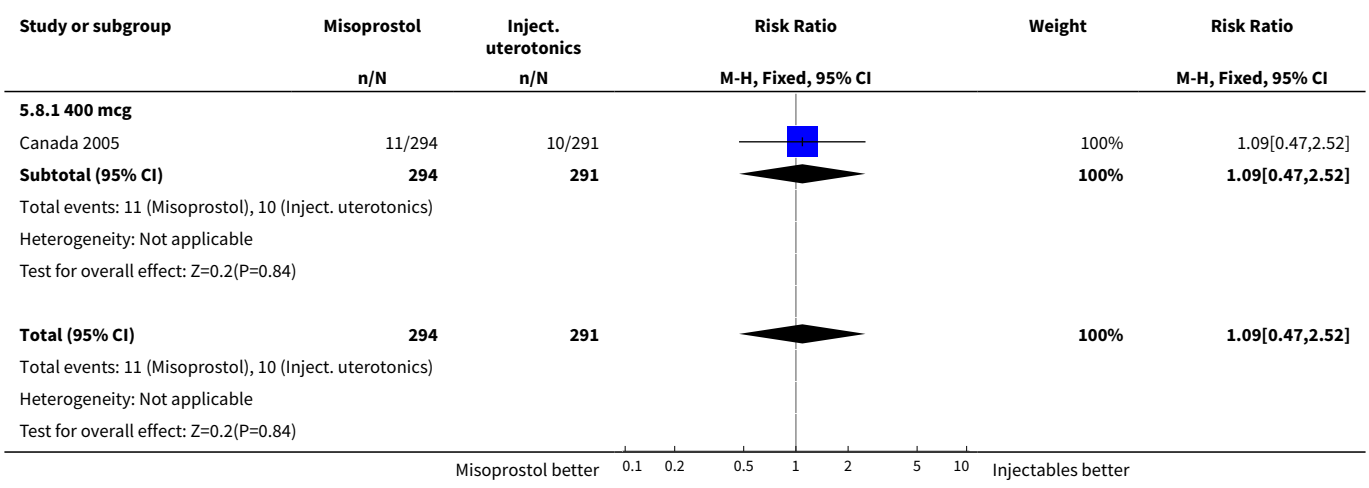


Analysis 5.7. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 7 Postpartum haemoglobin.

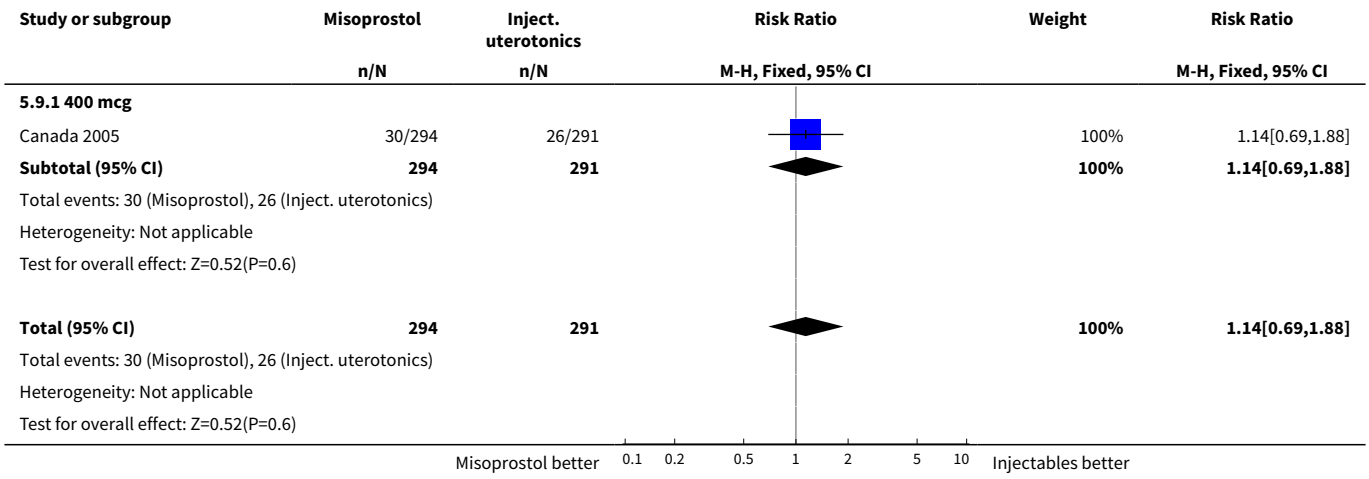




Analysis 5.8. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 8 Haematocrit drop 10% or more.

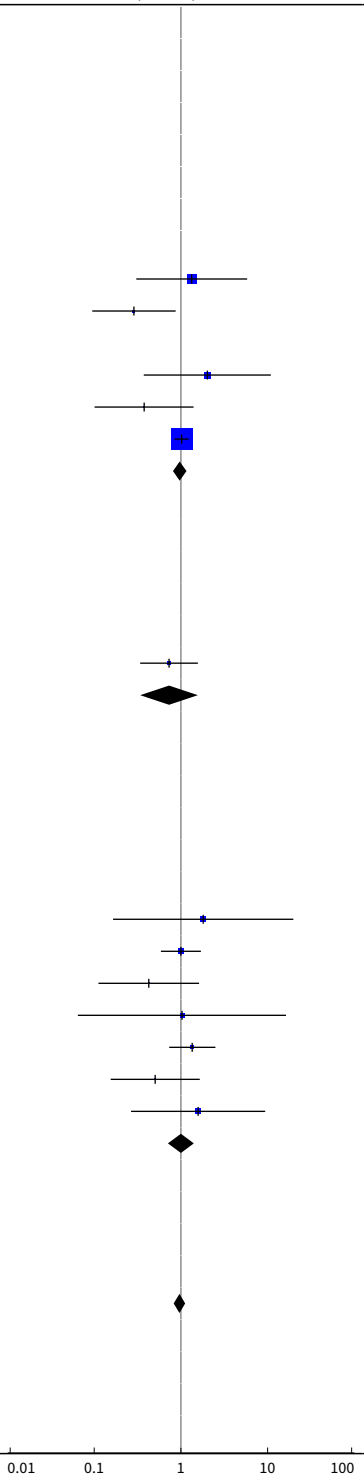


Analysis 5.9. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 9 Haemoglobin drop 30 mg/L or more.



Analysis 5.10. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 10 Manual removal of placenta.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.10.1 800 mcg					
Ghana 2006	0/225	0/225			Not estimable
Subtotal (95% CI)	**225**	**225**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.10.2 600 mcg					
Belgium 1999	4/100	3/100		0.94%	1.33[0.31,5.81]
Hong Kong 2001	4/1026	14/1032		4.39%	0.29[0.09,0.87]
India 2005a	0/100	0/100			Not estimable
Nigeria 2003	4/247	2/249		0.63%	2.02[0.37,10.91]
WHO 1999	3/199	8/200		2.51%	0.38[0.1,1.4]
WHO 2001	219/9225	215/9228		67.62%	1.02[0.85,1.23]
Subtotal (95% CI)	**10897**	**10909**		**76.09%**	**0.97[0.81,1.16]**
Total events: 234 (Misoprostol), 242 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=7.8, df=4(P=0.1); I^2=48.73%					
Test for overall effect: Z=0.36(P=0.72)					
5.10.3 500 mcg					
United Kingdom 2000	11/501	15/499		4.73%	0.73[0.34,1.57]
Subtotal (95% CI)	**501**	**499**		**4.73%**	**0.73[0.34,1.57]**
Total events: 11 (Misoprostol), 15 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
5.10.4 400 mcg					
Australia 1999	0/1	0/1			Not estimable
Bangladesh 2007	2/210	1/190		0.33%	1.81[0.17,19.8]
Canada 2005	25/311	25/311		7.86%	1[0.59,1.7]
China 2007	3/178	7/177		2.21%	0.43[0.11,1.62]
Ghana 2000	1/182	1/187		0.31%	1.03[0.06,16.3]
Nigeria 2007	23/432	17/432		5.35%	1.35[0.73,2.5]
WHO 1999	4/198	8/200		2.5%	0.51[0.15,1.65]
Zimbabwe 2001	3/243	2/256		0.61%	1.58[0.27,9.38]
Subtotal (95% CI)	**1755**	**1754**		**19.18%**	**1[0.71,1.41]**
Total events: 61 (Misoprostol), 61 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=4.27, df=6(P=0.64); I^2=0%					
Test for overall effect: Z=0(P=1)					
Total (95% CI)	**13378**	**13387**		**100%**	**0.96[0.82,1.12]**
Total events: 306 (Misoprostol), 318 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=12.66, df=12(P=0.39); I^2=5.19%					
Test for overall effect: Z=0.48(P=0.63)					
Test for subgroup differences: Chi^2=0.55, df=1 (P=0.76), I^2=0%					

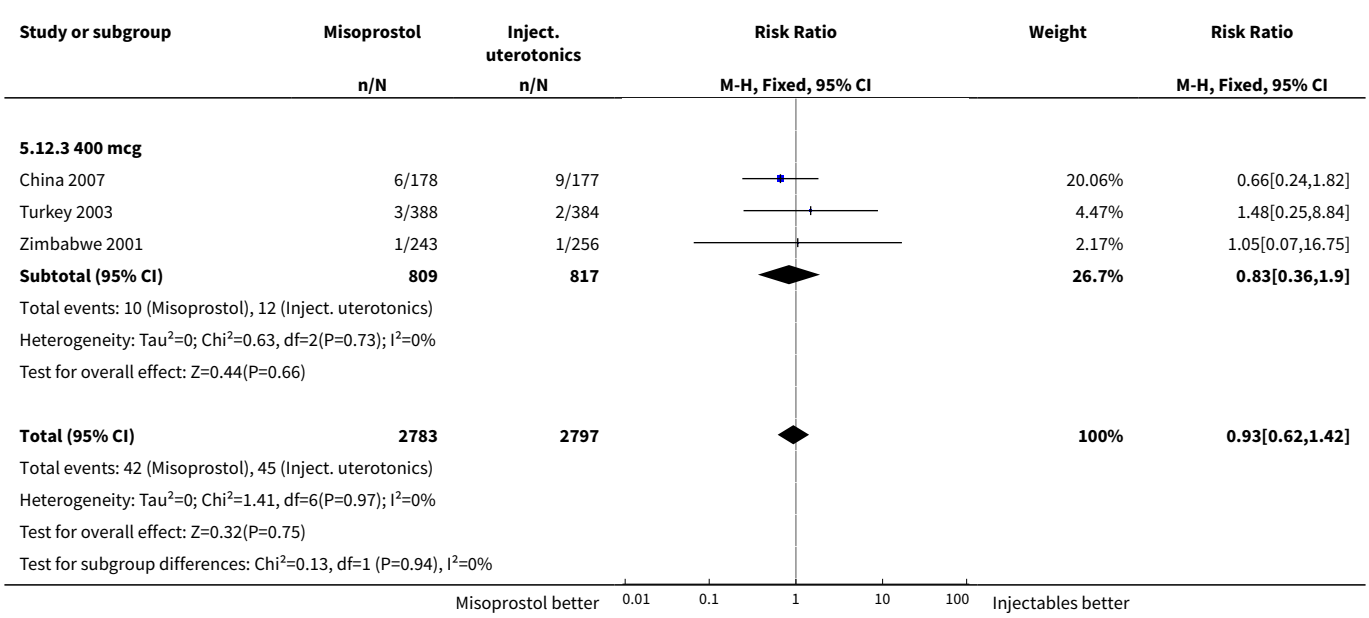


Analysis 5.11. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 11 Duration of third stage (minutes).

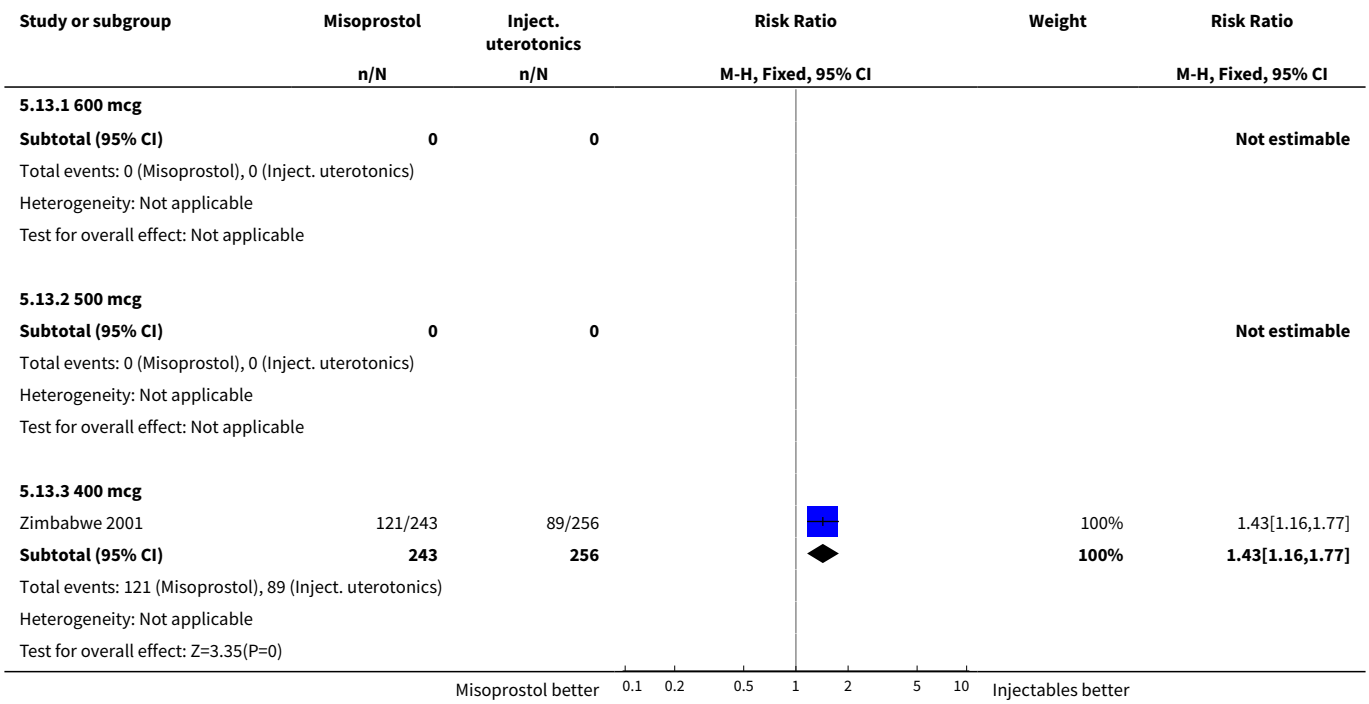
Study or subgroup	Misoprostol N	Misoprostol Mean(SD)	Inject. uterotonics N	Inject. uterotonics Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.11.1 600 mcg							
WHO 1999	199	6.4 (6.6)	200	6.3 (4)		4.14%	0.1[-0.97,1.17]
WHO 2001	9208	8.4 (16)	9204	8.2 (13.1)		26.79%	0.2[-0.22,0.62]
Subtotal ***	**9407**		**9404**			**30.93%**	**0.19[-0.21,0.58]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%							
Test for overall effect: Z=0.93(P=0.35)							
5.11.2 400 mcg							
Australia 1999	424	8.4 (8.2)	439	9 (16.8)		1.56%	-0.6[-2.35,1.15]
India 2006b	730	4.9 (5.3)	617	4.4 (4.7)		16.96%	0.5[-0.03,1.03]
Turkey 2003	388	9.2 (3)	384	8.7 (1.7)		40.5%	0.5[0.16,0.84]
WHO 1999	198	8.6 (14.5)	200	6.3 (4)		1.09%	2.3[0.2,4.4]
Zimbabwe 2001	243	6.9 (4.7)	256	6 (3.5)		8.97%	0.9[0.17,1.63]
Subtotal ***	**1983**		**1896**			**69.07%**	**0.56[0.29,0.82]**
Heterogeneity: Tau^2=0; Chi^2=5.32, df=4(P=0.26); I^2=24.83%							
Test for overall effect: Z=4.14(P<0.0001)							
Total ***	**11390**		**11300**			**100%**	**0.44[0.22,0.66]**
Heterogeneity: Tau^2=0; Chi^2=7.69, df=6(P=0.26); I^2=21.93%							
Test for overall effect: Z=3.96(P<0.0001)							
Test for subgroup differences: Chi^2=2.34, df=1 (P=0.13), I^2=57.18%							

Analysis 5.12. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 12 Third stage >= 30 minutes.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.12.1 600 mcg					
Belgium 1999	2/100	1/100		2.22%	2[0.18,21.71]
Hong Kong 2001	14/1026	16/1032		35.47%	0.88[0.43,1.79]
India 2005a	0/100	0/100			Not estimable
Nigeria 2003	3/247	2/249		4.43%	1.51[0.25,8.97]
Subtotal (95% CI)	**1473**	**1481**		**42.12%**	**1.01[0.53,1.89]**
Total events: 19 (Misoprostol), 19 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.66, df=2(P=0.72); I^2=0%					
Test for overall effect: Z=0.02(P=0.99)					
5.12.2 500 mcg					
United Kingdom 2000	13/501	14/499		31.19%	0.92[0.44,1.95]
Subtotal (95% CI)	**501**	**499**		**31.19%**	**0.92[0.44,1.95]**
Total events: 13 (Misoprostol), 14 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.21(P=0.84)					

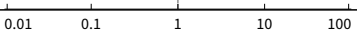


Analysis 5.13. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 13 Any side-effect.



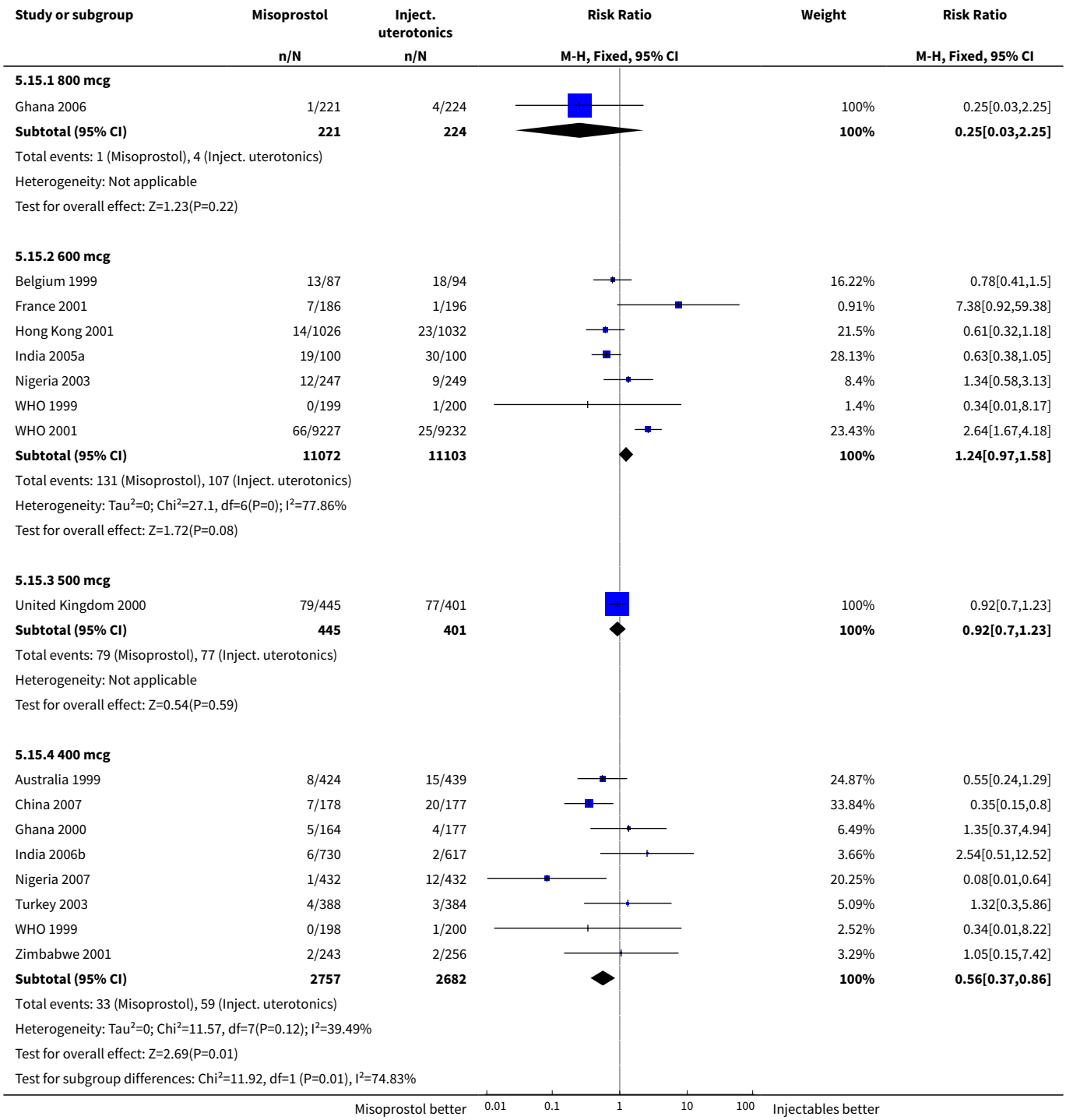
Analysis 5.14. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 14 Nausea.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.14.1 800 mcg					
Ghana 2006	2/223	4/222		71.71%	0.5[0.09,2.69]
Switzerland 2006	0/28	1/25		28.29%	0.3[0.01,7.02]
Subtotal (95% CI)	**251**	**247**		**100%**	**0.44[0.1,1.94]**
Total events: 2 (Misoprostol), 5 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
5.14.2 600 mcg					
Belgium 1999	20/87	30/94		22.06%	0.72[0.44,1.17]
Hong Kong 2001	20/1026	27/1032		20.6%	0.75[0.42,1.32]
India 2005a	20/100	30/100		22.95%	0.67[0.41,1.09]
Nigeria 2003	8/247	10/249		7.62%	0.81[0.32,2.01]
WHO 1999	1/199	1/200		0.76%	1.01[0.06,15.96]
WHO 2001	77/9227	34/9232		26%	2.27[1.52,3.39]
Subtotal (95% CI)	**10886**	**10907**		**100%**	**1.12[0.9,1.41]**
Total events: 146 (Misoprostol), 132 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=21.7, df=5(P=0); I^2=76.95%					
Test for overall effect: Z=1.02(P=0.31)					
5.14.3 500 mcg					
United Kingdom 2000	138/445	175/401		100%	0.71[0.59,0.85]
Subtotal (95% CI)	**445**	**401**		**100%**	**0.71[0.59,0.85]**
Total events: 138 (Misoprostol), 175 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.77(P=0)					
5.14.4 400 mcg					
China 2007	13/178	16/177		28.55%	0.81[0.4,1.63]
Ghana 2000	5/152	6/159		10.44%	0.87[0.27,2.8]
India 2006b	5/730	11/617		21.22%	0.38[0.13,1.1]
Nigeria 2007	10/432	16/432		28.47%	0.63[0.29,1.36]
WHO 1999	0/198	1/200		2.66%	0.34[0.01,8.22]
Zimbabwe 2001	7/243	5/256		8.67%	1.47[0.47,4.58]
Subtotal (95% CI)	**1933**	**1841**		**100%**	**0.72[0.48,1.07]**
Total events: 40 (Misoprostol), 55 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=3.46, df=5(P=0.63); I^2=0%					
Test for overall effect: Z=1.65(P=0.1)					
Test for subgroup differences: Chi^2=11.19, df=1 (P=0.01), I^2=73.2%					



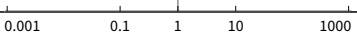
Misoprostol better — Injectables better

Analysis 5.15. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 15 Vomiting.



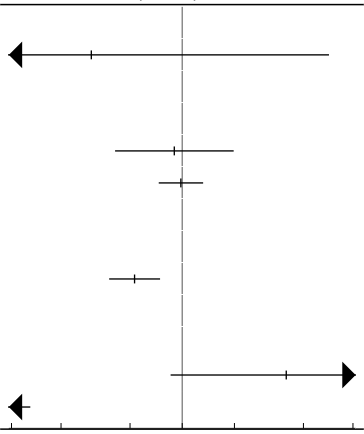
Analysis 5.16. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 16 Diarrhoea.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.16.1 800 mcg					
Ghana 2006	5/221	0/218		0.84%	10.85[0.6,195.06]
Subtotal (95% CI)	**221**	**218**		**0.84%**	**10.85[0.6,195.06]**
Total events: 5 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.11)					
5.16.2 600 mcg					
India 2005a	3/100	3/100		5.03%	1[0.21,4.84]
Nigeria 2003	7/247	2/249		3.34%	3.53[0.74,16.82]
Turkey 2003	15/388	12/384		20.21%	1.24[0.59,2.61]
WHO 1999	4/199	0/200		0.84%	9.05[0.49,166.9]
WHO 2001	35/9227	8/9232		13.4%	4.38[2.03,9.43]
Subtotal (95% CI)	**10161**	**10165**		**42.81%**	**2.52[1.6,3.98]**
Total events: 64 (Misoprostol), 25 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=7.73, df=4(P=0.1); I^2=48.22%					
Test for overall effect: Z=3.99(P<0.0001)					
5.16.3 500 mcg					
United Kingdom 2000	17/445	14/401		24.68%	1.09[0.55,2.19]
Subtotal (95% CI)	**445**	**401**		**24.68%**	**1.09[0.55,2.19]**
Total events: 17 (Misoprostol), 14 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					
5.16.4 400 mcg					
Australia 1999	1/424	0/439		0.82%	3.11[0.13,76.03]
China 2007	0/178	0/177			Not estimable
Ghana 2000	2/146	5/156		8.1%	0.43[0.08,2.17]
India 2006b	1/730	0/617		0.91%	2.54[0.1,62.15]
Nigeria 2007	0/432	0/432			Not estimable
Turkey 2003	15/388	12/384		20.21%	1.24[0.59,2.61]
WHO 1999	0/198	0/200			Not estimable
Zimbabwe 2001	3/243	1/256		1.63%	3.16[0.33,30.18]
Subtotal (95% CI)	**2739**	**2661**		**31.67%**	**1.21[0.67,2.22]**
Total events: 22 (Misoprostol), 18 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=2.82, df=4(P=0.59); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
Total (95% CI)	**13566**	**13445**		**100%**	**1.83[1.34,2.5]**
Total events: 108 (Misoprostol), 57 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=16.48, df=11(P=0.12); I^2=33.24%					
Test for overall effect: Z=3.78(P=0)					
Test for subgroup differences: Chi^2=7.19, df=1 (P=0.07), I^2=58.28%					



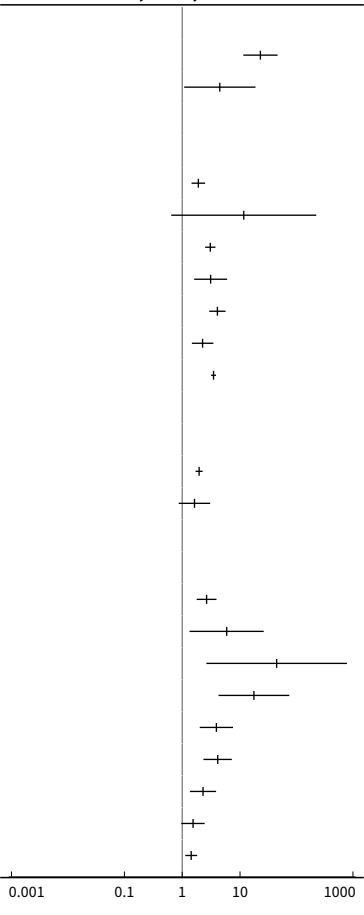
Analysis 5.17. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 17 Headache.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.17.1 800 mcg				
Switzerland 2006	0/28	1/25		0.3[0.01,7.02]
5.17.2 600 mcg				
Belgium 1999	10/87	12/94		0.9[0.41,1.98]
Hong Kong 2001	81/1026	83/1032		0.98[0.73,1.32]
5.17.3 500 mcg				
United Kingdom 2000	46/445	78/401		0.53[0.38,0.75]
5.17.4 400 mcg				
China 2007	8/178	2/177		3.98[0.86,18.47]
Nigeria 2007	1/432	54/432		0.02[0,0.13]

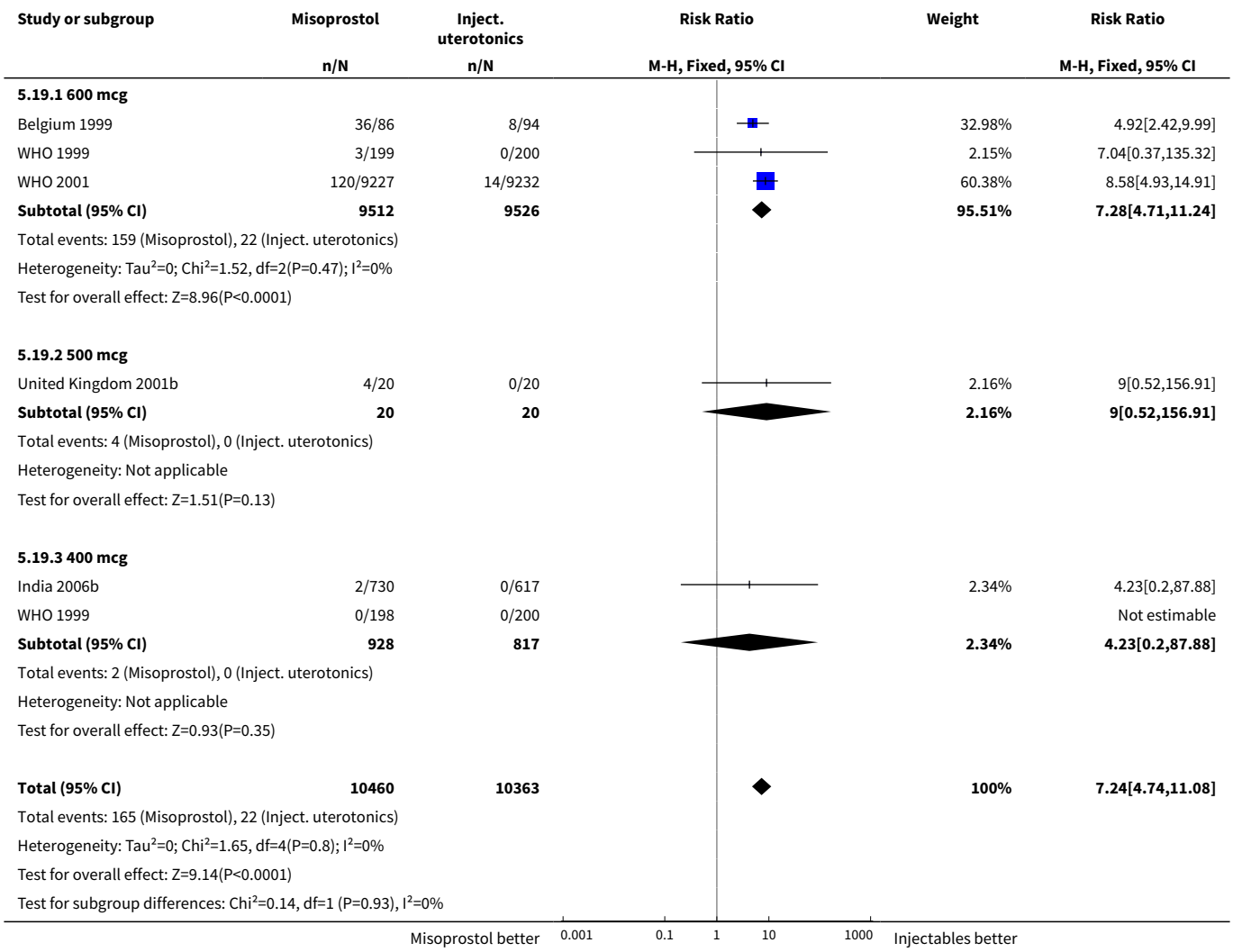


Analysis 5.18. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 18 Any shivering.

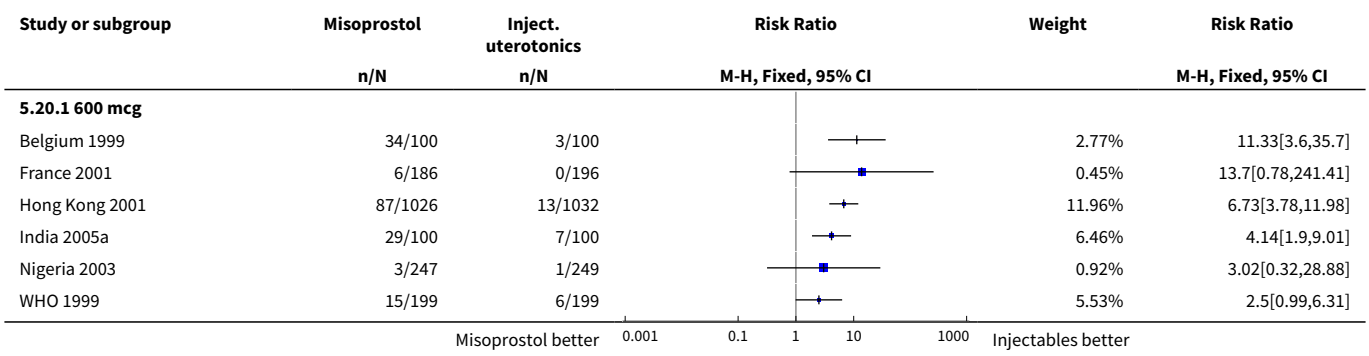
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.18.1 800 mcg				
Ghana 2006	180/223	8/223		22.5[11.36,44.56]
Switzerland 2006	10/28	2/25		4.46[1.08,18.45]
5.18.2 600 mcg				
Belgium 1999	66/86	38/94		1.9[1.45,2.49]
France 2001	5/186	0/196		11.59[0.65,208.12]
Hong Kong 2001	310/1026	102/1032		3.06[2.49,3.76]
India 2005a	31/100	10/100		3.1[1.61,5.98]
Nigeria 2003	141/247	35/249		4.06[2.93,5.62]
WHO 1999	56/199	25/200		2.25[1.47,3.46]
WHO 2001	1620/9227	466/9232		3.48[3.15,3.84]
5.18.3 500 mcg				
United Kingdom 2000	319/445	147/401		1.96[1.7,2.25]
United Kingdom 2001b	13/20	8/20		1.63[0.87,3.04]
5.18.4 400 mcg				
Australia 1999	79/424	31/439		2.64[1.78,3.91]
Bangladesh 2007	13/210	2/190		5.88[1.34,25.72]
Canada 2005	21/311	0/311		43[2.62,706.74]
China 2007	35/178	2/177		17.4[4.25,71.25]
Ghana 2000	39/176	10/176		3.9[2.01,7.57]
India 2006b	68/730	14/617		4.11[2.33,7.22]
Turkey 2003	44/388	19/384		2.29[1.36,3.85]
WHO 1999	38/198	25/200		1.54[0.96,2.44]
Zimbabwe 2001	106/243	78/256		1.43[1.13,1.81]

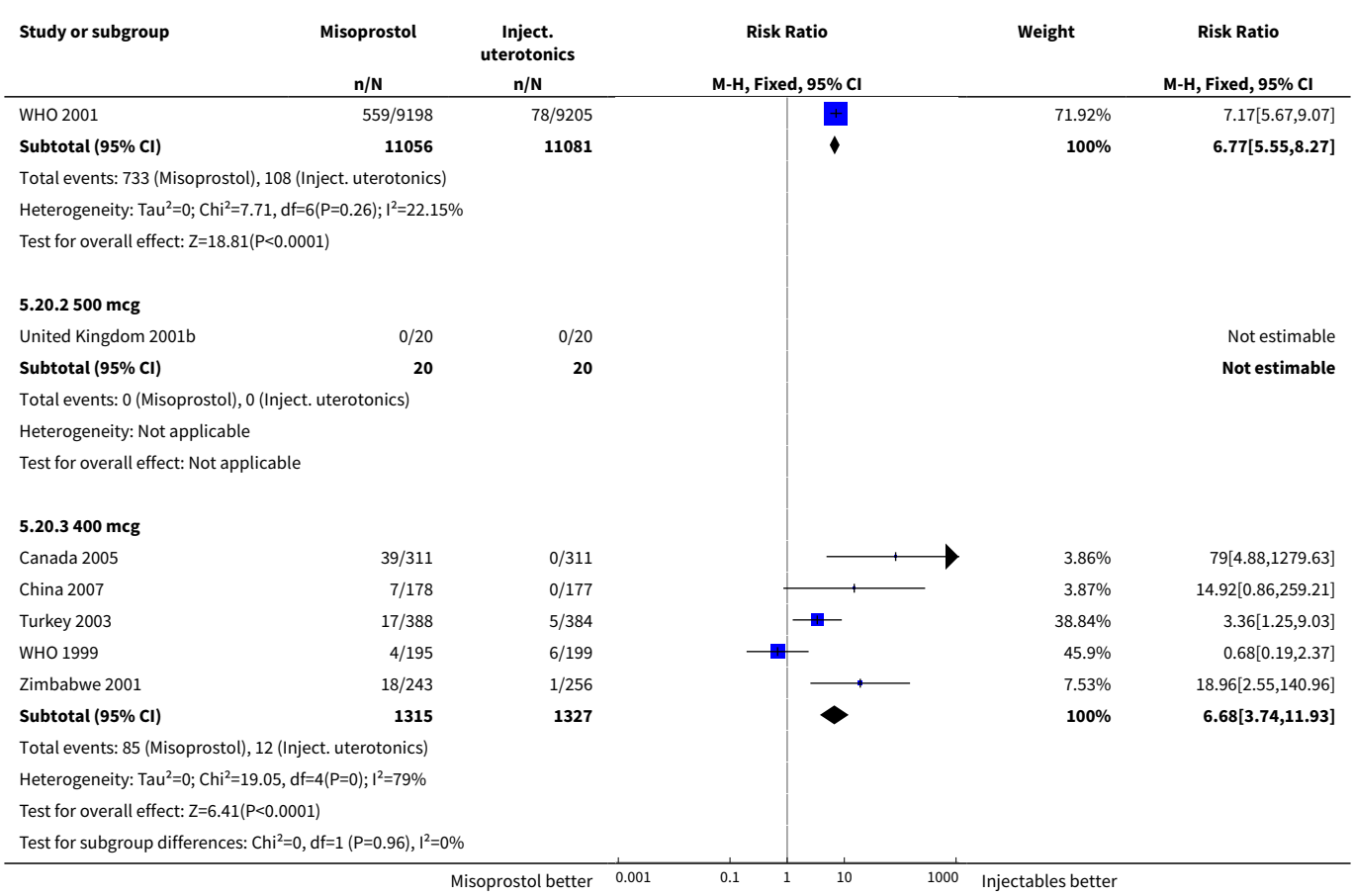


Analysis 5.19. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 19 Severe shivering.



Analysis 5.20. Comparison 5 Oral misoprostol versus injectable uterotonics (subgroups by dose), Outcome 20 Pyrexia (>= 38 degrees C).





Comparison 6. Rectal misoprostol versus injectable uterotonics (subgroups by dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	3	1393	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.21]
1.1 800 mcg	1	450	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.21]
1.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 400 mcg	2	943	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Postpartum haemorrhage (>= 500 mL)	7	3399	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
2.1 800 mcg	2	955	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.60, 2.09]
2.2 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]
2.3 400 mcg	4	2244	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.43]
3 Severe postpartum haemorrhage (>= 1000 mL)	4	2221	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.69, 1.77]

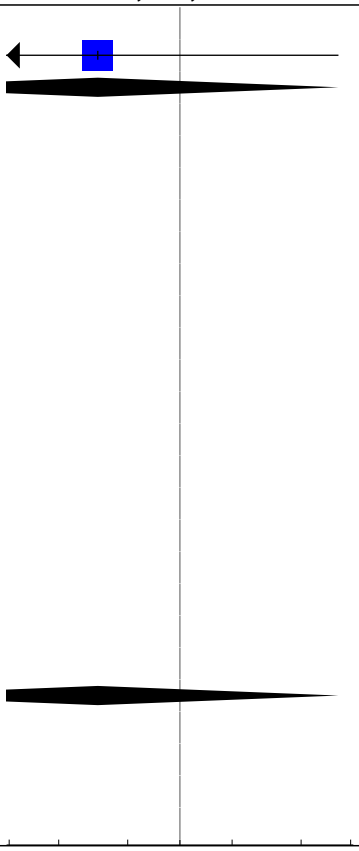
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 800 mcg	1	441	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.40]
3.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 400 mcg	3	1780	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.70, 1.85]
4 Blood loss (mL)	6		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 800 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 600 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 400 mcg	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Use of additional uterotonics	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 800 mcg	2	961	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.35, 1.24]
5.2 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.59, 42.04]
5.3 400 mcg	3	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.16, 2.31]
6 Blood transfusion	7	3105	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.59, 1.77]
6.1 800 mcg	2	952	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.40, 2.52]
6.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 400 mcg	5	2153	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.52, 2.04]
7 Manual removal of placenta	3	563	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.17, 1.67]
7.1 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 28.35]
7.2 400 mcg	2	363	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.04, 1.16]
8 Duration of third stage (minutes)	7	3245	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.05, 0.46]
8.1 800 mcg	2	964	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.25, 0.56]
8.2 600 mcg	1	200	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.25, 1.25]
8.3 400 mcg	4	2081	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.08, 0.58]
9 Third stage >= 30 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 400 mcg	1	803	Risk Ratio (M-H, Fixed, 95% CI)	6.17 [1.39, 27.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Postpartum haemoglobin	2	954	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.16, 0.16]
10.1 800 mcg	2	954	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.16, 0.16]
11 Nausea	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 800 mcg	2	942	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.08]
11.2 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.85]
11.3 400 mcg	2	355	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.41, 2.61]
12 Vomiting	6	2759	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.59, 2.26]
12.1 800 mcg	2	941	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.82]
12.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 400 mcg	4	1818	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.53, 3.12]
13 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 400 mcg	1	215	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [0.75, 7.42]
14 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 400 mcg	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.46, 2.02]
15 Diarrhoea	3	1978	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.56, 2.11]
15.1 800 mcg	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.37, 3.88]
15.2 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 400 mcg	2	1464	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.31]
16 Any shivering	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 800 mcg	2	940	Risk Ratio (M-H, Fixed, 95% CI)	38.6 [11.04, 134.95]
16.2 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.63, 2.42]
16.3 400 mcg	5	2143	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [1.88, 2.92]
17 Pyrexia (>= 38 degrees C)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 600 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 400 mcg	2	1022	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.21, 3.57]

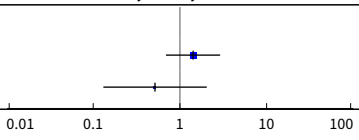
Analysis 6.1. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 1 Maternal death.

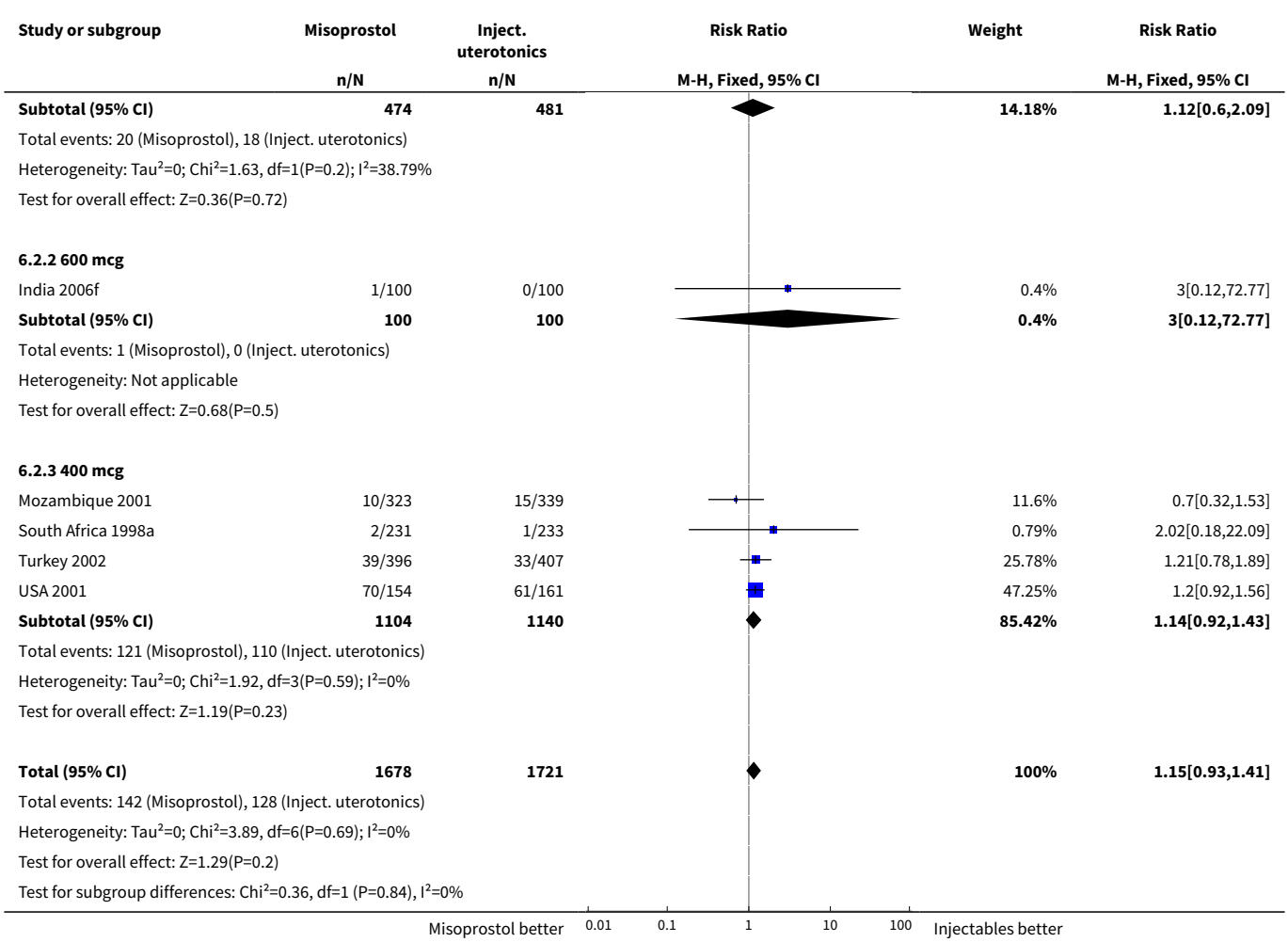
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 800 mcg					
Ghana 2007	0/224	1/226		100%	0.34[0.01,8.21]
Subtotal (95% CI)	**224**	**226**		**100%**	**0.34[0.01,8.21]**
Total events: 0 (Misoprostol), 1 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
6.1.2 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.3 400 mcg					
Jamaica 2009	0/70	0/70			Not estimable
Turkey 2002	0/396	0/407			Not estimable
Subtotal (95% CI)	**466**	**477**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**690**	**703**		**100%**	**0.34[0.01,8.21]**
Total events: 0 (Misoprostol), 1 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					



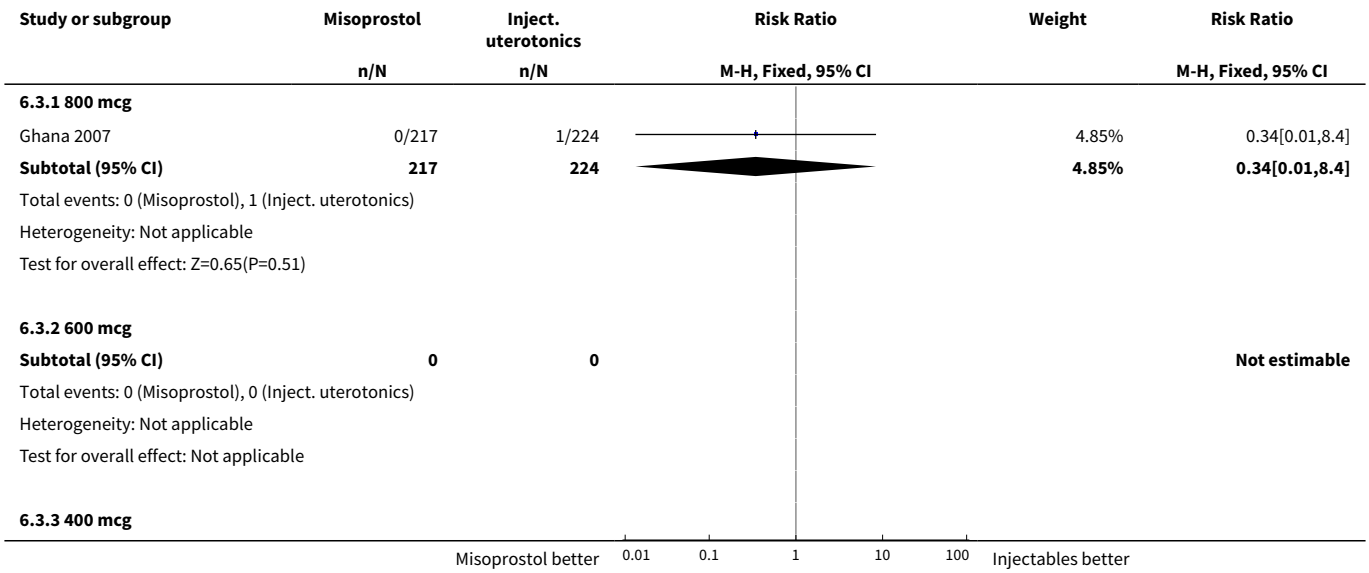
Analysis 6.2. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 2 Postpartum haemorrhage (>= 500 mL).

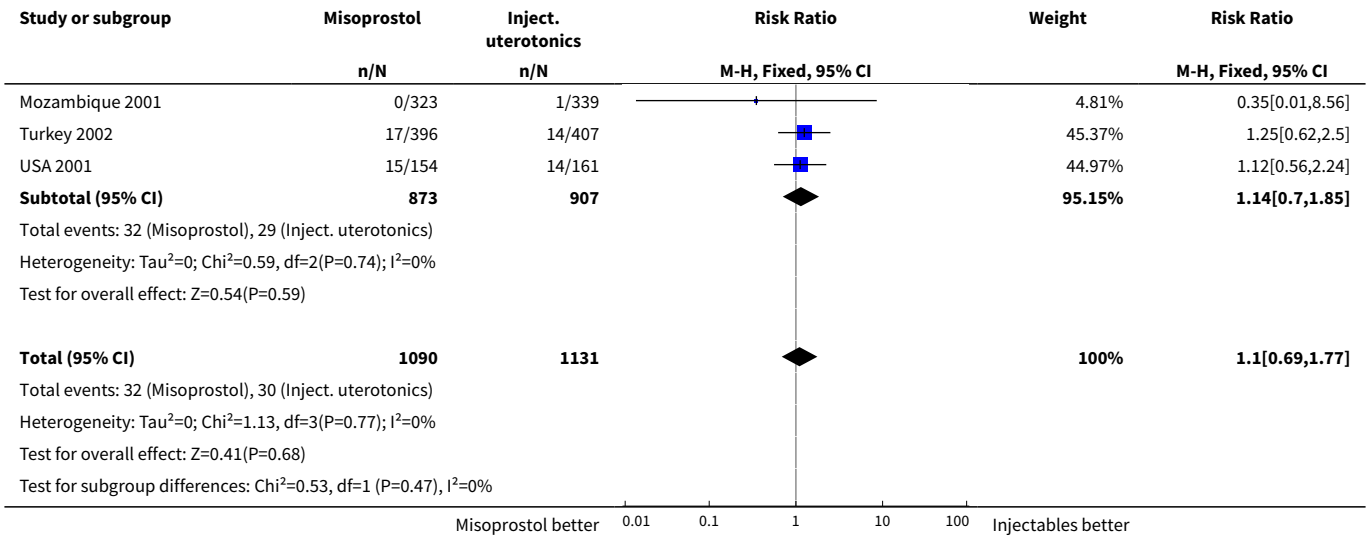
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 800 mcg					
Egypt 2009	17/257	12/257		9.51%	1.42[0.69,2.91]
Ghana 2007	3/217	6/224		4.68%	0.52[0.13,2.04]



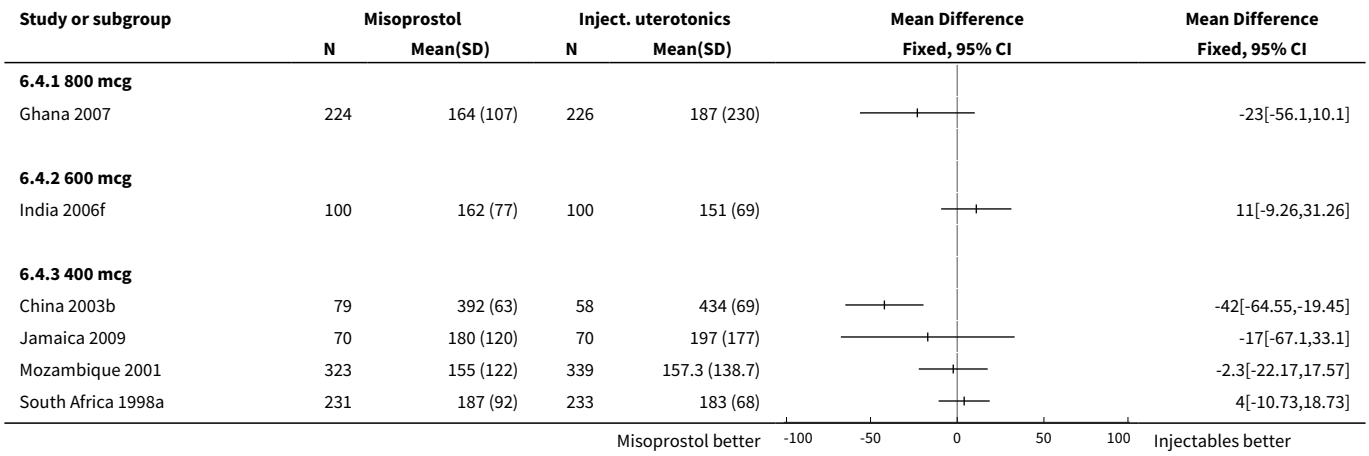


Analysis 6.3. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 3 Severe postpartum haemorrhage (>= 1000 mL).

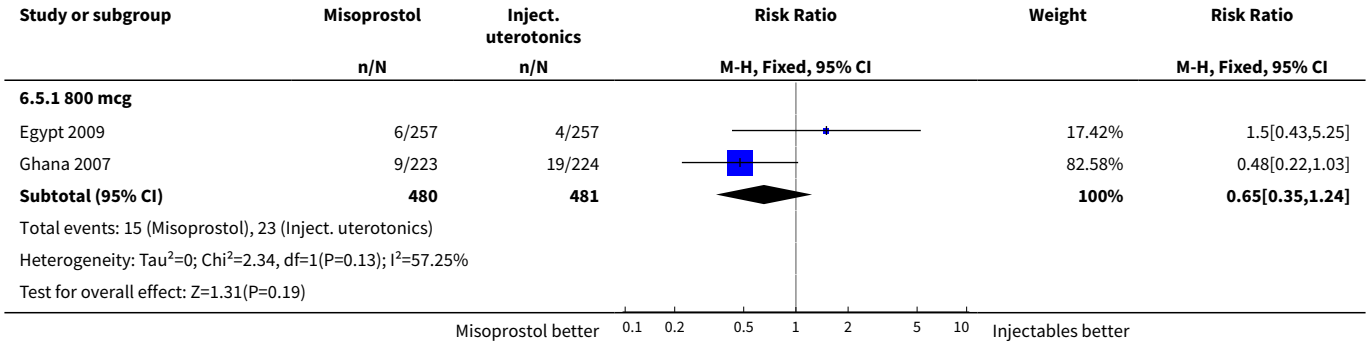


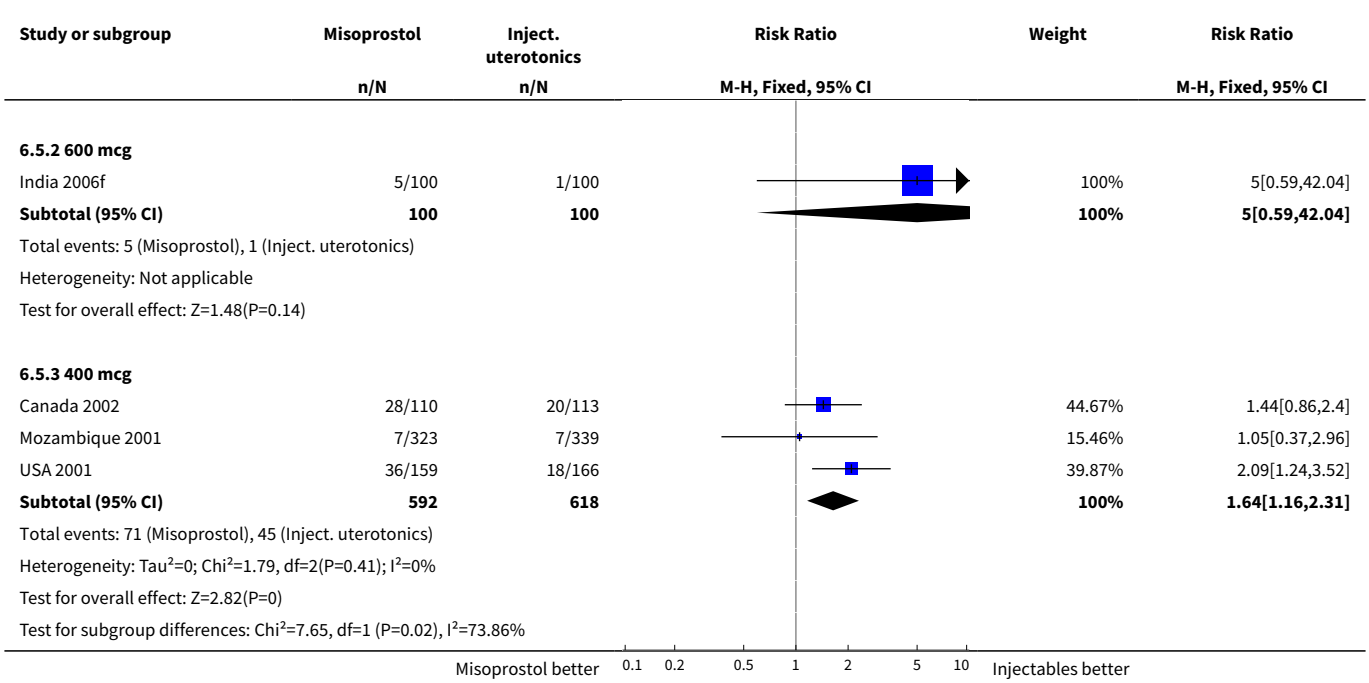


Analysis 6.4. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 4 Blood loss (mL).

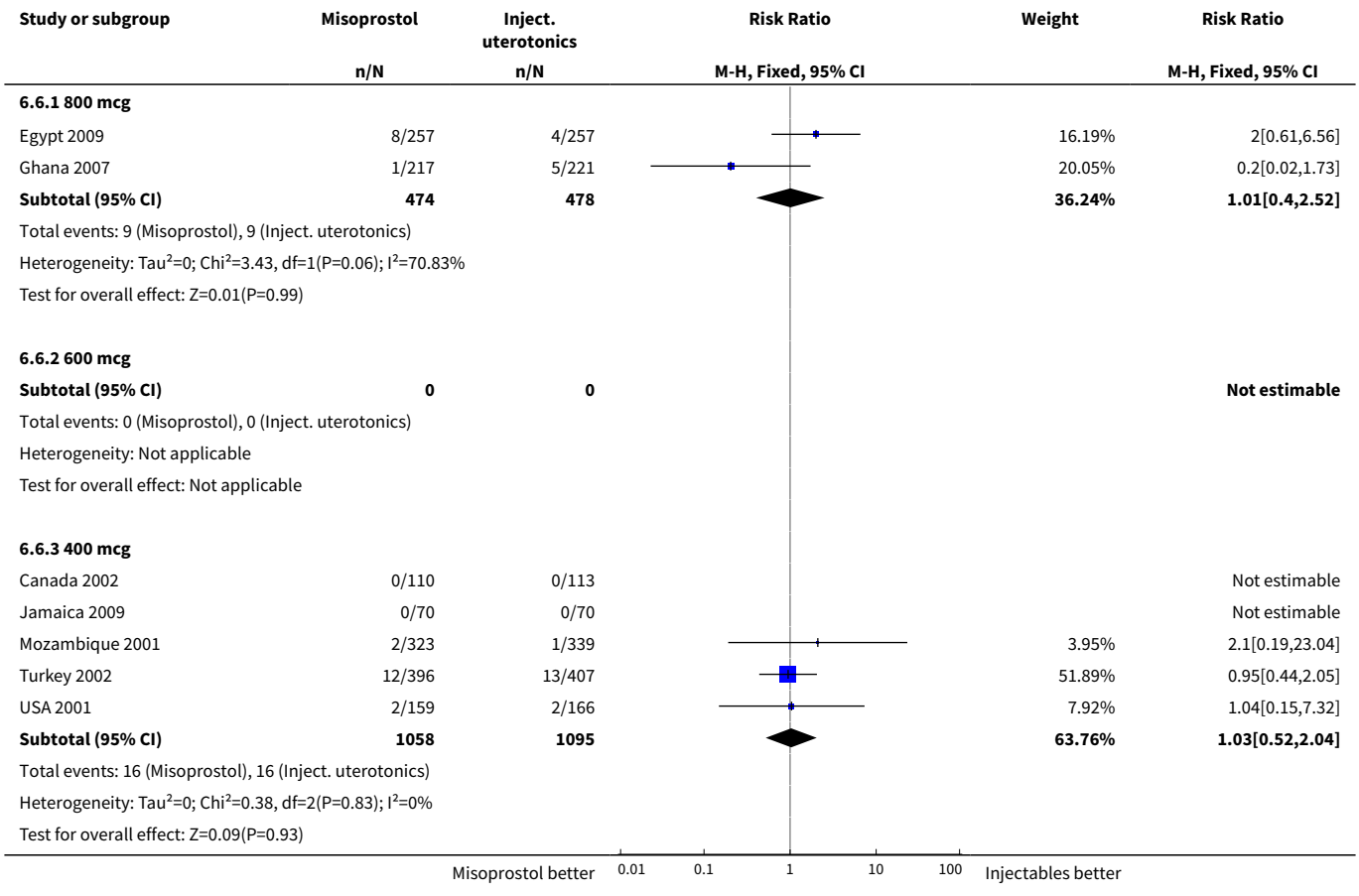


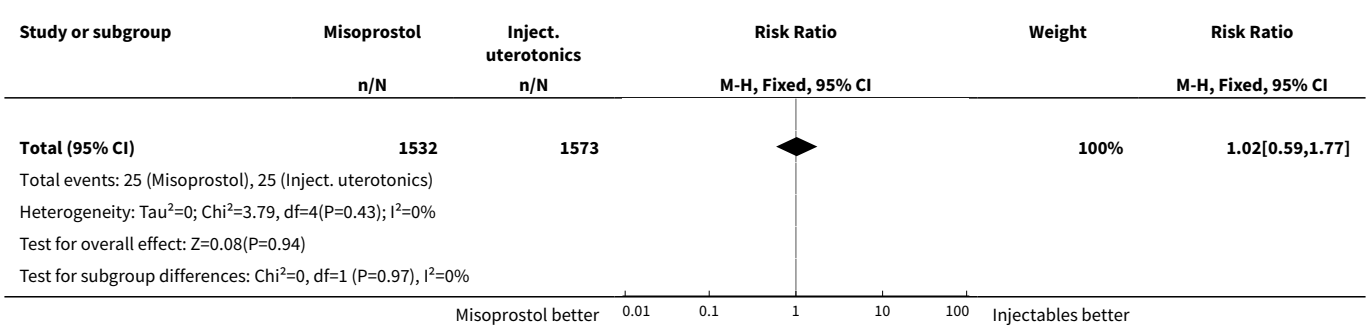
Analysis 6.5. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 5 Use of additional uterotonics.



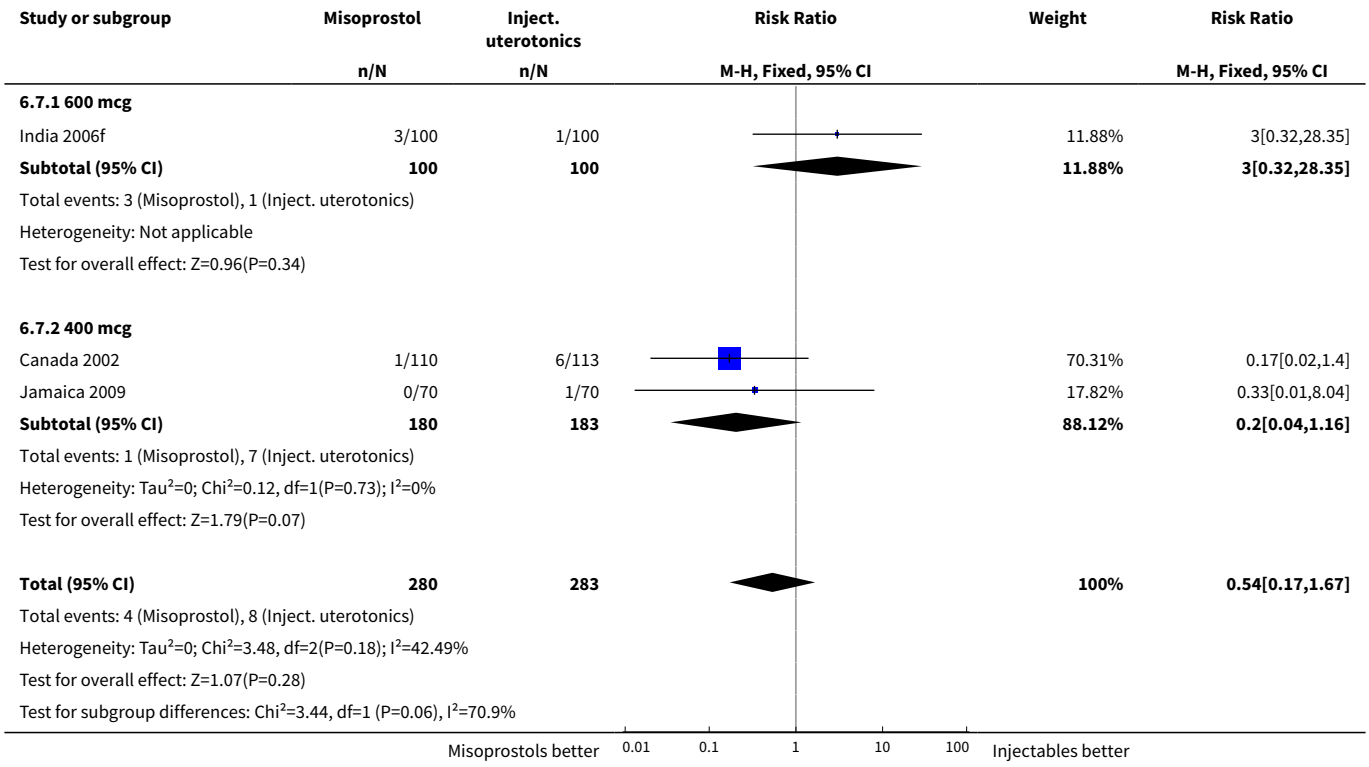


Analysis 6.6. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 6 Blood transfusion.

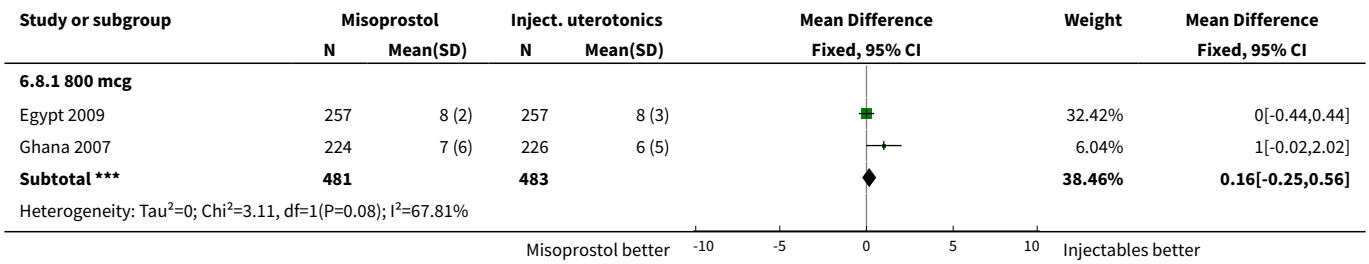


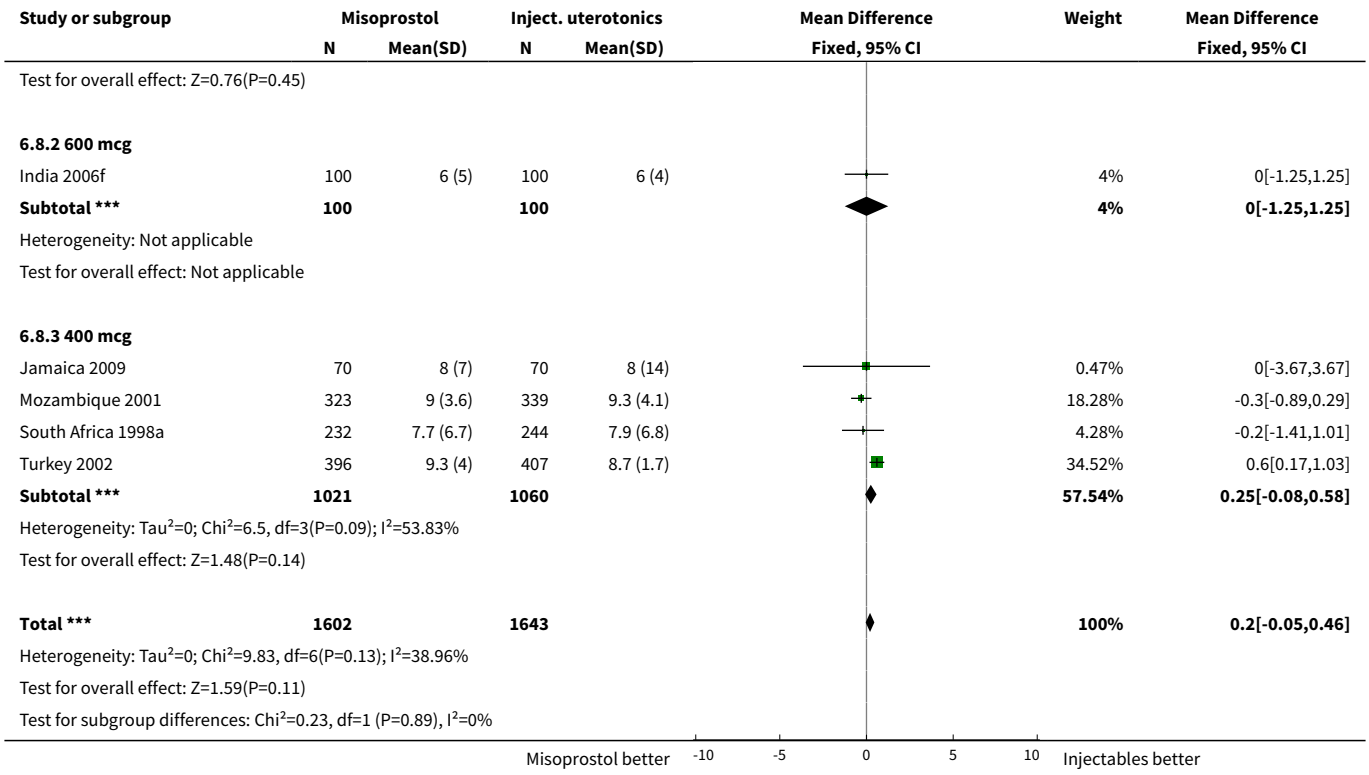


Analysis 6.7. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 7 Manual removal of placenta.

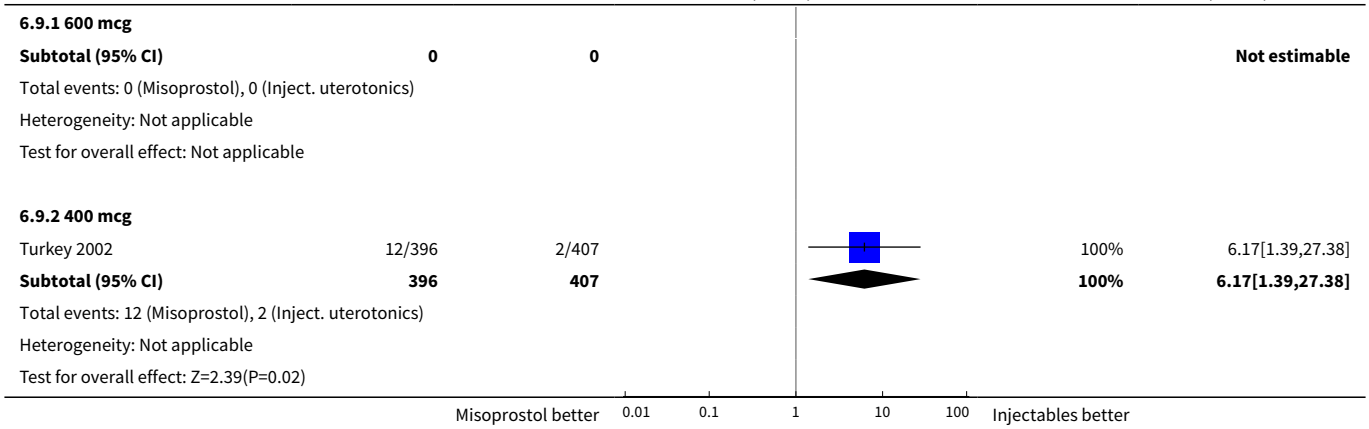


Analysis 6.8. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 8 Duration of third stage (minutes).





Analysis 6.9. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 9 Third stage >= 30 minutes.

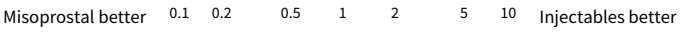


Analysis 6.10. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 10 Postpartum haemoglobin.

Study or subgroup	Misoprostol N	Misoprostol Mean(SD)	Inject. uterotonics N	Inject. uterotonics Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.10.1 800 mcg							
Egypt 2009	257	10 (1)	257	10 (1)		82.37%	0[-0.17,0.17]
Ghana 2007	220	10 (2)	220	10 (2)		17.63%	0[-0.37,0.37]
Subtotal ***	**477**		**477**			**100%**	**0[-0.16,0.16]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Not applicable							
Total ***	**477**		**477**			**100%**	**0[-0.16,0.16]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Not applicable							

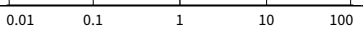
Analysis 6.11. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 11 Nausea.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.11.1 800 mcg					
Egypt 2009	1/257	1/257		20.15%	1[0.06,15.9]
Ghana 2007	1/212	4/216		79.85%	0.25[0.03,2.26]
Subtotal (95% CI)	**469**	**473**		**100%**	**0.4[0.08,2.08]**
Total events: 2 (Misoprostol), 5 (Inject. uterotonics)					
Heterogeneity: Tau²=0; Chi²=0.58, df=1(P=0.44); I²=0%					
Test for overall effect: Z=1.08(P=0.28)					
6.11.2 600 mcg					
India 2006f	2/100	0/100		100%	5[0.24,102.85]
Subtotal (95% CI)	**100**	**100**		**100%**	**5[0.24,102.85]**
Total events: 2 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
6.11.3 400 mcg					
Canada 2002	8/105	5/110		58.25%	1.68[0.57,4.96]
Jamaica 2009	0/70	3/70		41.75%	0.14[0.01,2.72]
Subtotal (95% CI)	**175**	**180**		**100%**	**1.04[0.41,2.61]**
Total events: 8 (Misoprostol), 8 (Inject. uterotonics)					
Heterogeneity: Tau²=0; Chi²=2.49, df=1(P=0.11); I²=59.91%					
Test for overall effect: Z=0.08(P=0.94)					



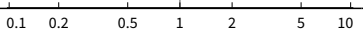
Analysis 6.12. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 12 Vomiting.

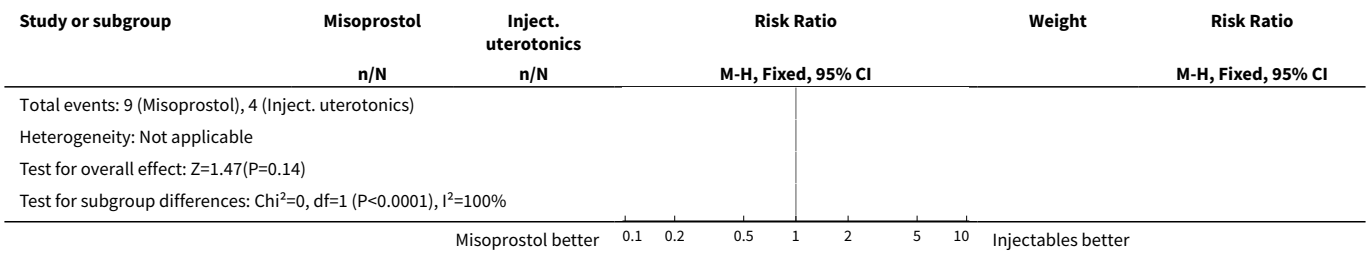
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.12.1 800 mcg					
Egypt 2009	6/257	5/257		32.55%	1.2[0.37,3.88]
Ghana 2007	1/214	2/213		13.05%	0.5[0.05,5.45]
Subtotal (95% CI)	**471**	**470**		**45.59%**	**1[0.35,2.82]**
Total events: 7 (Misoprostol), 7 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=0(P=1)					
6.12.2 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.12.3 400 mcg					
Canada 2002	6/105	4/110		25.43%	1.57[0.46,5.41]
Jamaica 2009	0/70	1/70		9.76%	0.33[0.01,8.04]
Mozambique 2001	2/323	1/337		6.37%	2.09[0.19,22.9]
Turkey 2002	2/396	2/407		12.84%	1.03[0.15,7.26]
Subtotal (95% CI)	**894**	**924**		**54.41%**	**1.28[0.53,3.12]**
Total events: 10 (Misoprostol), 8 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=1, df=3(P=0.8); I^2=0%					
Test for overall effect: Z=0.55(P=0.59)					
Total (95% CI)	**1365**	**1394**		**100%**	**1.15[0.59,2.26]**
Total events: 17 (Misoprostol), 15 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=5(P=0.91); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.72), I^2=0%					



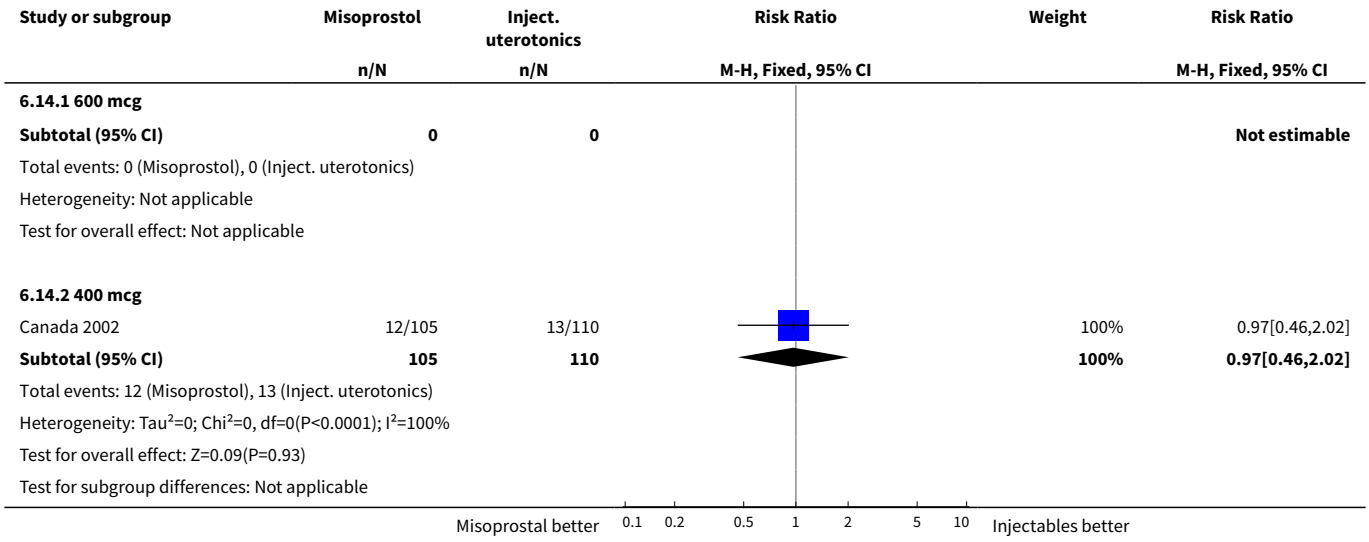
Analysis 6.13. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 13 Headache.

Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.13.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.13.2 400 mcg					
Canada 2002	9/105	4/110		100%	2.36[0.75,7.42]
Subtotal (95% CI)	**105**	**110**		**100%**	**2.36[0.75,7.42]**

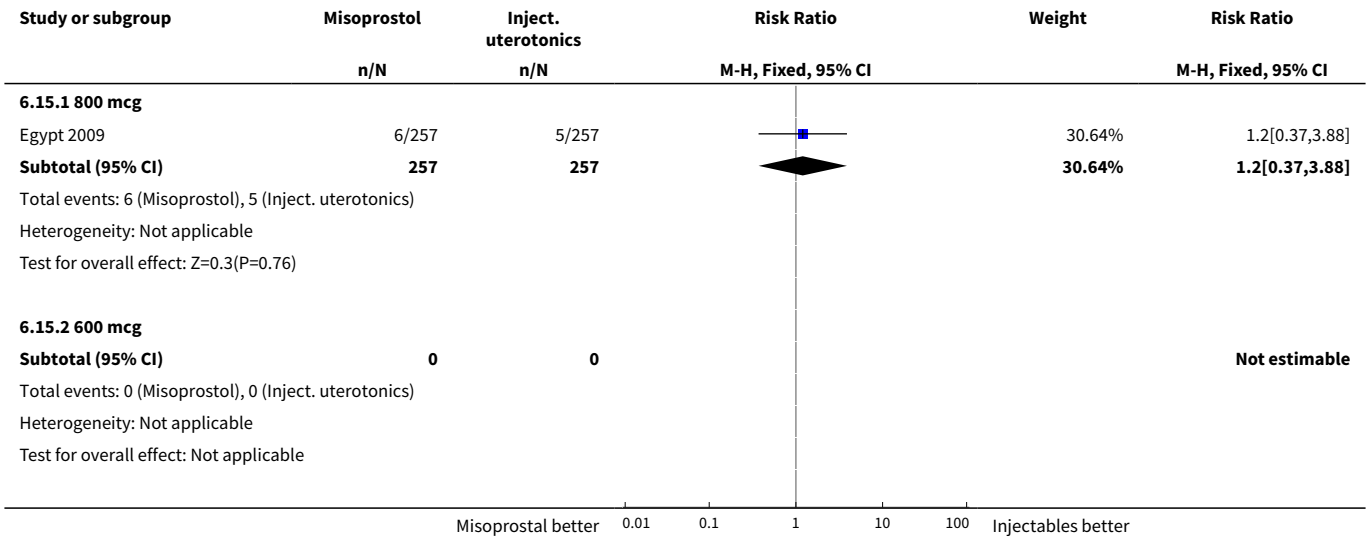


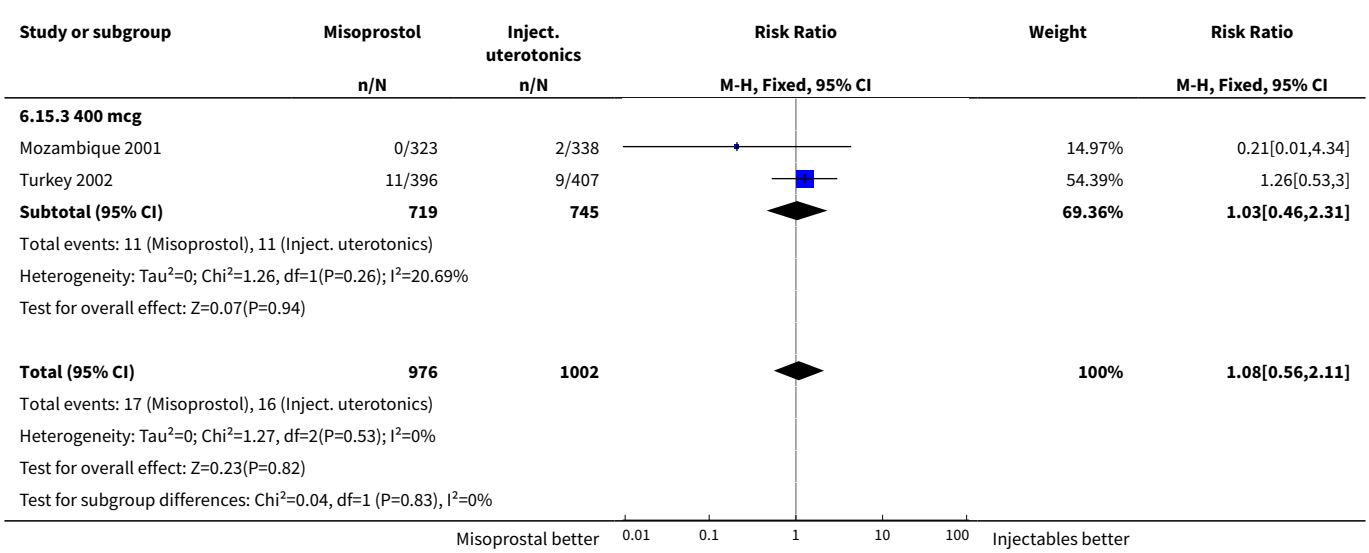


Analysis 6.14. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 14 Abdominal pain.

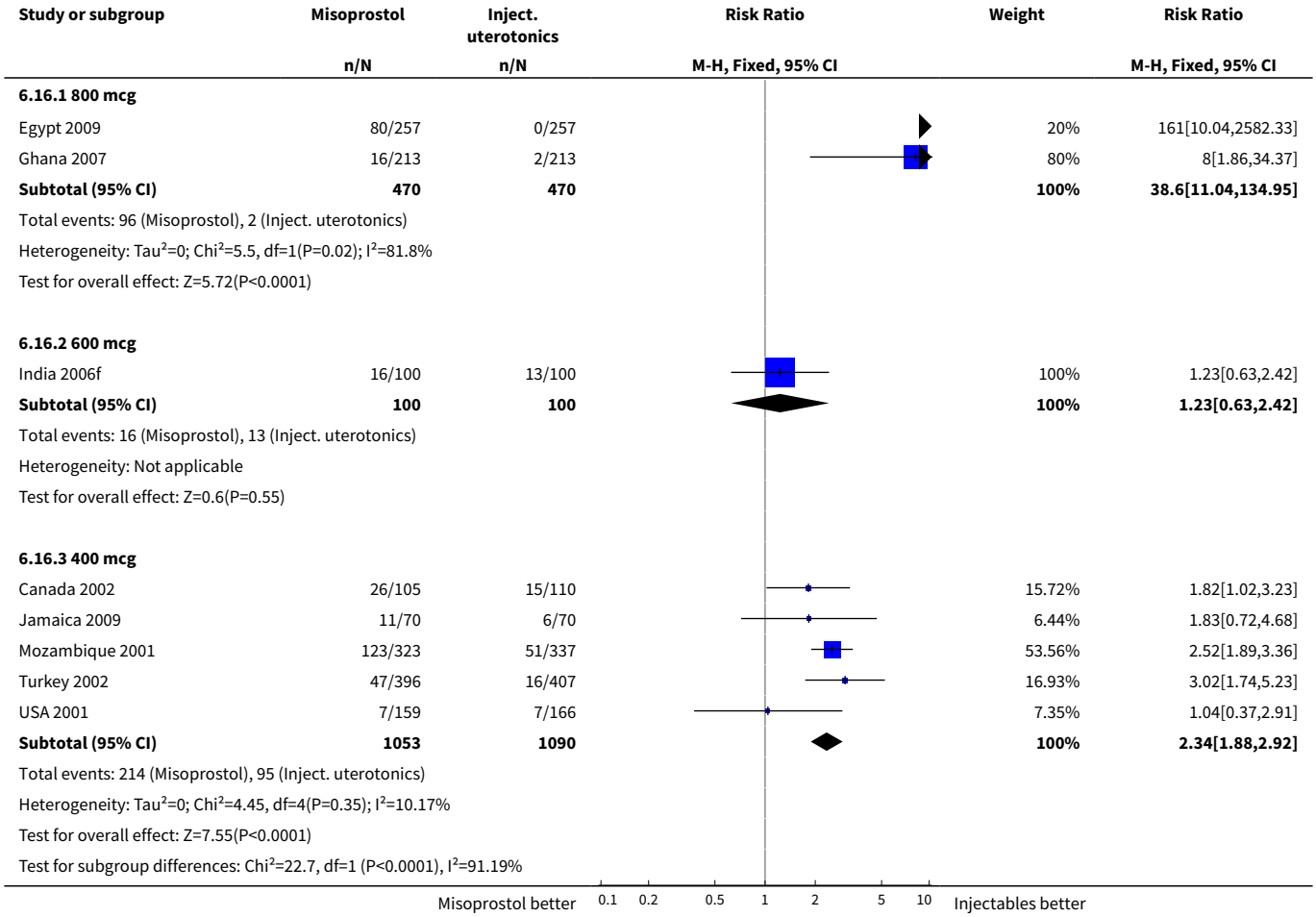


Analysis 6.15. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 15 Diarrhoea.

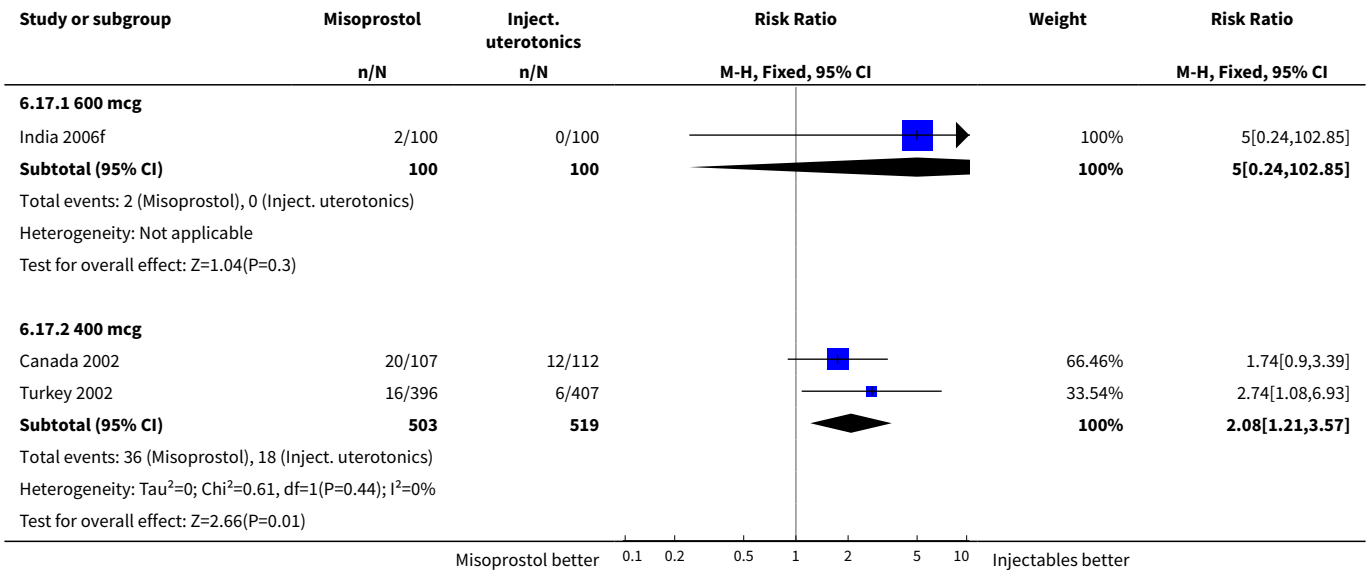




Analysis 6.16. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 16 Any shivering.



Analysis 6.17. Comparison 6 Rectal misoprostol versus injectable uterotonics (subgroups by dose), Outcome 17 Pyrexia (>= 38 degrees C).



Comparison 7. Sublingual misoprostol versus injectable uterotonic (subgroups by dose)

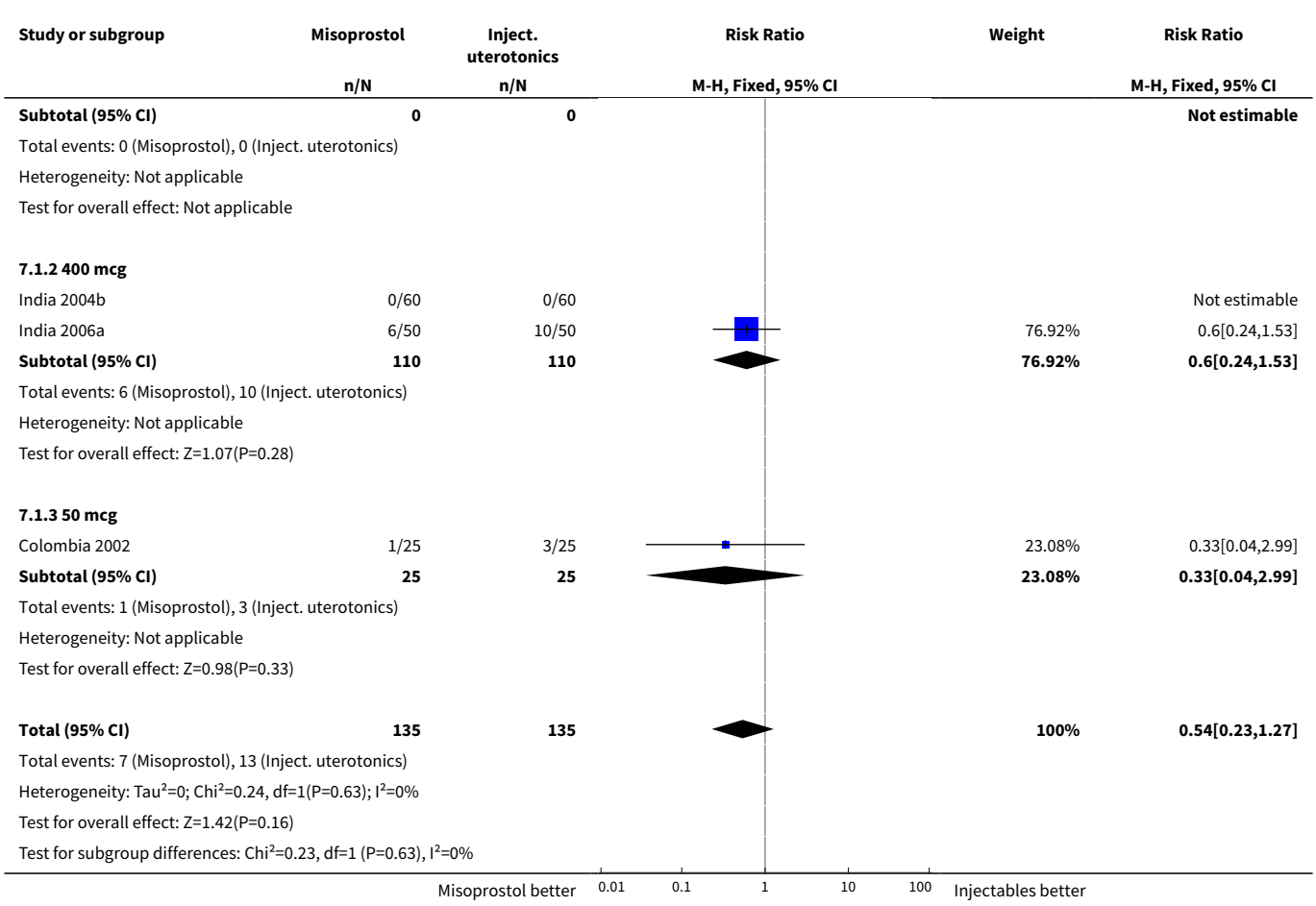
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum haemorrhage (>= 1000 mL)	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.27]
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 400 mcg	2	220	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.24, 1.53]
1.3 50 mcg	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.99]
2 Postpartum haemorrhage (>= 500 mL)	6	663	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.21]
2.1 600 mcg	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.40, 10.11]
2.2 400 mcg	3	353	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.17]
2.3 200 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 50 mcg	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.37, 2.05]
3 Blood loss (mL)	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 600 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 400 mcg	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 200 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 50 mcg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Use of additional uterotonics	7	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.85]
4.1 600 mcg	2	210	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.11, 1.02]
4.2 400 mcg	5	603	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.90]
4.3 200 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.81]
5 Blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Postpartum haemoglobin	4	533	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.25, 0.21]
6.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 400 mcg	3	333	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.36]
6.3 200 mcg	1	200	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.28, 0.28]
7 Manual removal of placenta	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
7.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
8 Duration of third stage (minutes)	2	500	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.22, 0.22]
8.1 600 mcg	1	150	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.32, 0.32]
8.2 400 mcg	1	150	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.32, 0.32]
8.3 200 mcg	1	200	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.39, 1.39]
9 Any side-effect	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.87, 2.29]
9.1 400 mcg	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.87, 2.29]
10 Nausea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 400 mcg	1	133	Risk Ratio (M-H, Fixed, 95% CI)	6.09 [0.75, 49.22]
10.2 200 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.22, 1.12]

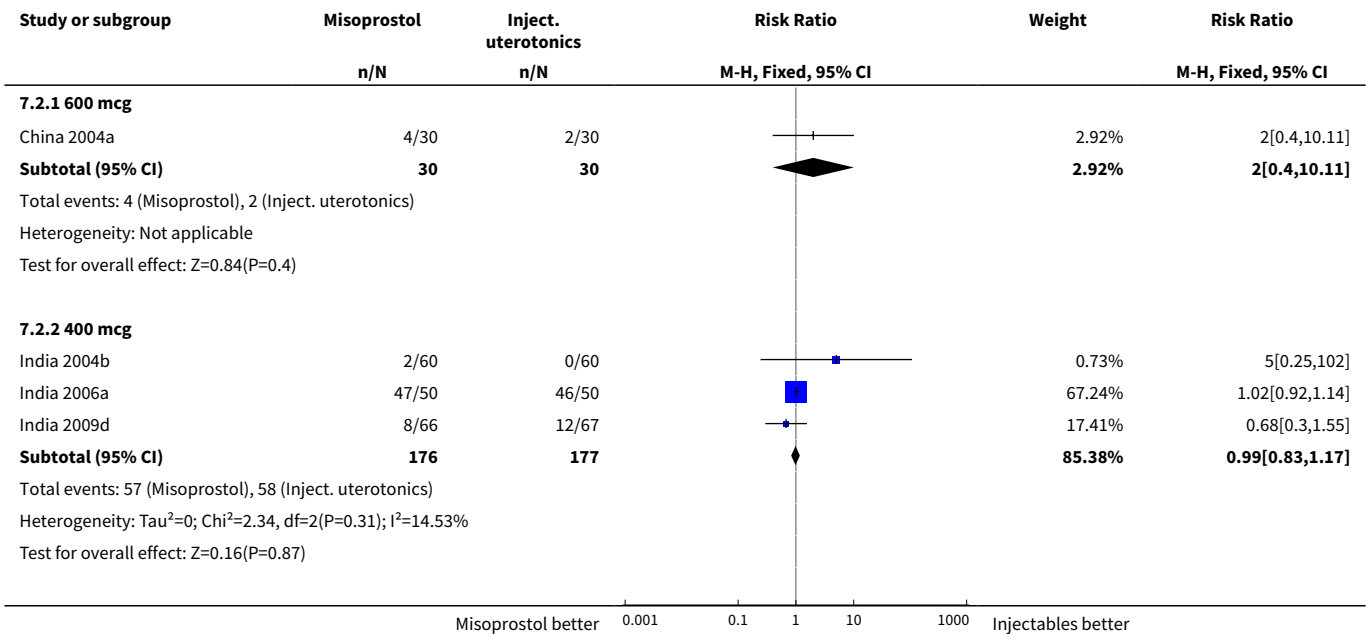
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Vomiting	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 600 mcg	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 400 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 50 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.4 200 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Headache	2	300	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.37, 1.52]
12.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 400 mcg	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.00]
12.3 200 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.08]
13 Abdominal pain	1	133	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.73]
13.1 400 mcg	1	133	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.73]
14 Diarrhoea	1	133	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.42]
14.1 400 mcg	1	133	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.42]
15 Any shivering	5	783	Risk Ratio (M-H, Fixed, 95% CI)	9.06 [4.46, 18.39]
15.1 600 mcg	1	150	Risk Ratio (M-H, Fixed, 95% CI)	27.0 [1.63, 446.10]
15.2 400 mcg	3	383	Risk Ratio (M-H, Fixed, 95% CI)	7.53 [3.44, 16.49]
15.3 200 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	17.0 [0.99, 290.62]
15.4 50 mcg	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.30]
16 Pyrexia >= 38 degrees C	4	653	Risk Ratio (M-H, Fixed, 95% CI)	13.04 [4.77, 35.62]
16.1 600 mcg	1	150	Risk Ratio (M-H, Fixed, 95% CI)	33.0 [2.02, 540.22]
16.2 400 mcg	4	503	Risk Ratio (M-H, Fixed, 95% CI)	10.18 [3.45, 30.06]

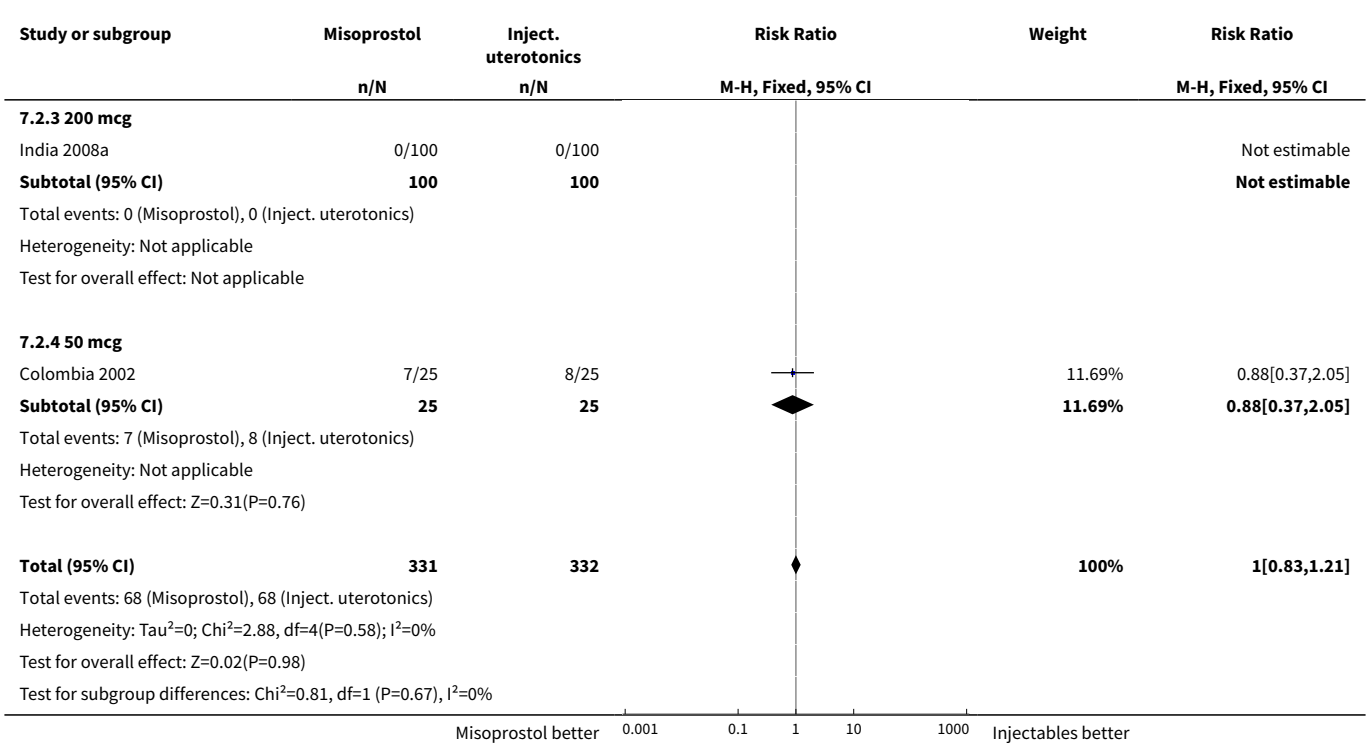
Analysis 7.1. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 1 Severe postpartum haemorrhage (>= 1000 mL).

Study or subgroup	Misoprostol	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
7.1.1 600 mcg					

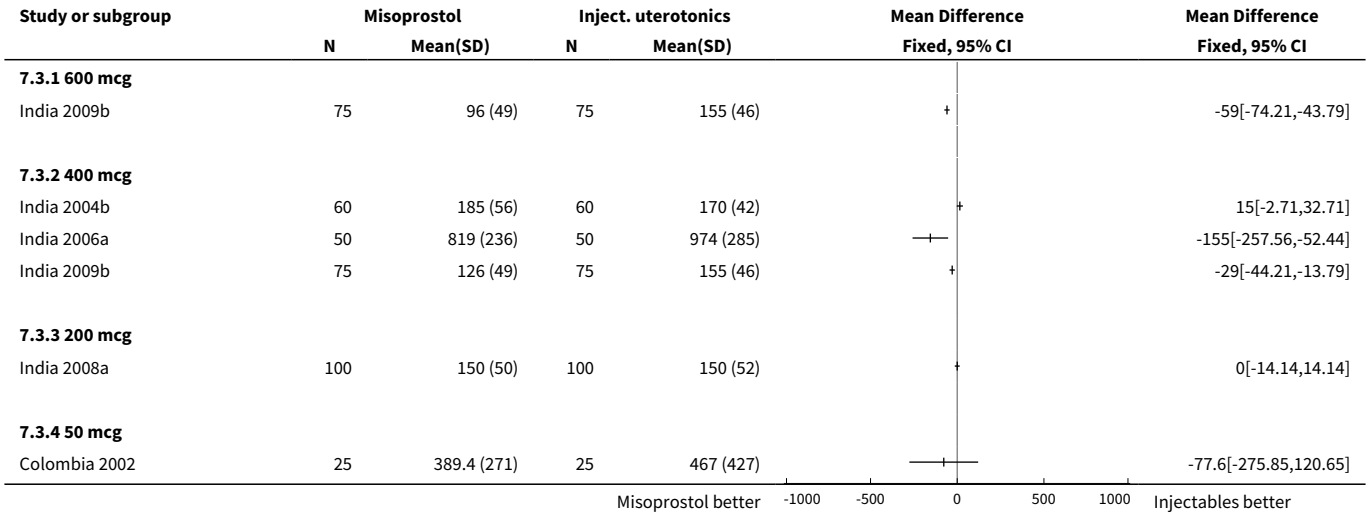


Analysis 7.2. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 2 Postpartum haemorrhage (>= 500 mL).



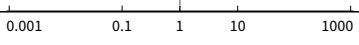


Analysis 7.3. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 3 Blood loss (mL).



Analysis 7.4. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 4 Use of additional uterotonics.

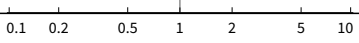
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 600 mcg					
China 2004a	3/30	0/30		0.65%	7[0.38,129.93]
India 2009b	0/75	11/75		14.96%	0.04[0,0.72]
Subtotal (95% CI)	**105**	**105**		**15.61%**	**0.33[0.11,1.02]**
Total events: 3 (Misoprostol), 11 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=6.19, df=1(P=0.01); I^2=83.84%					
Test for overall effect: Z=1.92(P=0.06)					
7.4.2 400 mcg					
India 2004b	5/60	3/60		3.9%	1.67[0.42,6.66]
India 2006a	16/50	18/50		23.41%	0.89[0.51,1.54]
India 2009b	2/75	11/75		14.31%	0.18[0.04,0.79]
India 2009d	9/66	14/67		18.07%	0.65[0.3,1.4]
Iran 2009	7/50	16/50		20.81%	0.44[0.2,0.97]
Subtotal (95% CI)	**301**	**302**		**80.49%**	**0.63[0.44,0.9]**
Total events: 39 (Misoprostol), 62 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=6.95, df=4(P=0.14); I^2=42.47%					
Test for overall effect: Z=2.53(P=0.01)					
7.4.3 200 mcg					
India 2008a	4/100	3/100		3.9%	1.33[0.31,5.81]
Subtotal (95% CI)	**100**	**100**		**3.9%**	**1.33[0.31,5.81]**
Total events: 4 (Misoprostol), 3 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					
Total (95% CI)	**506**	**507**		**100%**	**0.61[0.44,0.85]**
Total events: 46 (Misoprostol), 76 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=14.25, df=7(P=0.05); I^2=50.89%					
Test for overall effect: Z=2.92(P=0)					
Test for subgroup differences: Chi^2=2.23, df=1 (P=0.33), I^2=10.12%					



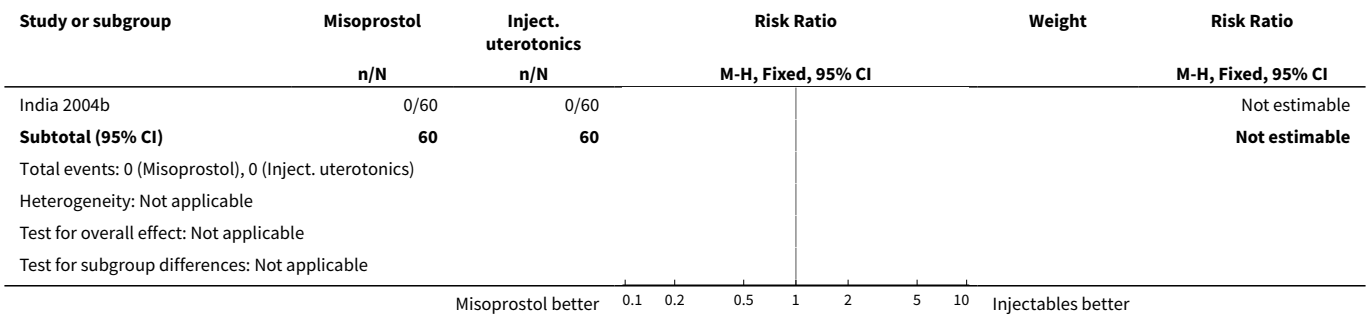
Misoprostol better — Injectables better

Analysis 7.5. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 5 Blood transfusion.

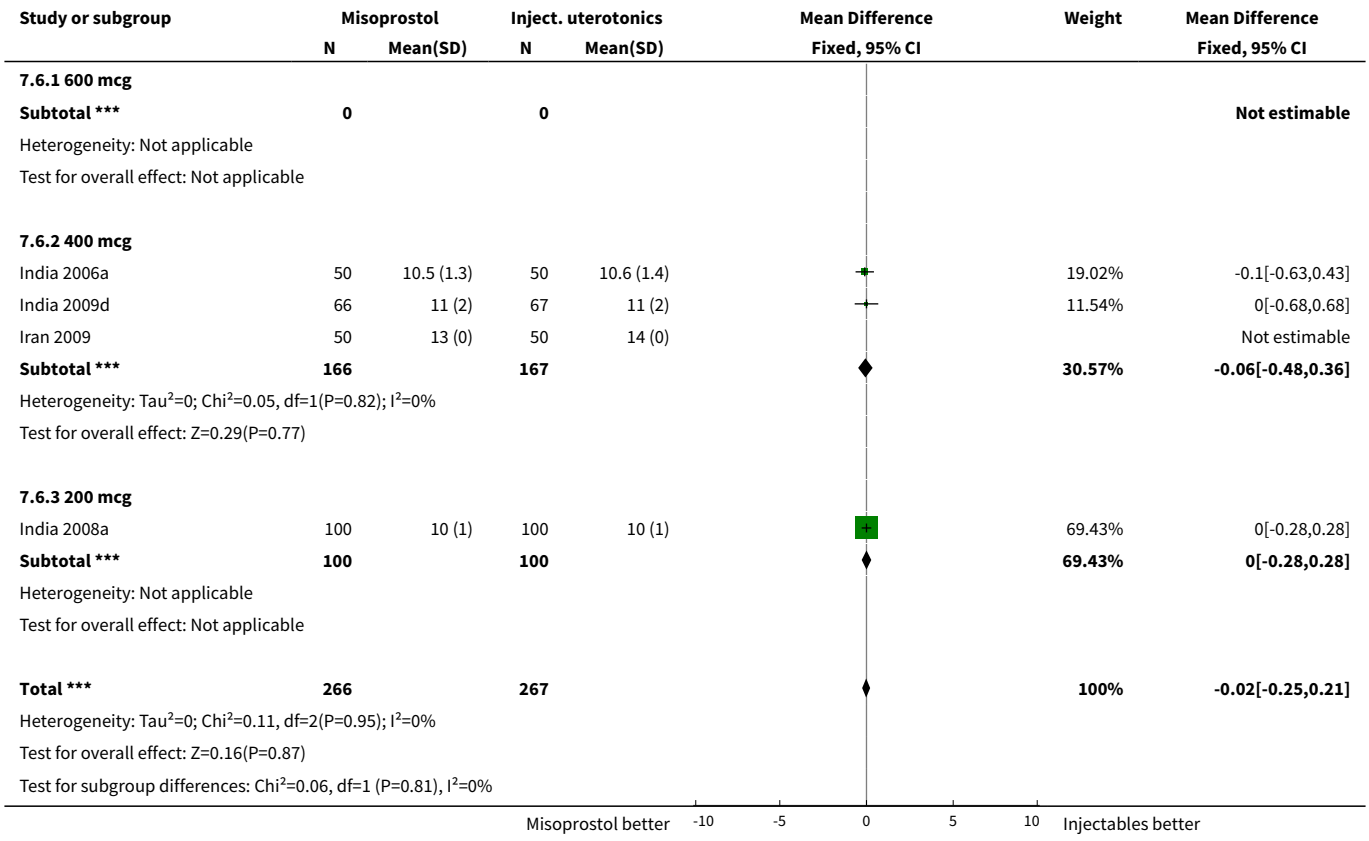
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.5.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
7.5.2 400 mcg					



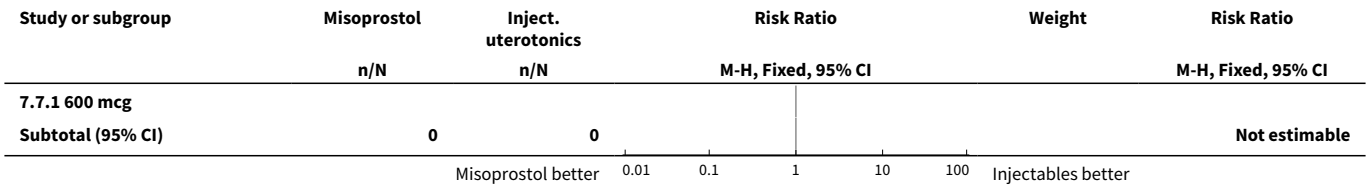
Misoprostol better — Injectables better

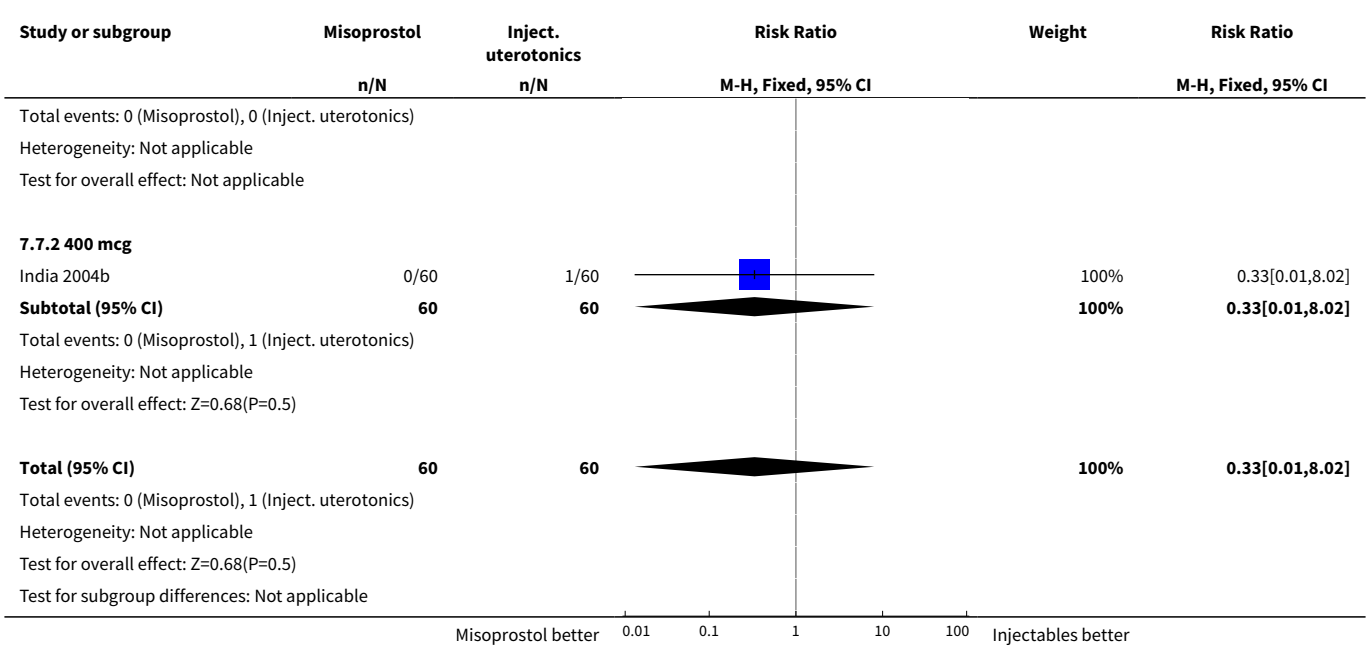


Analysis 7.6. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 6 Postpartum haemoglobin.

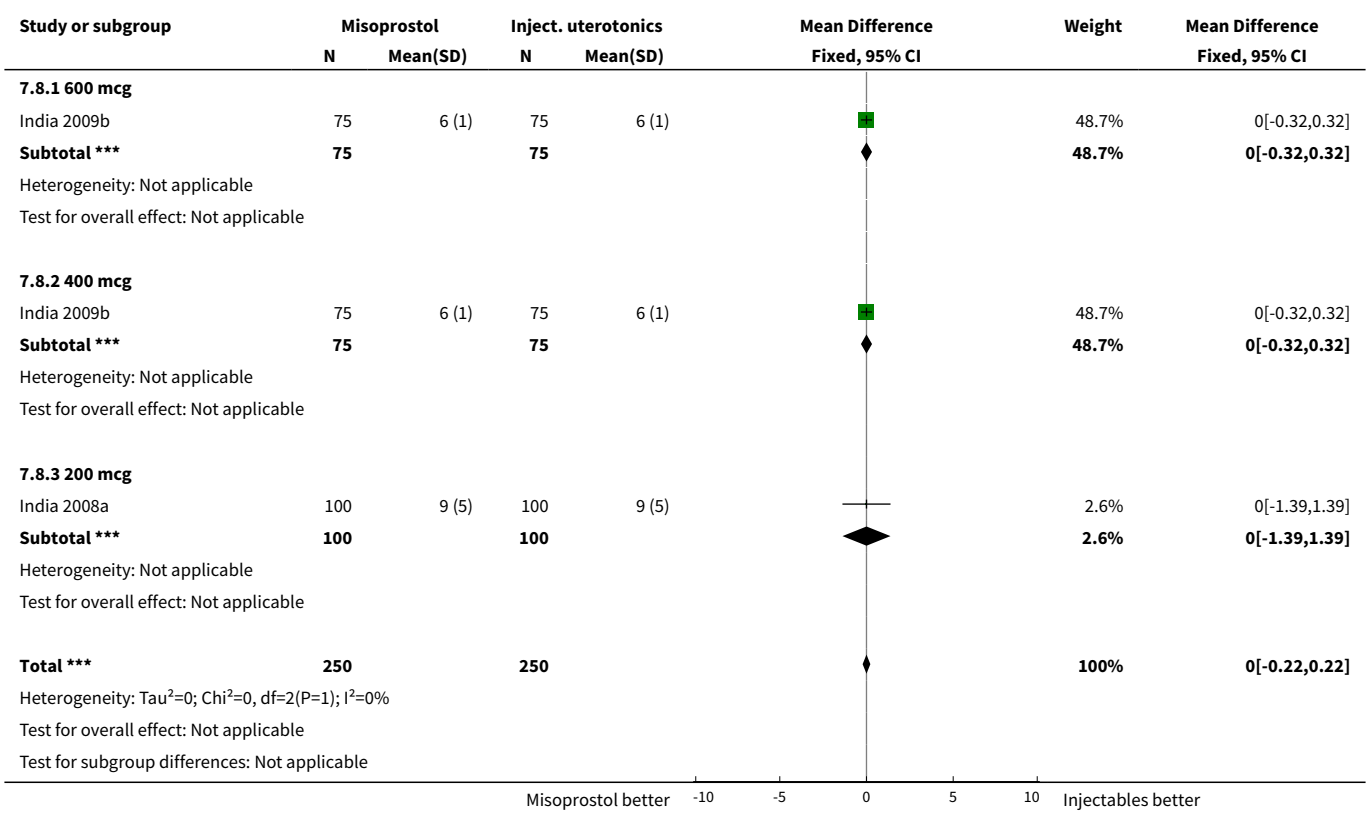


Analysis 7.7. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 7 Manual removal of placenta.

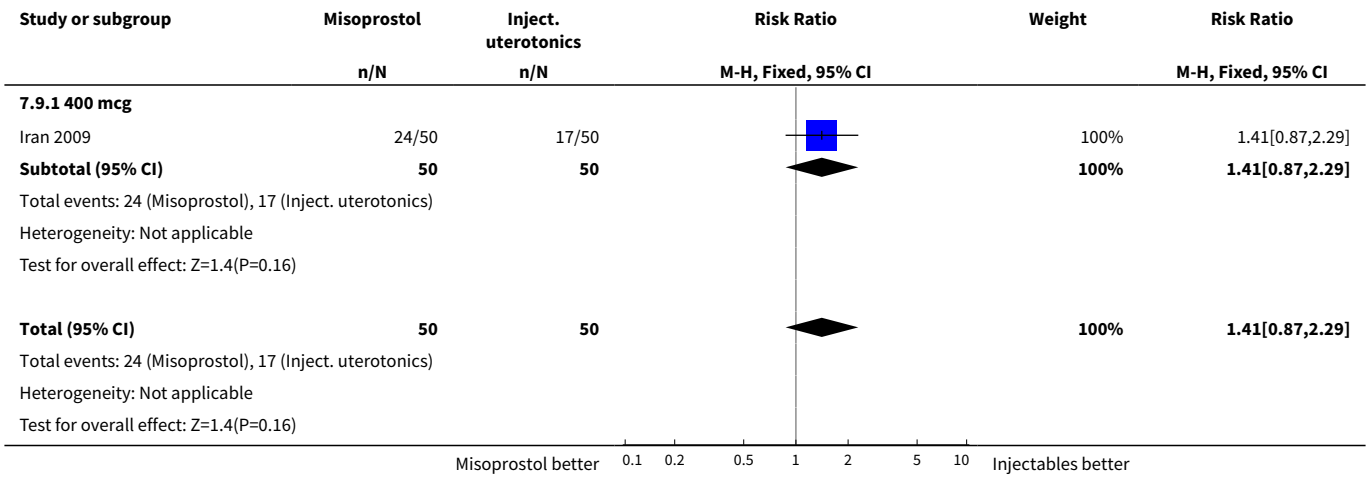




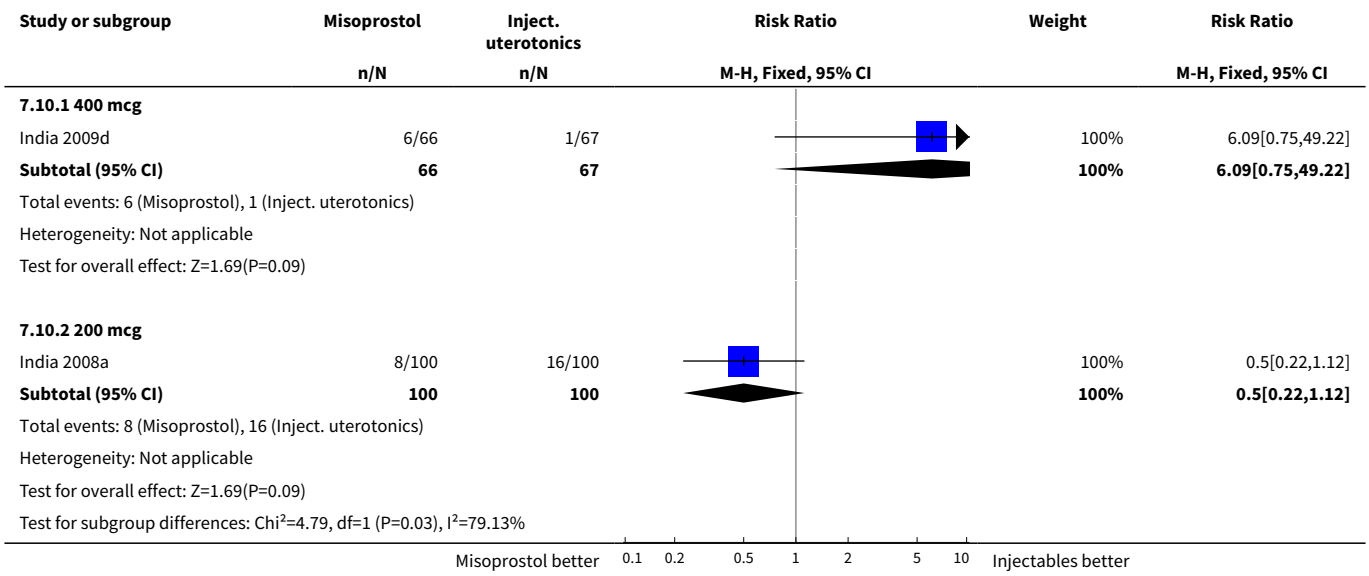
Analysis 7.8. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 8 Duration of third stage (minutes).



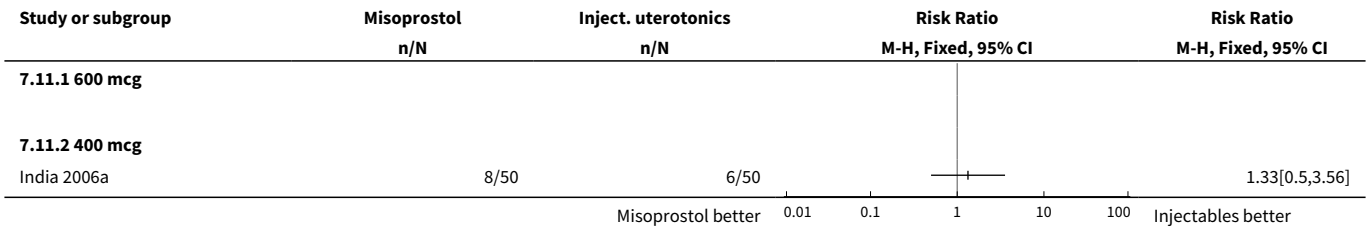
Analysis 7.9. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 9 Any side-effect.



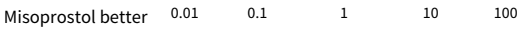
Analysis 7.10. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 10 Nausea.



Analysis 7.11. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 11 Vomiting.

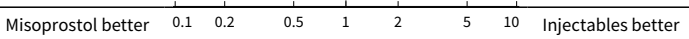


Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
India 2009d	8/66	1/67		8.12[1.04,63.14]
7.11.3 50 mcg				
Colombia 2002	0/25	1/25		0.33[0.01,7.81]
7.11.4 200 mcg				
India 2008a	4/100	8/100		0.5[0.16,1.61]

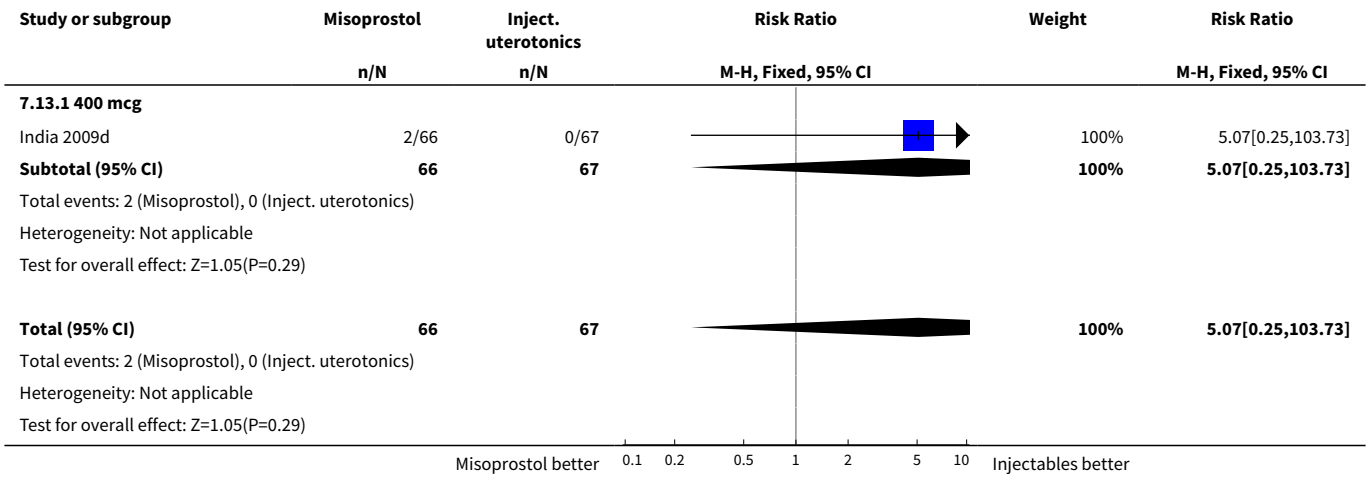


Analysis 7.12. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 12 Headache.

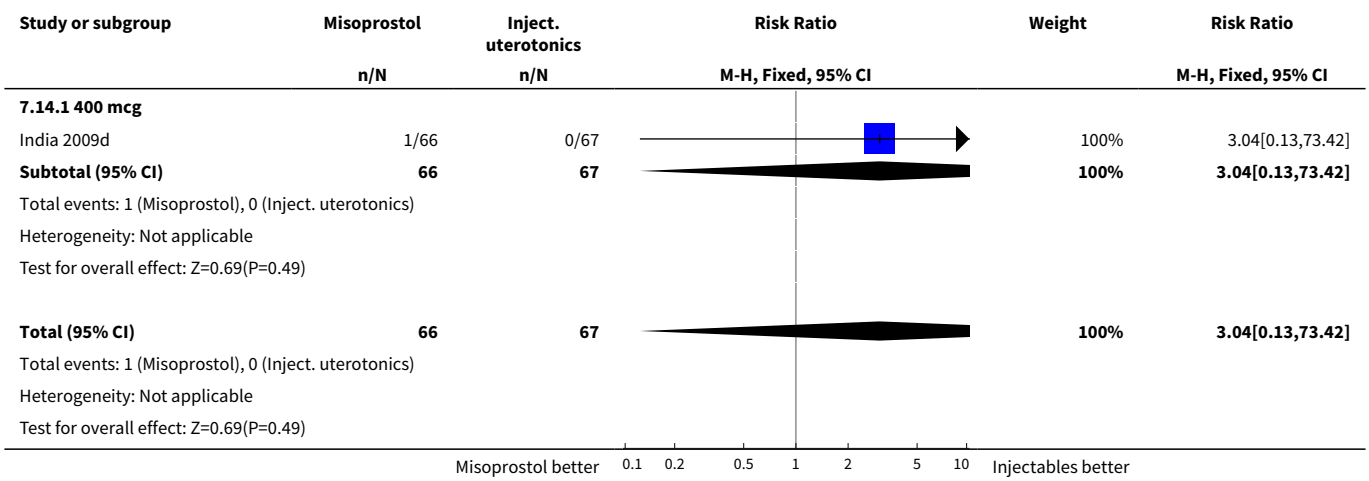
Study or subgroup	Misoprostol n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.12.1 600 mcg					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
7.12.2 400 mcg					
India 2006a	6/50	8/50		50%	0.75[0.28,2]
Subtotal (95% CI)	**50**	**50**		**50%**	**0.75[0.28,2]**
Total events: 6 (Misoprostol), 8 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
7.12.3 200 mcg					
India 2008a	6/100	8/100		50%	0.75[0.27,2.08]
Subtotal (95% CI)	**100**	**100**		**50%**	**0.75[0.27,2.08]**
Total events: 6 (Misoprostol), 8 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					
Total (95% CI)	**150**	**150**		**100%**	**0.75[0.37,1.52]**
Total events: 12 (Misoprostol), 16 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.8(P=0.43)					
Test for subgroup differences: Not applicable					



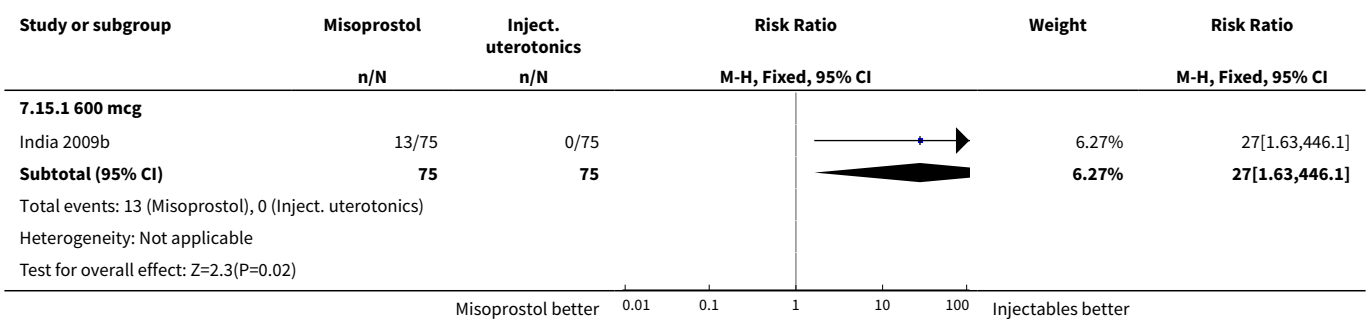
Analysis 7.13. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 13 Abdominal pain.

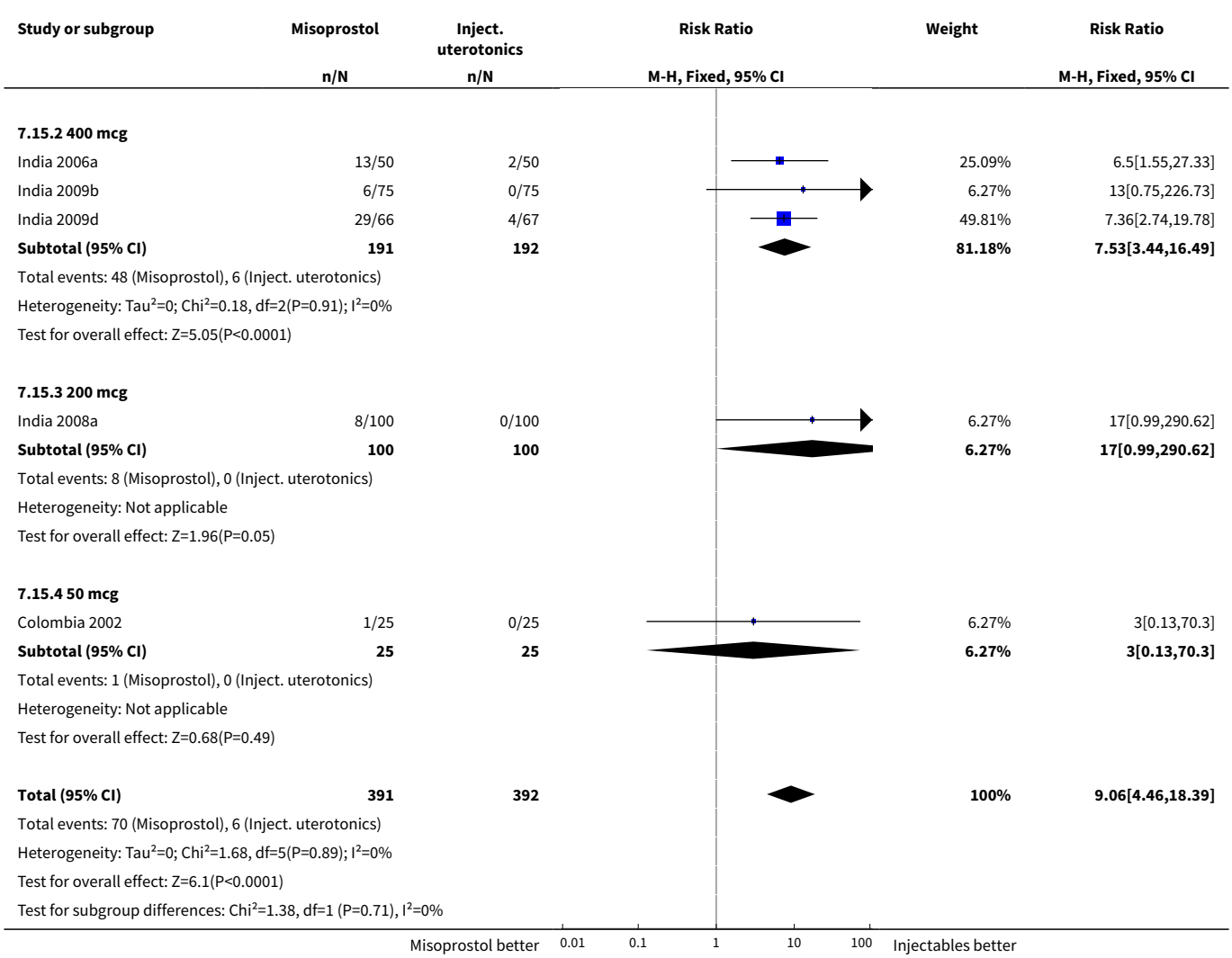


Analysis 7.14. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 14 Diarrhoea.

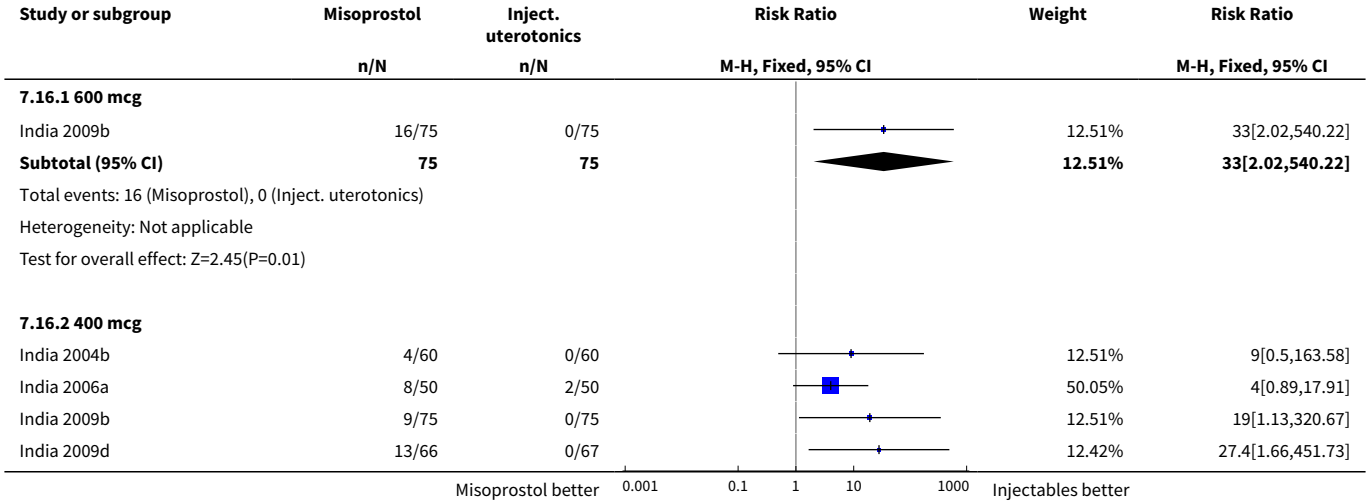


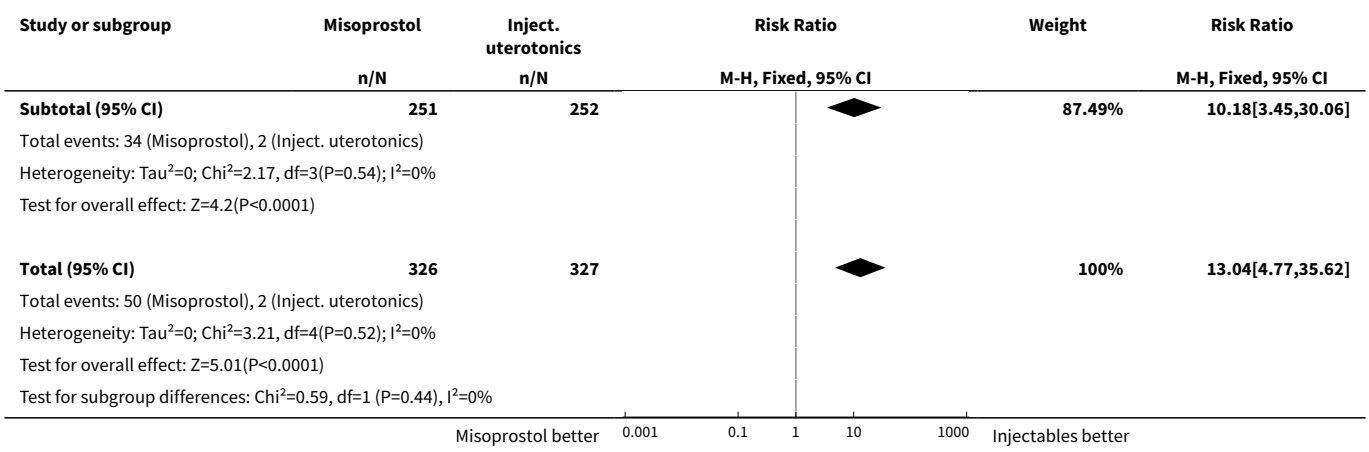
Analysis 7.15. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 15 Any shivering.





Analysis 7.16. Comparison 7 Sublingual misoprostol versus injectable uterotonic (subgroups by dose), Outcome 16 Pyrexia >= 38 degrees C.



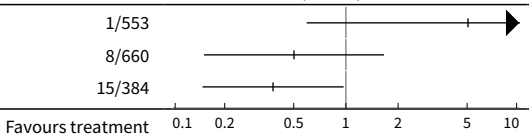


Comparison 8. Oral misoprostol plus injectable uterotonics versus injectable uterotonics

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Severe postpartum haemorrhage (>= 1000 mL)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Postpartum haemorrhage (>= 500 mL)	3	3205	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.53, 0.95]
3 Blood loss (mL)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Duration of third stage (mins)	1	788	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.31, 0.51]
5 Third stage >= 30 minutes	1	788	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.24, 8.49]
6 Manual removal of placenta	2	2229	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.64, 1.35]
7 Blood transfusion	1	788	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.02]
8 Vomiting	1	788	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.19, 4.68]
9 Diarrhoea	1	788	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.48, 2.23]
10 Any shivering	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Pyrexia (>= 38 degrees C)	2	2022	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [1.80, 5.28]

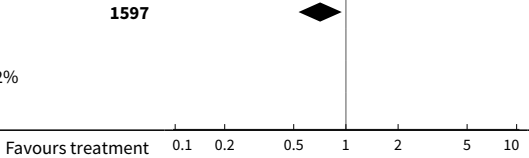
Analysis 8.1. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 1 Severe postpartum haemorrhage (>= 1000 mL).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Africa 2011	5/546	1/553		0%	5.06[0.59,43.2]
Nigeria 2011	4/658	8/660		0%	0.5[0.15,1.66]
Turkey 2003	6/404	15/384		0%	0.38[0.15,0.97]



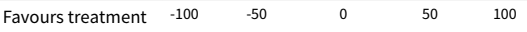
Analysis 8.2. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 2 Postpartum haemorrhage (>= 500 mL).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Africa 2011	22/546	35/553		32.99%	0.64[0.38,1.07]
Nigeria 2011	40/658	42/660		39.78%	0.96[0.63,1.45]
Turkey 2003	13/404	28/384		27.23%	0.44[0.23,0.84]
Total (95% CI)	**1608**	**1597**		**100%**	**0.71[0.53,0.95]**
Total events: 75 (Treatment), 105 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.19, df=2(P=0.12); I^2=52.32%					
Test for overall effect: Z=2.33(P=0.02)					



Analysis 8.3. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 3 Blood loss (mL).

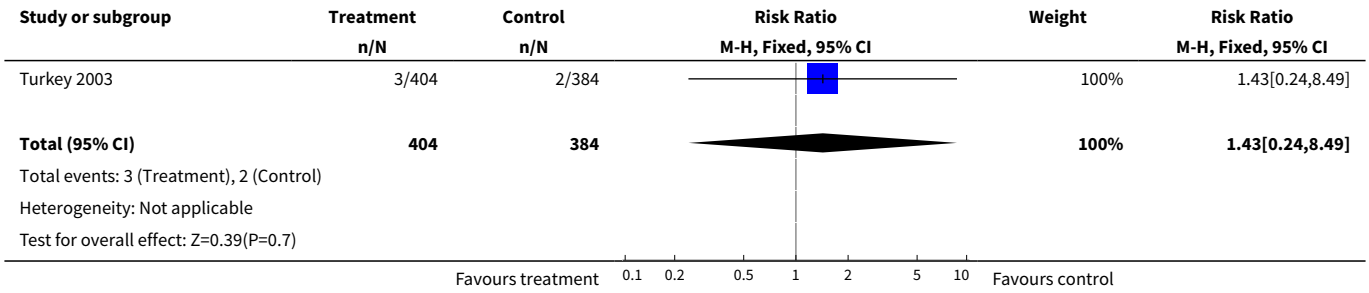
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nigeria 2011	657	212 (205)	660	218 (202)		0%	-6[-27.98,15.98]
Turkey 2003	404	280 (182)	384	312 (176)		0%	-32[-57,-7]



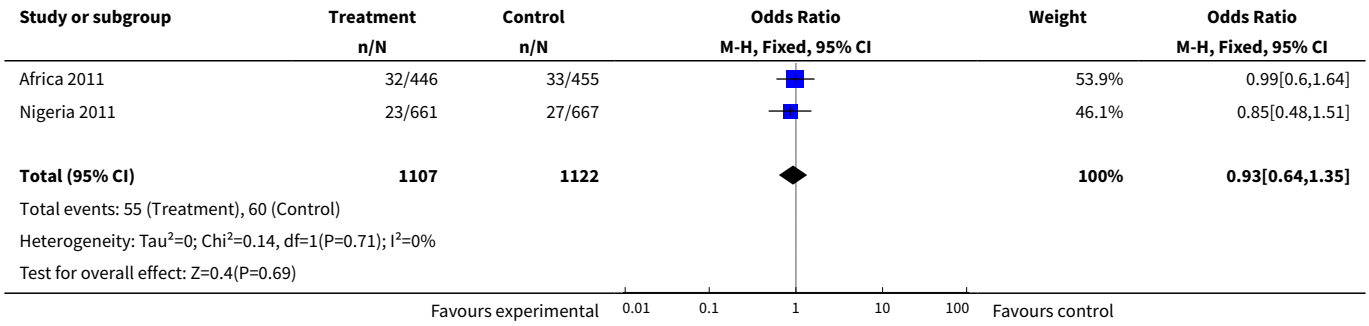
Analysis 8.4. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 4 Duration of third stage (mins).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Turkey 2003	404	8.8 (3.8)	384	8.7 (1.7)		100%	0.1[-0.31,0.51]
Total ***	**404**		**384**			**100%**	**0.1[-0.31,0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.48(P=0.63)							

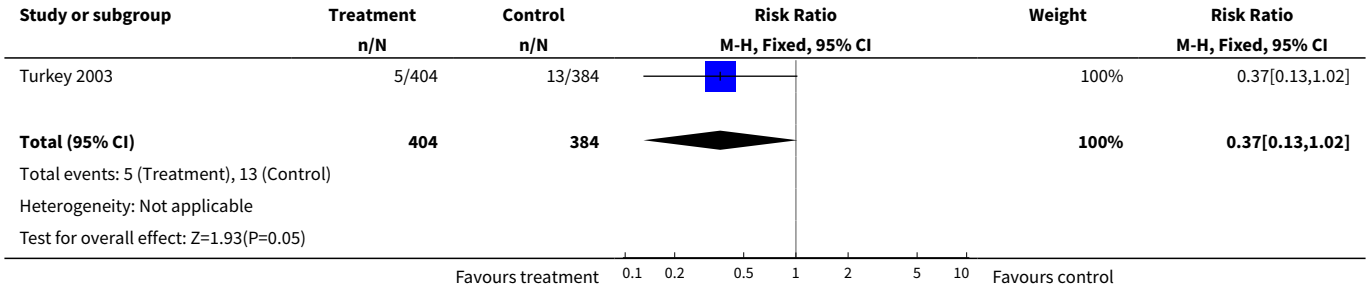
Analysis 8.5. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 5 Third stage >= 30 minutes.



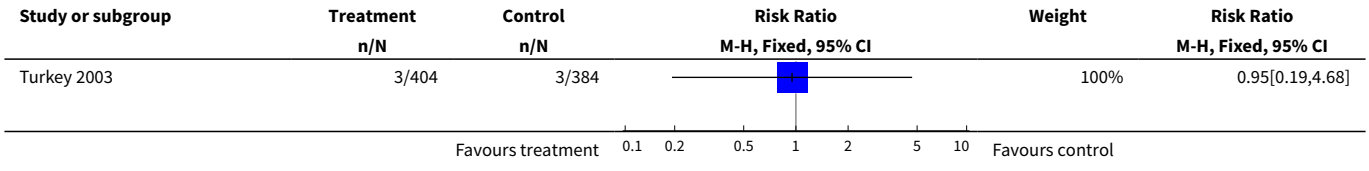
Analysis 8.6. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 6 Manual removal of placenta.

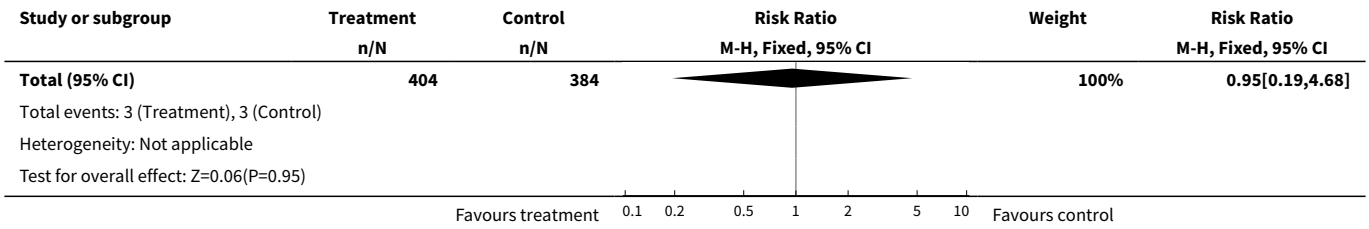


Analysis 8.7. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 7 Blood transfusion.

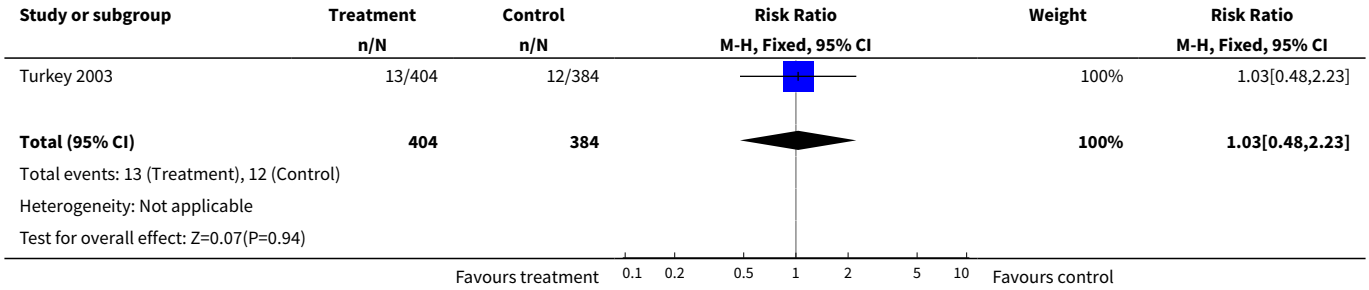


Analysis 8.8. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 8 Vomiting.

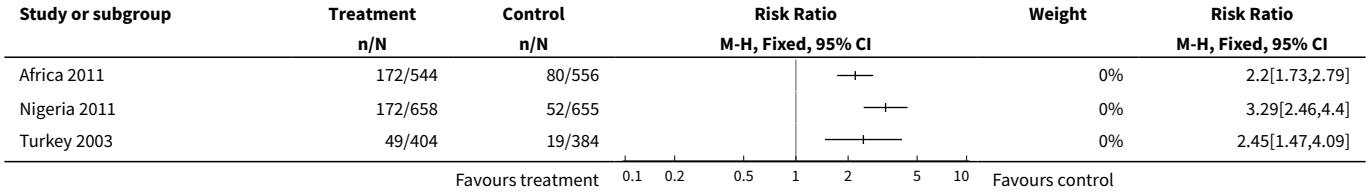




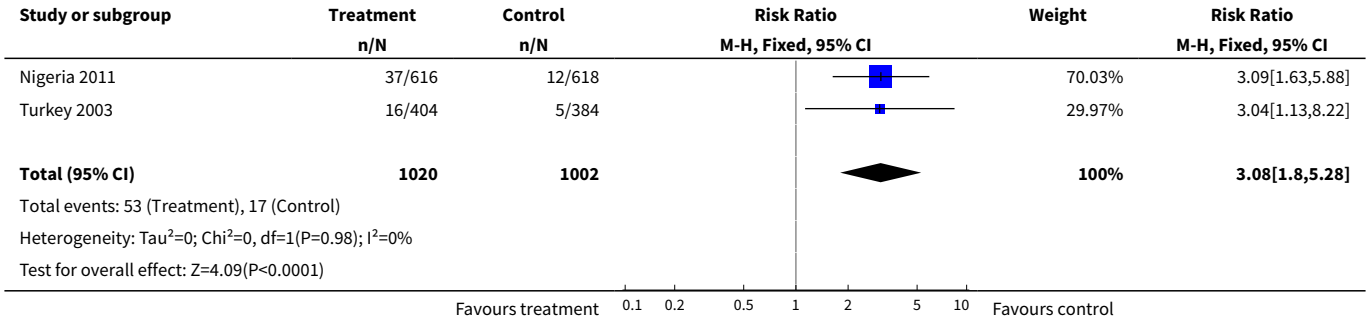
Analysis 8.9. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 9 Diarrhoea.



Analysis 8.10. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 10 Any shivering.



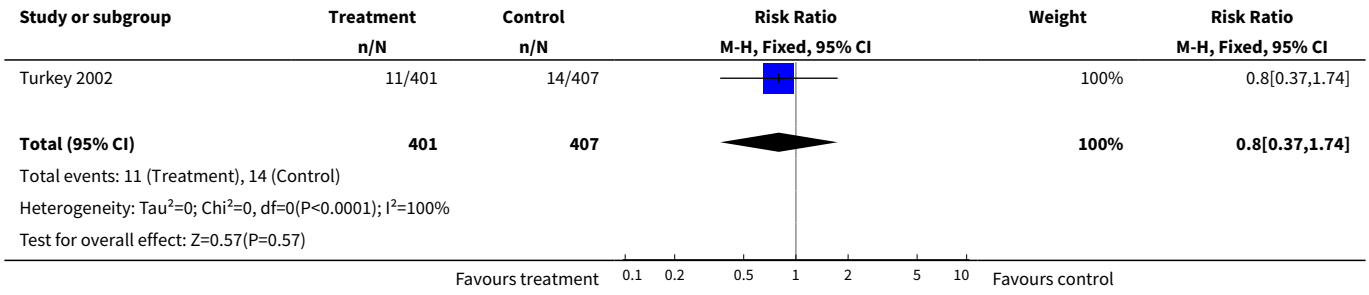
Analysis 8.11. Comparison 8 Oral misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 11 Pyrexia (>= 38 degrees C).



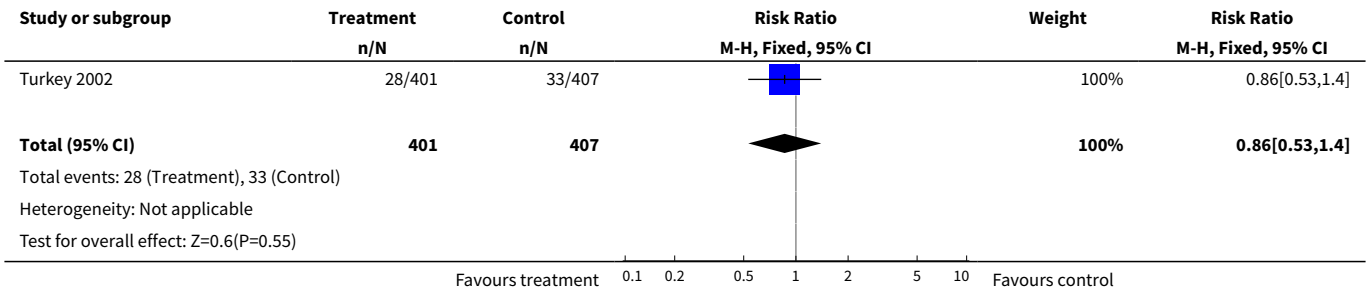
Comparison 9. Rectal misoprostol plus injectable uterotonics versus injectable uterotonics

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Severe postpartum haemorrhage (>= 1000 mL)	1	808	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.37, 1.74]
2 Postpartum haemorrhage (>= 500 mL)	1	808	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.53, 1.40]
3 Duration of third stage (minutes)	1	808	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.46, 0.26]
4 Third stage >= 30 minutes	1	808	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.14, 7.17]
5 Blood transfusion	1	808	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.95]
6 Vomiting	1	808	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 9.06]
7 Diarrhoea	1	808	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.41, 2.53]
8 Any shivering	1	808	Risk Ratio (M-H, Fixed, 95% CI)	3.30 [1.92, 5.68]
9 Pyrexia (>= 38 degrees C)	1	808	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [1.30, 7.96]

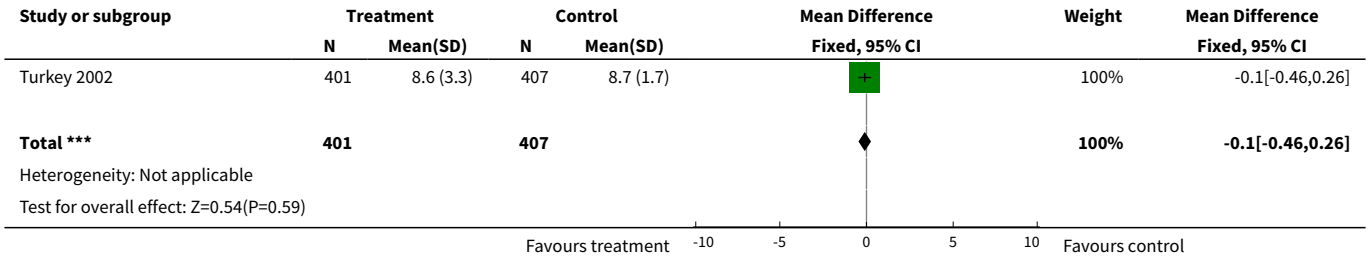
Analysis 9.1. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 1 Severe postpartum haemorrhage (>= 1000 mL).



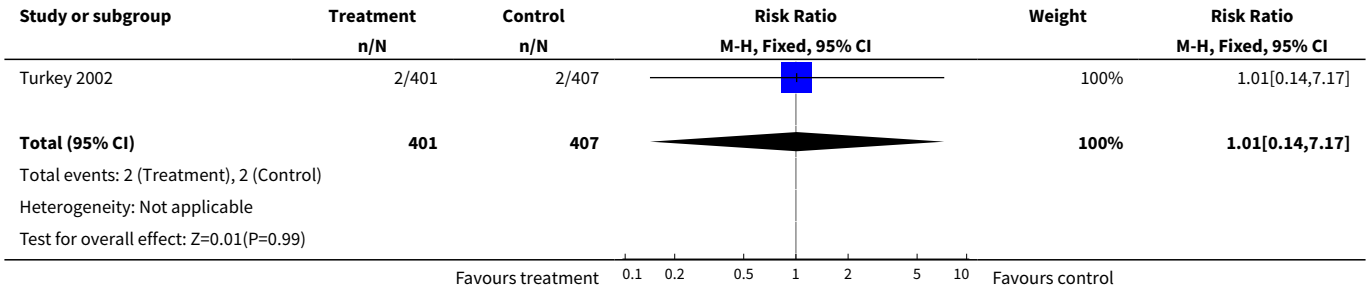
Analysis 9.2. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 2 Postpartum haemorrhage (>= 500 mL).



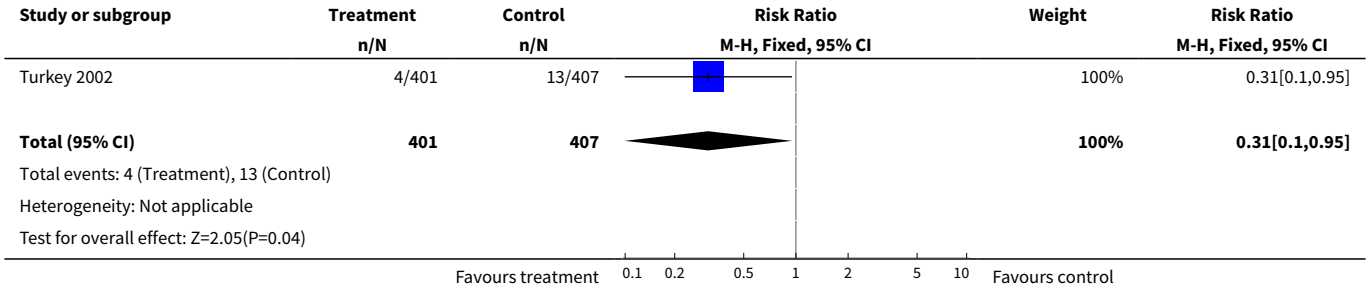
Analysis 9.3. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 3 Duration of third stage (minutes).



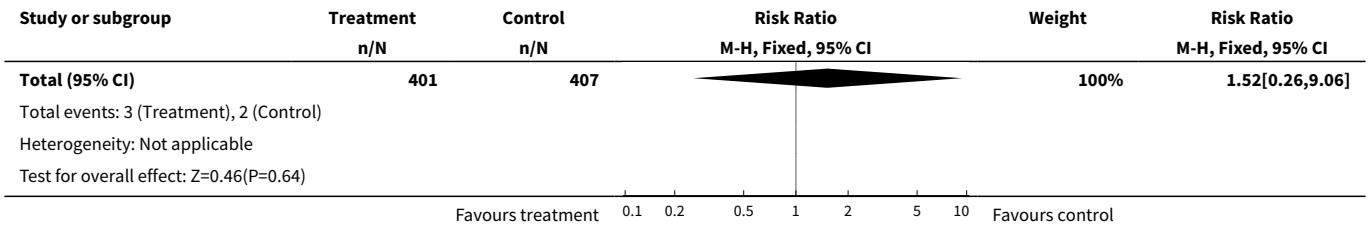
Analysis 9.4. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 4 Third stage >= 30 minutes.



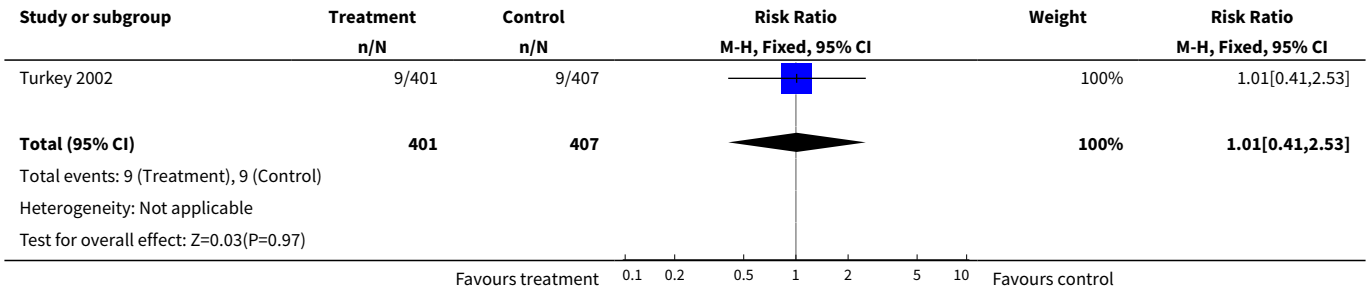
Analysis 9.5. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 5 Blood transfusion.



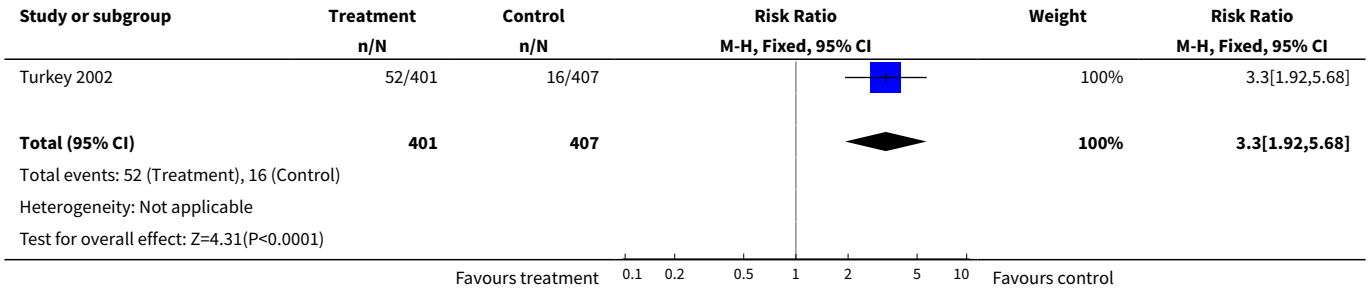
Analysis 9.6. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 6 Vomiting.



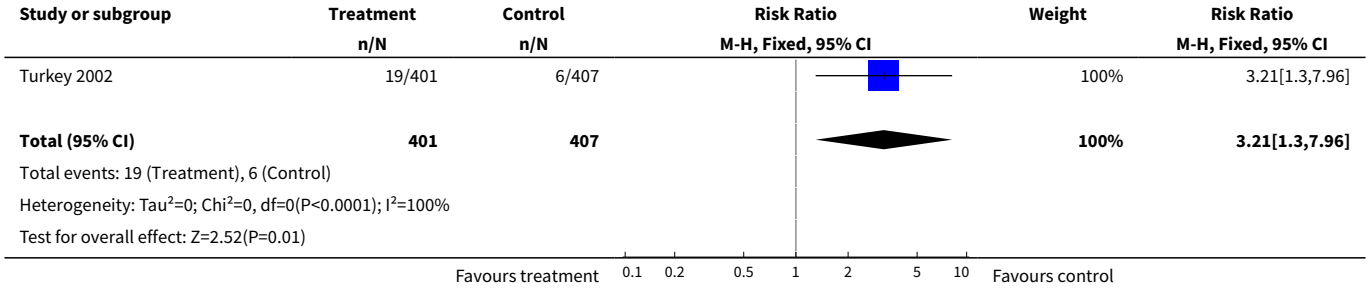
Analysis 9.7. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 7 Diarrhoea.



Analysis 9.8. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 8 Any shivering.



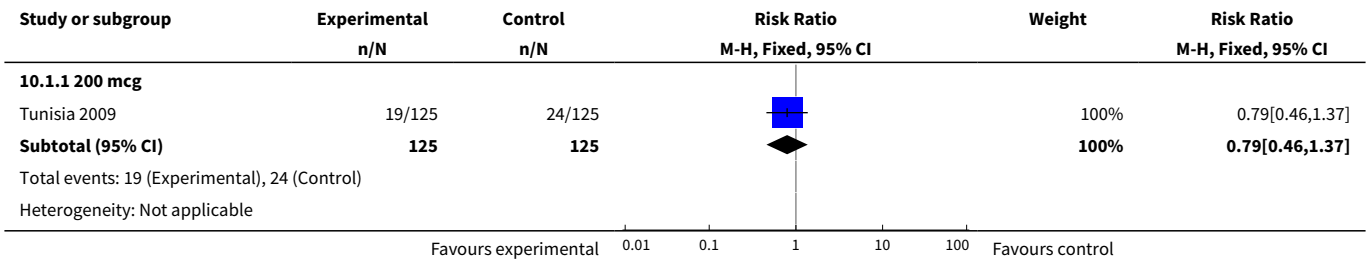
Analysis 9.9. Comparison 9 Rectal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 9 Pyrexia (>= 38 degrees C).

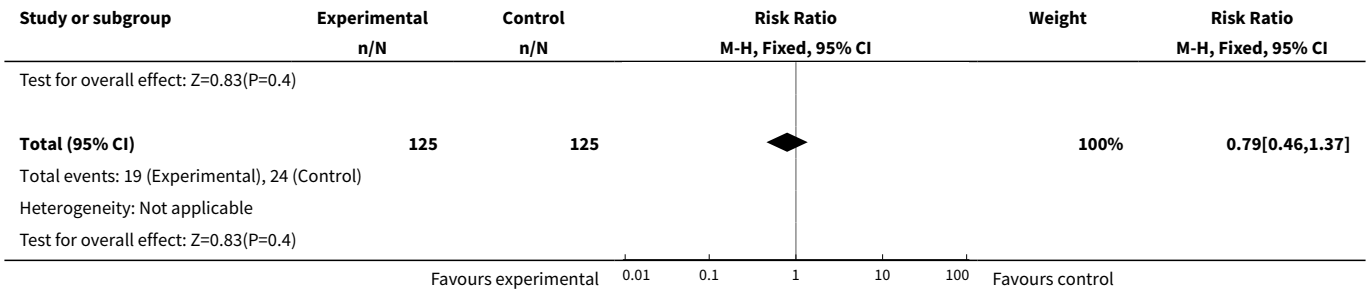


Comparison 10. Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics

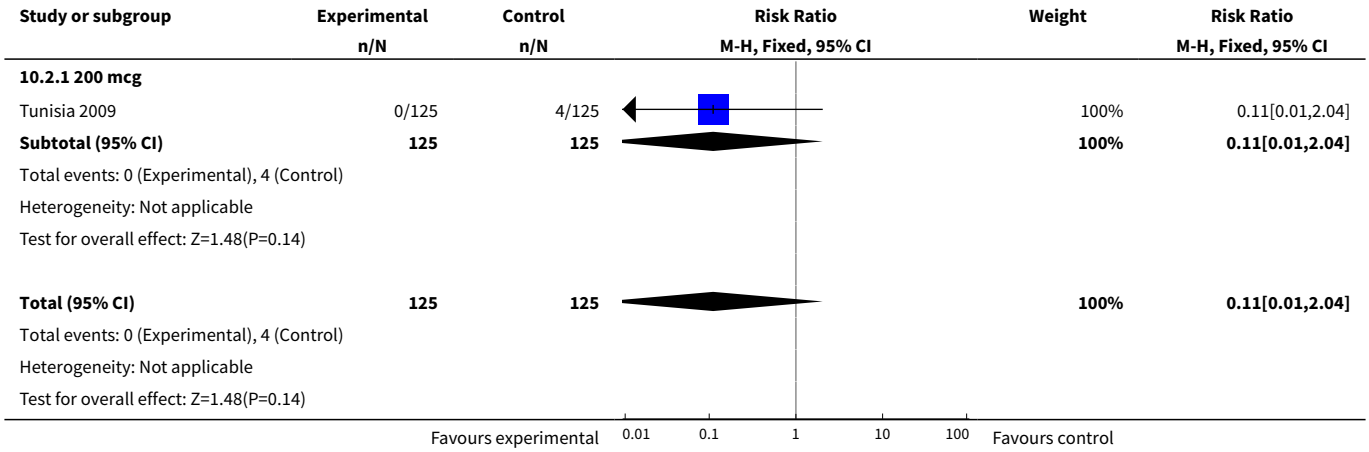
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe postpartum hemorrhage (>=1000 mL)	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.37]
1.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.37]
2 Blood transfusion	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.04]
2.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.04]
3 Any side effects	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.58, 4.04]
3.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.58, 4.04]
4 Vomiting	1	250	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.70, 3.21]
4.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.70, 3.21]
4.2 200 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Nausea	1	250	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.99, 20.41]
5.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.99, 20.41]
6 Headache	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.37, 10.72]
6.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.37, 10.72]
7 Shivering	1	250	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [1.85, 10.16]
7.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [1.85, 10.16]
8 Pyrexia (>= 38 C)	1	250	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.87, 56.06]
8.1 200 mcg	1	250	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.87, 56.06]

Analysis 10.1. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 1 Severe postpartum hemorrhage (>=1000 mL).

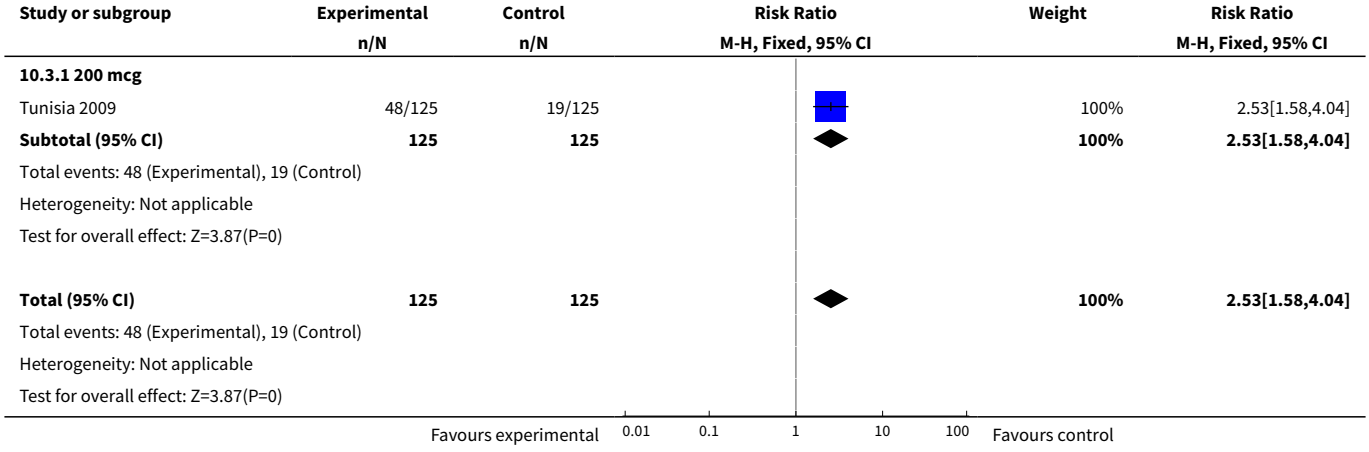




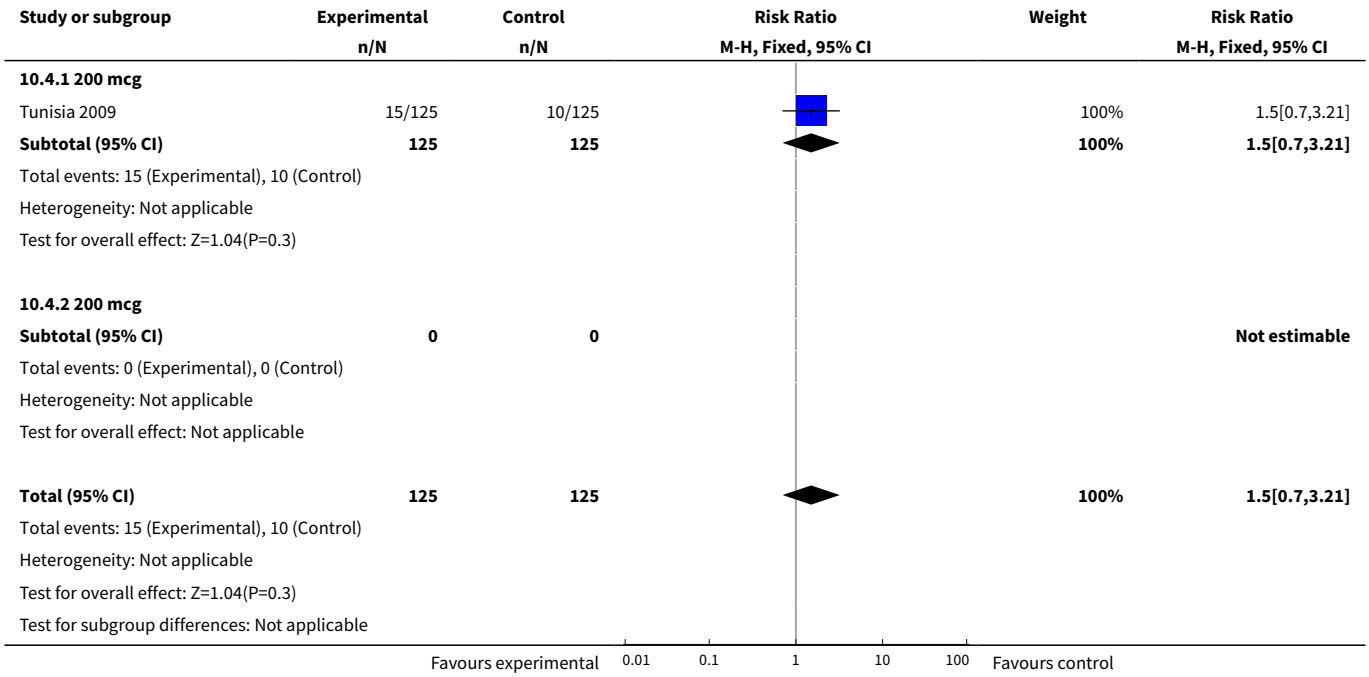
Analysis 10.2. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 2 Blood transfusion.



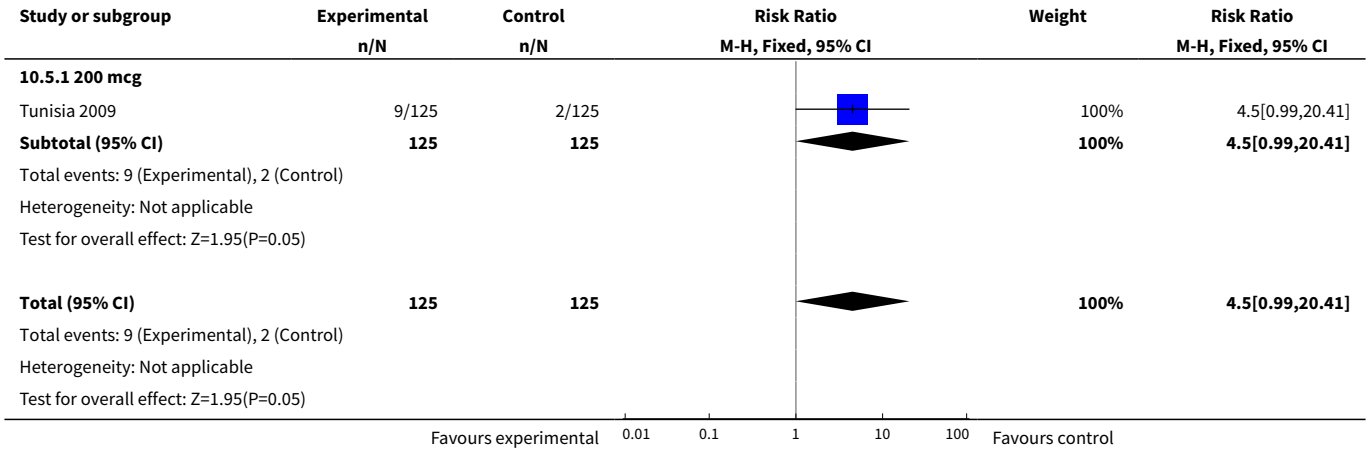
Analysis 10.3. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 3 Any side effects.



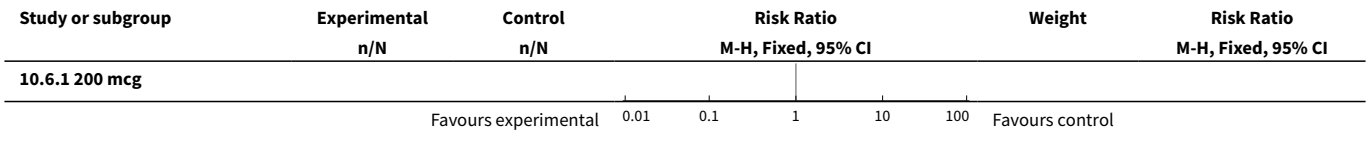
Analysis 10.4. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 4 Vomiting.

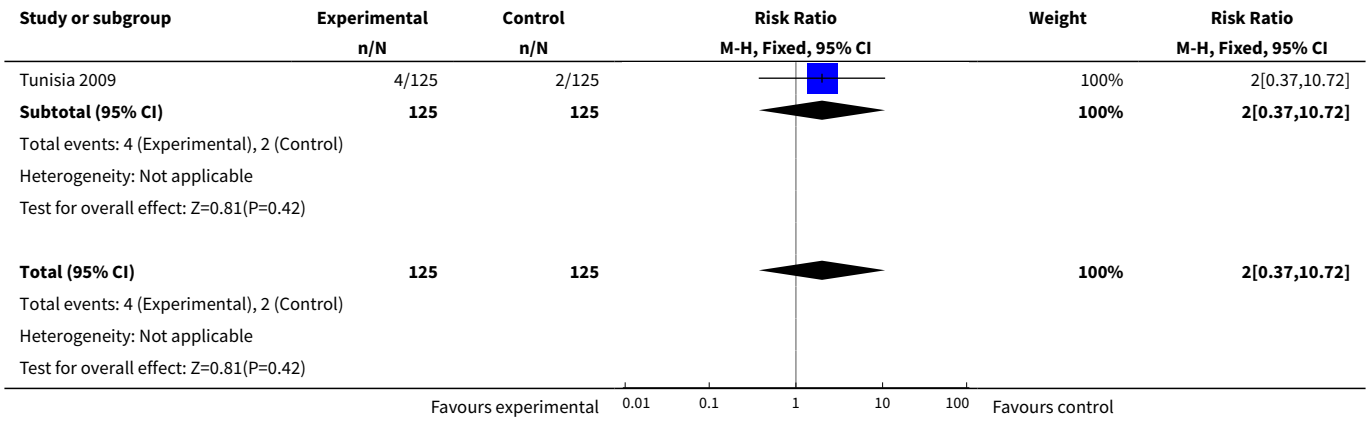


Analysis 10.5. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 5 Nausea.

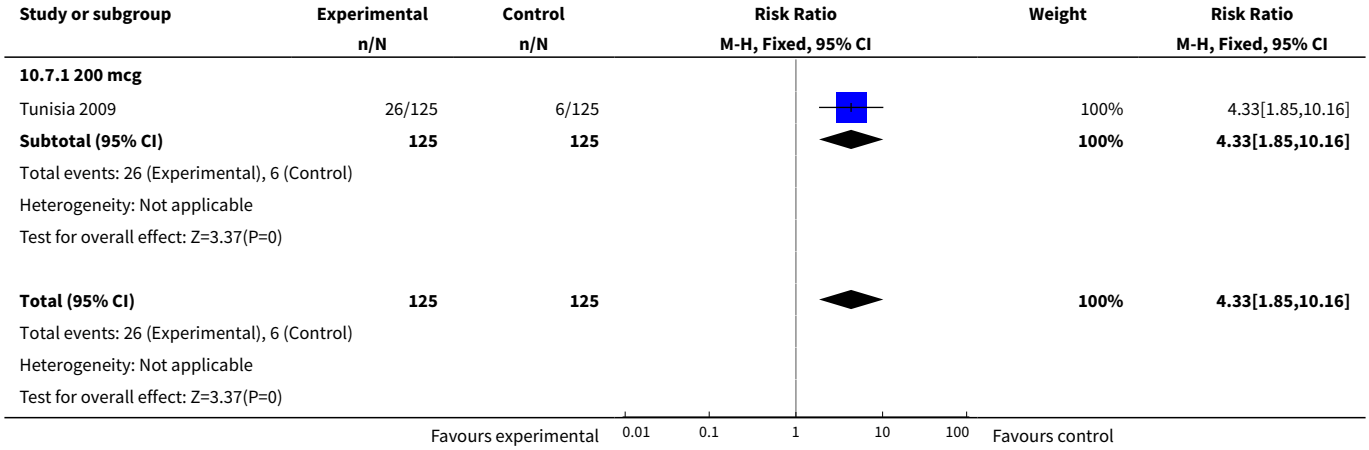


Analysis 10.6. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 6 Headache.

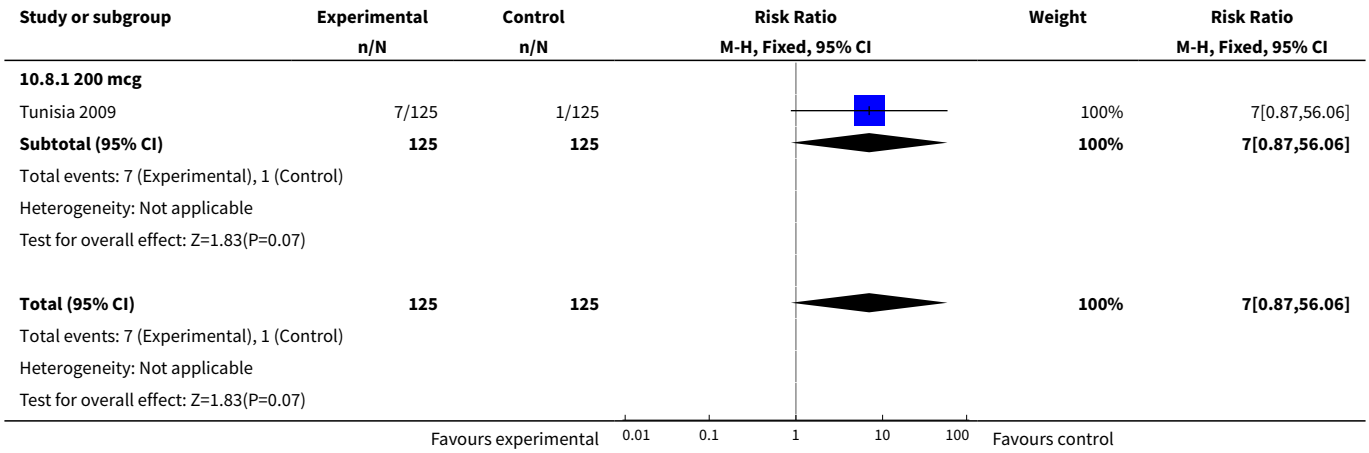




Analysis 10.7. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 7 Shivering.



Analysis 10.8. Comparison 10 Sublingual misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 8 Pyrexia (>= 38 C).

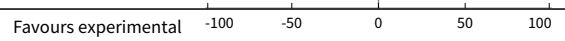


Comparison 11. Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics

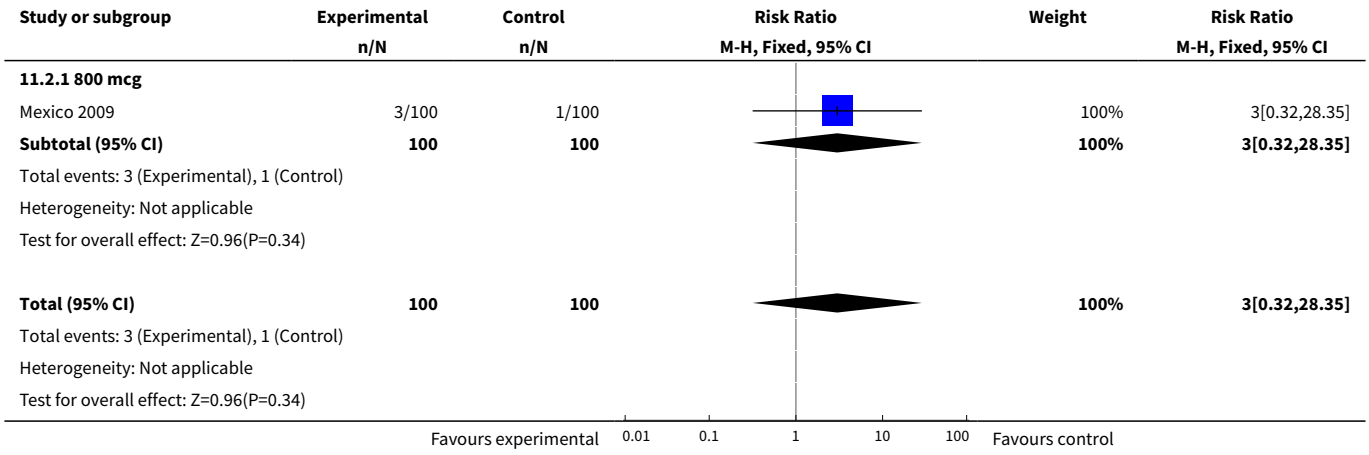
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum haemoglobin	1	200	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.72, 1.28]
1.1 800 mcg	1	200	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.72, 1.28]
2 Use of Additional Uterotonics	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 28.35]
2.1 800 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 28.35]
3 Any shivering	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.50, 12.59]
3.1 800 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.50, 12.59]
4 Nausea	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.50, 12.59]
4.1 800 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.50, 12.59]
5 Vomiting	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.84]
5.1 800 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.84]
6 Pyrexia (>= 38 C)	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.62, 6.43]
6.1 800 mcg	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.62, 6.43]

Analysis 11.1. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 1 Postpartum haemoglobin.

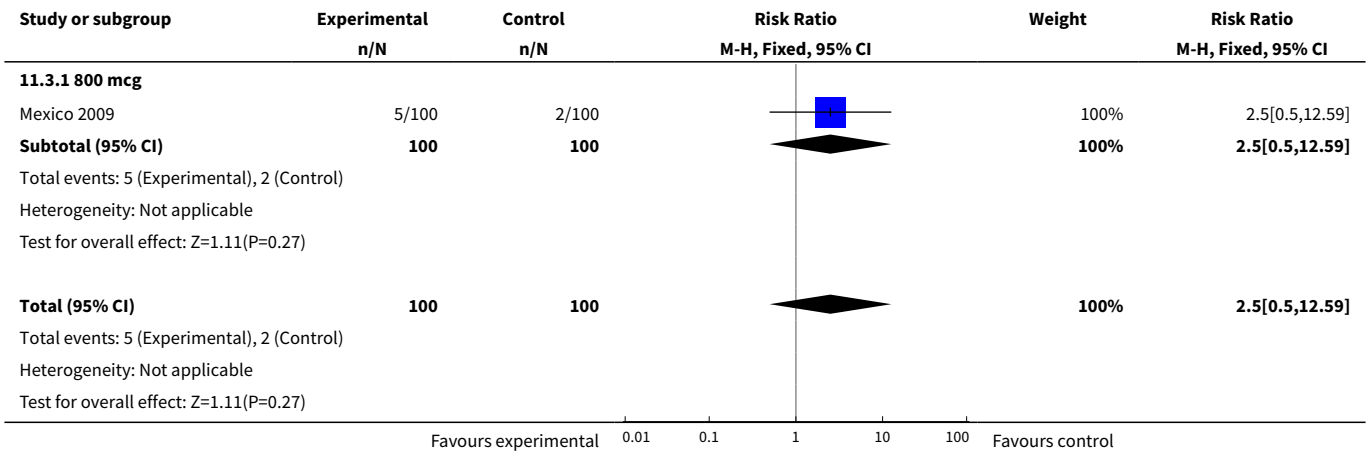
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.1.1 800 mcg							
Mexico 2009	100	12 (1)	100	11 (1)		100%	1[0.72,1.28]
Subtotal ***	**100**		**100**			**100%**	**1[0.72,1.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.07(P<0.0001)							
Total ***	**100**		**100**			**100%**	**1[0.72,1.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.07(P<0.0001)							



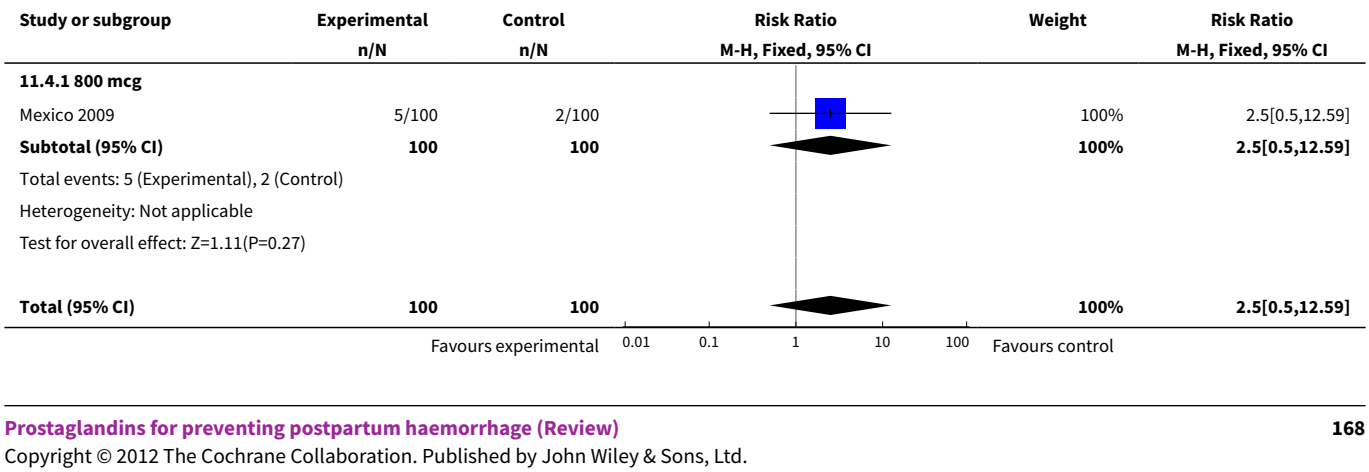
Analysis 11.2. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 2 Use of Additional Uterotonics.

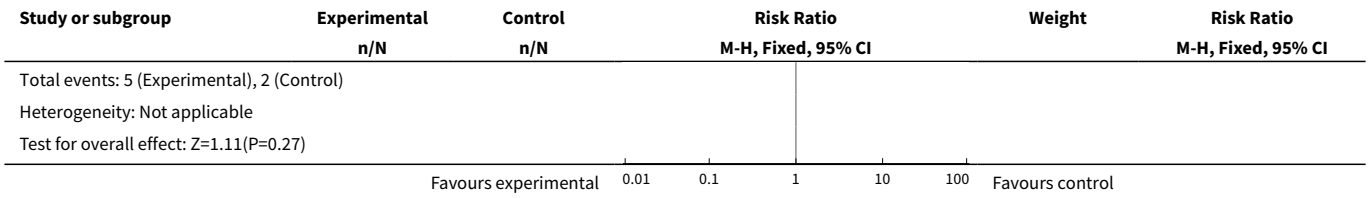


Analysis 11.3. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 3 Any shivering.

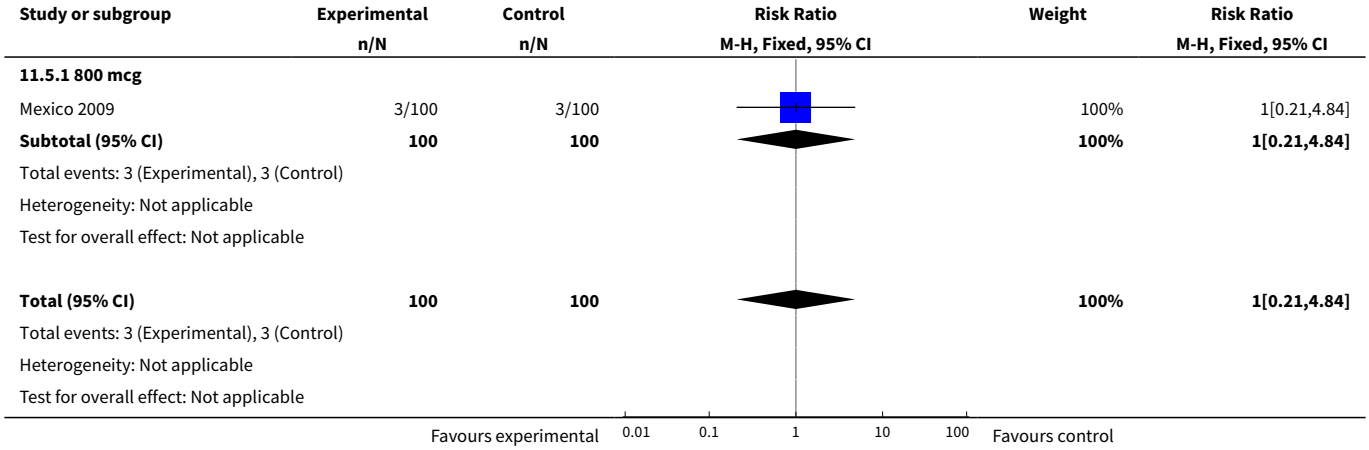


Analysis 11.4. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 4 Nausea.

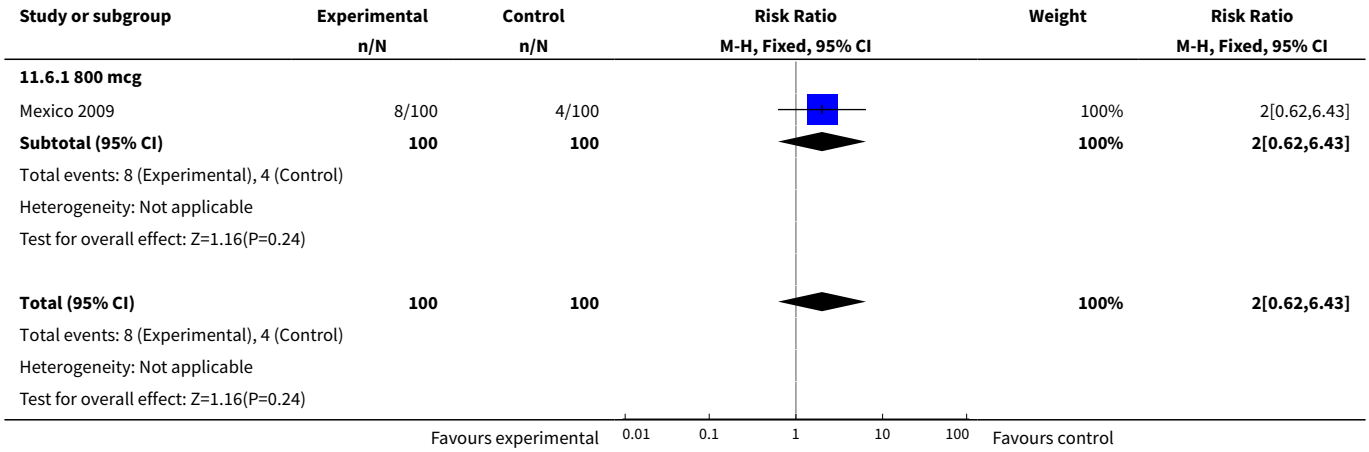




Analysis 11.5. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 5 Vomiting.



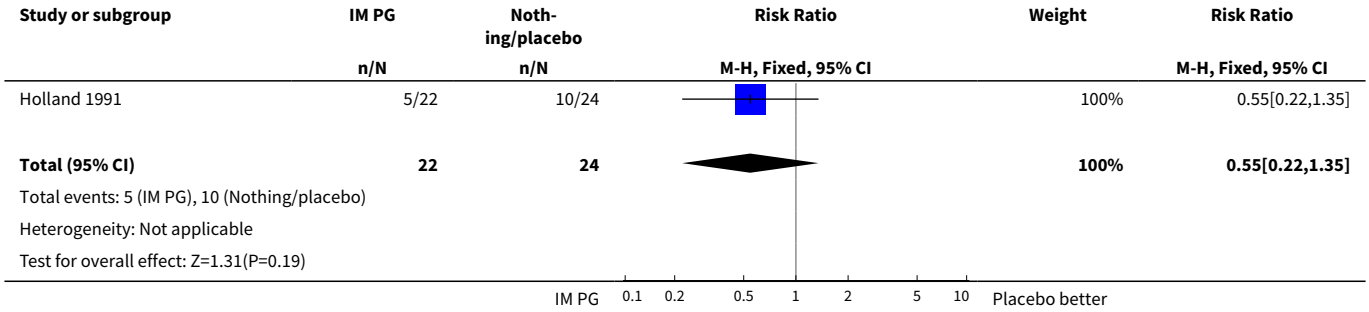
Analysis 11.6. Comparison 11 Intravaginal misoprostol plus injectable uterotonics versus injectable uterotonics, Outcome 6 Pyrexia (>= 38 C).



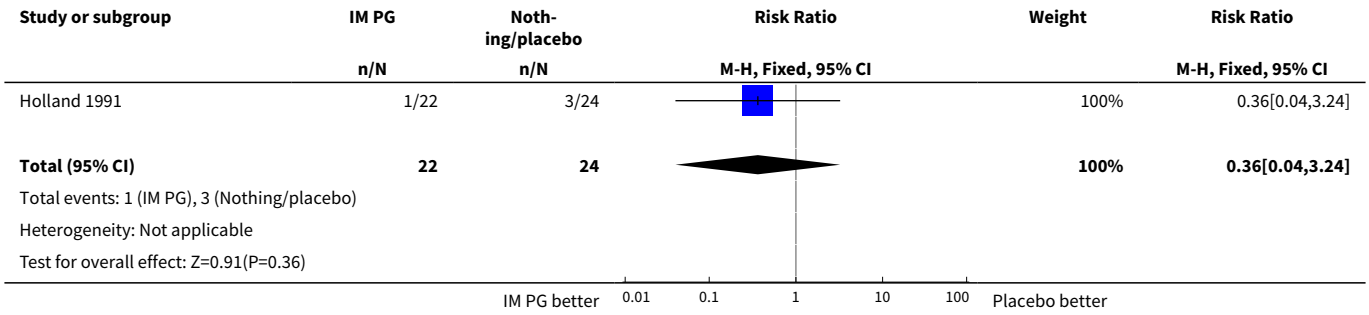
Comparison 12. Intramuscular prostaglandin versus no uterotonic/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum haemorrhage (>= 500 mL)	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.22, 1.35]
2 Severe postpartum haemorrhage (>= 1000 mL)	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.24]
3 Blood loss (mL)	1	46	Mean Difference (IV, Fixed, 95% CI)	-224.0 [-420.35, -27.65]
4 Use of additional uterotonics	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.29]
5 Manual removal of placenta	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Duration of third stage (minutes)	1	46	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-7.65, 0.45]
7 Any side-effect	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.46]
8 Nausea	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.46]

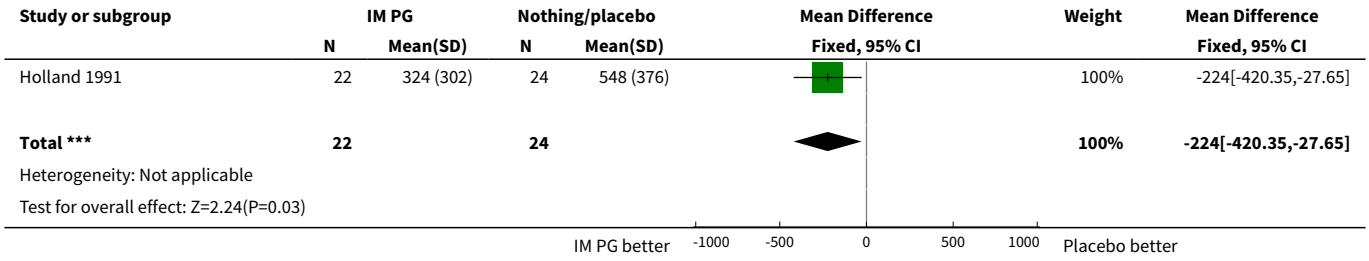
Analysis 12.1. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 1 Postpartum haemorrhage (>= 500 mL).



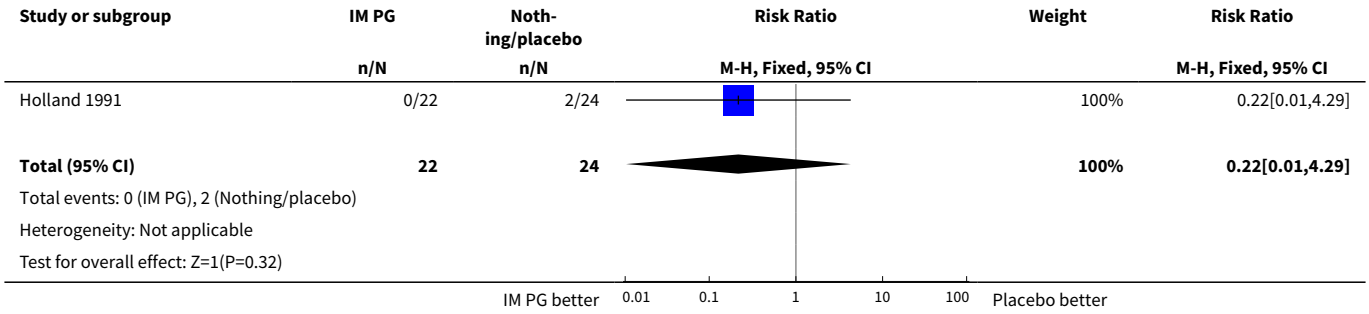
Analysis 12.2. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 2 Severe postpartum haemorrhage (>= 1000 mL).



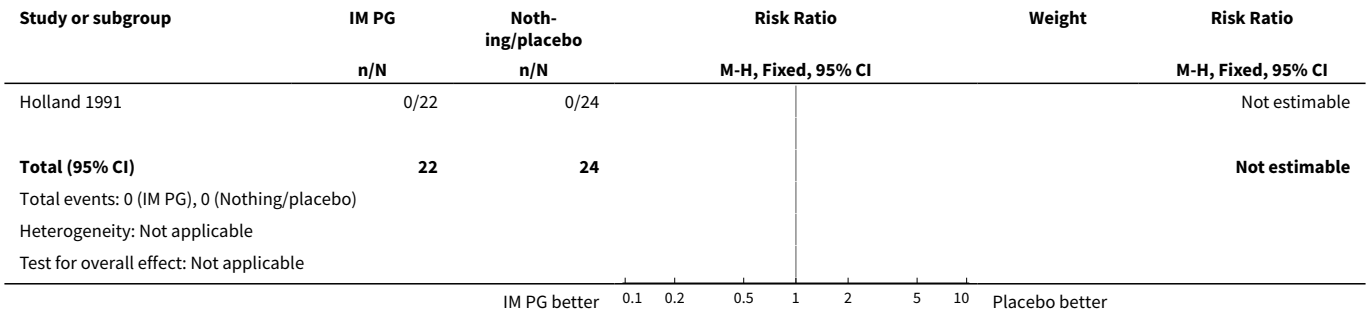
Analysis 12.3. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 3 Blood loss (mL).



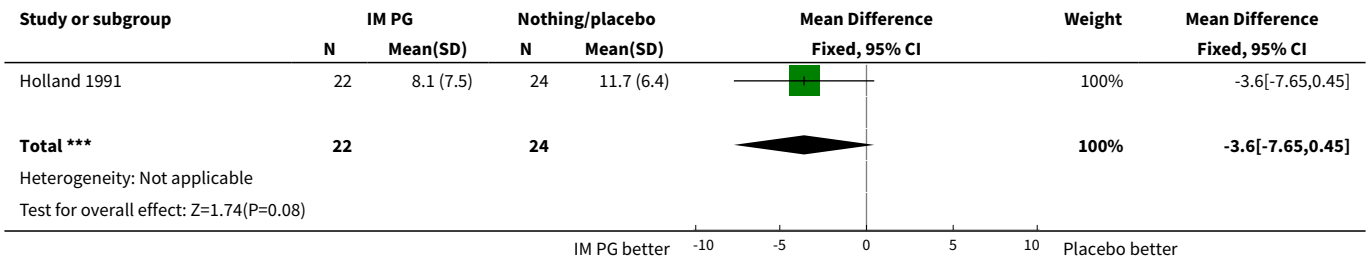
Analysis 12.4. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 4 Use of additional uterotonics.



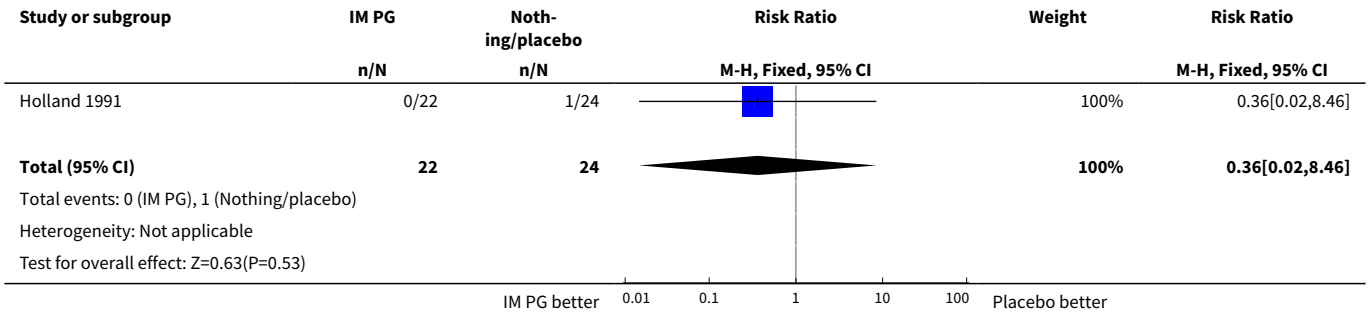
Analysis 12.5. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 5 Manual removal of placenta.



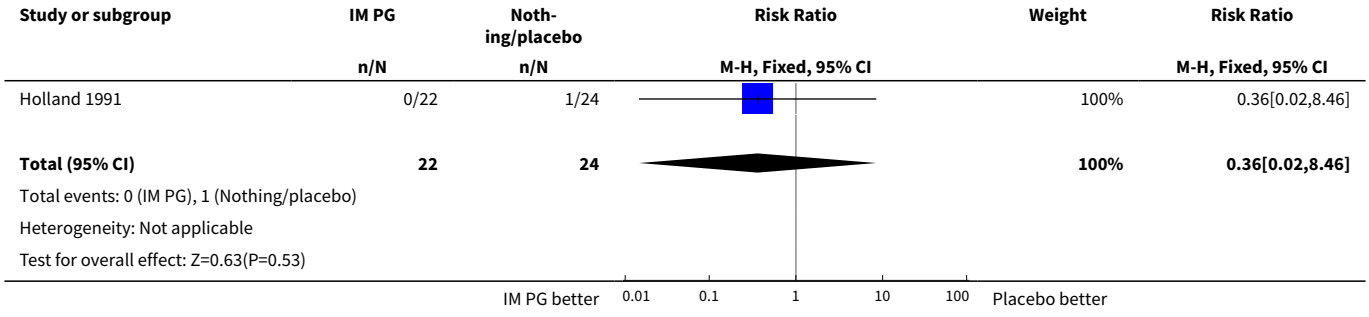
Analysis 12.6. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 6 Duration of third stage (minutes).



Analysis 12.7. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 7 Any side-effect.



Analysis 12.8. Comparison 12 Intramuscular prostaglandin versus no uterotonic/placebo, Outcome 8 Nausea.



Comparison 13. Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy)

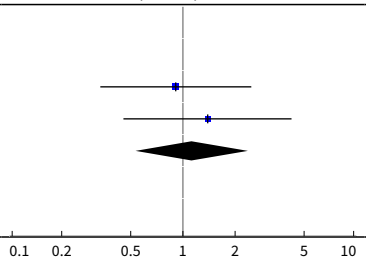
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Postpartum haemorrhage (>= 500 mL)	5	564	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.61]

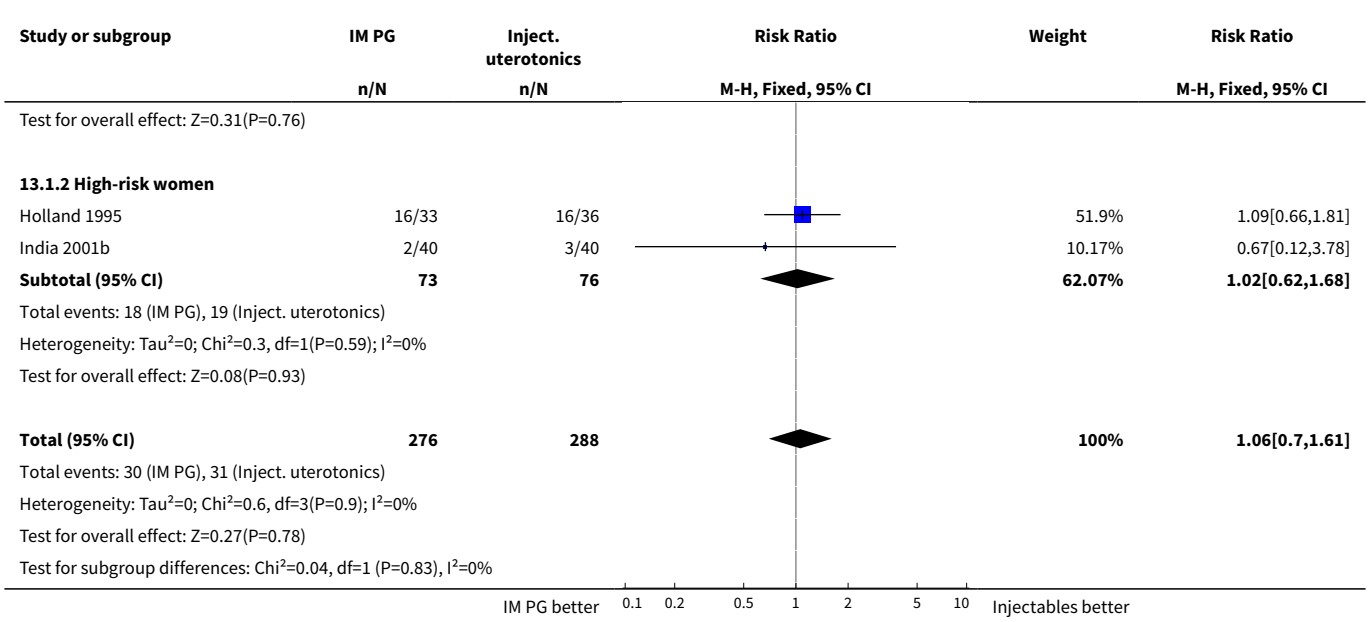
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Low-risk women	3	415	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.53, 2.37]
1.2 High-risk women	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.68]
2 Severe postpartum haemorrhage (>= 1000 mL)	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.14, 1.20]
2.1 Low-risk women	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.06, 6.57]
2.2 High-risk women	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.11, 1.23]
3 Blood loss (mL)	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Low-risk women	6		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 High-risk women	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Use of additional uterotonics	4	422	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.28, 3.68]
4.1 Low-risk women	4	422	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.28, 3.68]
4.2 High-risk women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Blood transfusion	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.39, 2.86]
5.1 Low-risk women	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.40, 10.11]
5.2 High-risk women	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.17, 2.53]
6 Manual removal of placenta	5	631	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.31, 3.81]
6.1 Low-risk women	4	562	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [0.13, 77.34]
6.2 High-risk women	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.20, 3.39]
7 Duration of third stage (minutes)	7		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Low-risk women	5		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 High-risk women	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Postpartum haemoglobin	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.27, 0.27]
8.1 Low-risk women	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.27, 0.27]
8.2 High-risk women	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Any side-effect	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 Low-risk women	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 High-risk women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Nausea	3	280	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.36, 16.09]
10.1 Low-risk women	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.55]
10.2 High-risk women	1	80	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 100.97]
11 Vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Low-risk women	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 High-risk women	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Headache	2	295	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.28, 3.57]
12.1 Low-risk women	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.08]
12.2 High-risk women	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.39, 10.31]
13 Abdominal pain	3	331	Risk Ratio (M-H, Fixed, 95% CI)	4.99 [1.46, 17.05]
13.1 Low-risk women	2	262	Risk Ratio (M-H, Fixed, 95% CI)	5.33 [1.40, 20.30]
13.2 High-risk women	1	69	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [0.14, 77.46]
14 Diarrhoea	5	617	Risk Ratio (M-H, Fixed, 95% CI)	12.28 [4.47, 33.70]
14.1 Low-risk women	4	537	Risk Ratio (M-H, Fixed, 95% CI)	11.88 [4.03, 35.03]
14.2 High-risk women	1	80	Risk Ratio (M-H, Fixed, 95% CI)	15.0 [0.89, 254.13]
15 Pyrexia (>= 38 degrees C)	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Low-risk women	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 High-risk women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

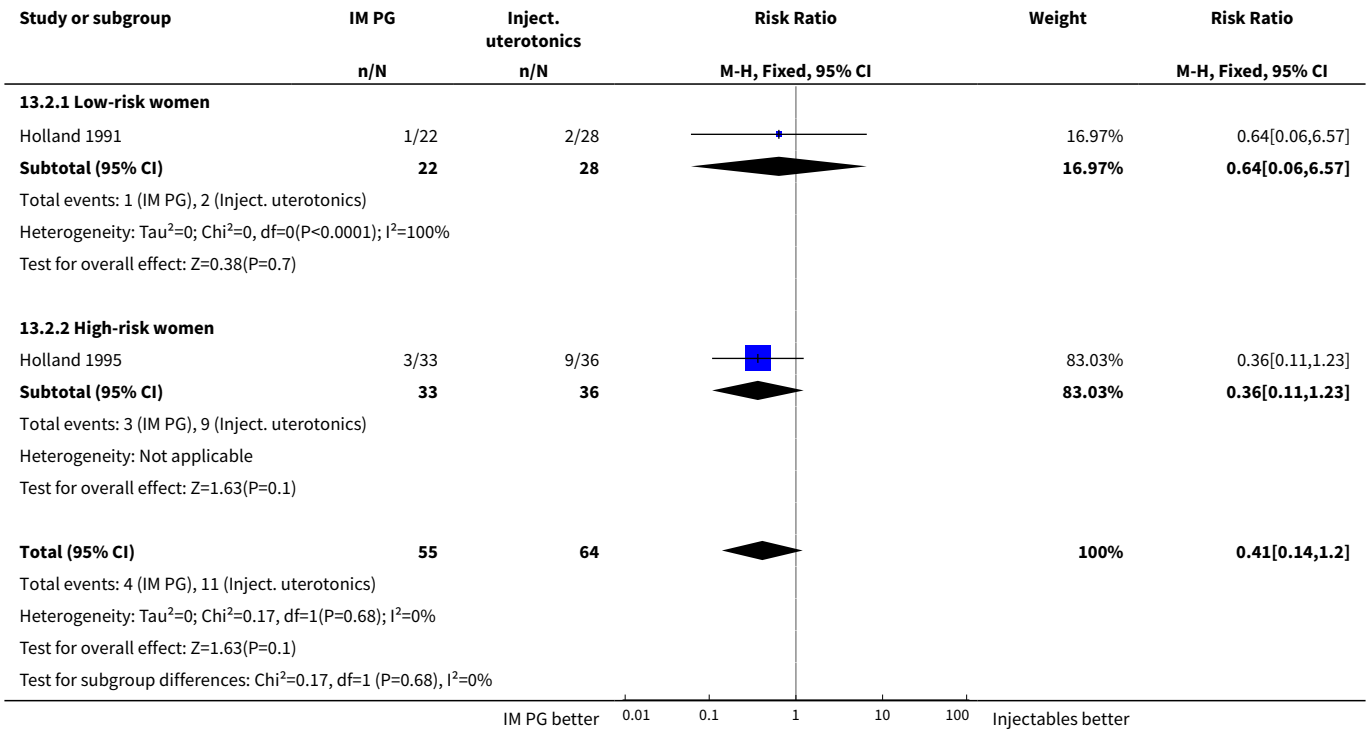
Analysis 13.1. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 1 Postpartum haemorrhage (>= 500 mL).

Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
13.1.1 Low-risk women					
Egypt 1993	0/73	0/77			Not estimable
Holland 1991	5/22	7/28		20.89%	0.91[0.33,2.48]
India 2008b	7/108	5/107		17.04%	1.39[0.45,4.23]
Subtotal (95% CI)	**203**	**212**		**37.93%**	**1.12[0.53,2.37]**
Total events: 12 (IM PG), 12 (Inject. uterotonics)					
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%					



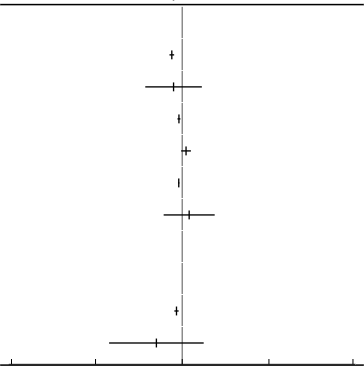


Analysis 13.2. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 2 Severe postpartum haemorrhage (>= 1000 mL).



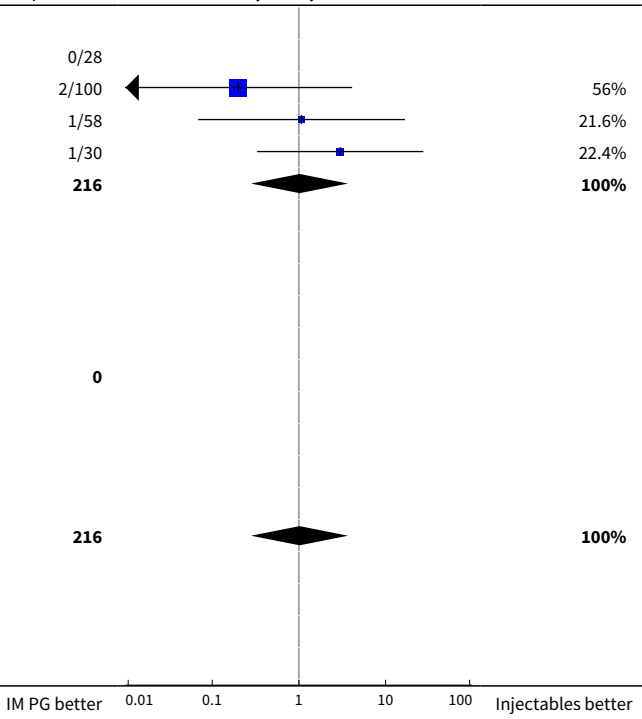
Analysis 13.3. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 3 Blood loss (mL).

Study or subgroup	IM PG		Inject. uterotonics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
13.3.1 Low-risk women						
Egypt 1993	73	85.2 (39.8)	77	145.3 (44.4)		-60.1[-73.58,-46.62]
Holland 1991	22	324 (302)	28	374 (279)		-50[-213.11,113.11]
India 2006g	100	75 (27)	100	94 (33)		-19[-27.36,-10.64]
India 2008b	108	236 (99)	107	214 (110)		22[-5.98,49.98]
India 2010	100	64 (10)	100	84 (14)		-20[-23.37,-16.63]
United Kingdom 1994	30	645 (278)	30	605 (303)		40[-107.15,187.15]
13.3.2 High-risk women						
Egypt 1997	45	93.1 (26.2)	43	126.2 (32.1)		-33.1[-45.37,-20.83]
Holland 1995	33	568 (457)	36	717 (685)		-149[-421.73,123.73]



Analysis 13.4. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 4 Use of additional uterotonics.

Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
13.4.1 Low-risk women					
Holland 1991	0/22	0/28			Not estimable
India 2006g	0/100	2/100		56%	0.2[0.01,4.11]
Singapore 1995	1/54	1/58		21.6%	1.07[0.07,16.75]
United Kingdom 1994	3/30	1/30		22.4%	3[0.33,27.23]
Subtotal (95% CI)	**206**	**216**		**100%**	**1.02[0.28,3.68]**
Total events: 4 (IM PG), 4 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=2.04, df=2(P=0.36); I^2=1.81%					
Test for overall effect: Z=0.02(P=0.98)					
13.4.2 High-risk women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**206**	**216**		**100%**	**1.02[0.28,3.68]**
Total events: 4 (IM PG), 4 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=2.04, df=2(P=0.36); I^2=1.81%					
Test for overall effect: Z=0.02(P=0.98)					
Test for subgroup differences: Not applicable					



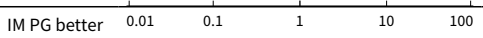
Analysis 13.5. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 5 Blood transfusion.

Study or subgroup	IM PG n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
13.5.1 Low-risk women					
United Kingdom 1994	4/30	2/30		29.49%	2[0.4,10.11]
Subtotal (95% CI)	**30**	**30**		**29.49%**	**2[0.4,10.11]**
Total events: 4 (IM PG), 2 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					
13.5.2 High-risk women					
Holland 1995	3/33	5/36		70.51%	0.65[0.17,2.53]
Subtotal (95% CI)	**33**	**36**		**70.51%**	**0.65[0.17,2.53]**
Total events: 3 (IM PG), 5 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
Total (95% CI)	**63**	**66**		**100%**	**1.05[0.39,2.86]**
Total events: 7 (IM PG), 7 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=1(P=0.3); I^2=7.21%					
Test for overall effect: Z=0.1(P=0.92)					
Test for subgroup differences: Chi^2=1.08, df=1 (P=0.3), I^2=7.14%					

Analysis 13.6. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 6 Manual removal of placenta.

Study or subgroup	IM PG n/N	Inject. uterotonics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
13.6.1 Low-risk women					
Holland 1991	0/22	0/28			Not estimable
India 2006g	0/100	0/100			Not estimable
India 2010	0/100	0/100			Not estimable
Singapore 1995	1/54	0/58		11.2%	3.22[0.13,77.34]
Subtotal (95% CI)	**276**	**286**		**11.2%**	**3.22[0.13,77.34]**
Total events: 1 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					
13.6.2 High-risk women					
Holland 1995	3/33	4/36		88.8%	0.82[0.2,3.39]
Subtotal (95% CI)	**33**	**36**		**88.8%**	**0.82[0.2,3.39]**
Total events: 3 (IM PG), 4 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
Total (95% CI)	**309**	**322**		**100%**	**1.09[0.31,3.81]**
Total events: 4 (IM PG), 4 (Inject. uterotonics)					

Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.6, df=1(P=0.44); I²=0%					
Test for overall effect: Z=0.13(P=0.9)					
Test for subgroup differences: Chi²=0.59, df=1 (P=0.44), I²=0%					

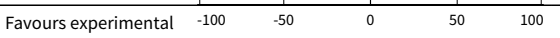


Analysis 13.7. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 7 Duration of third stage (minutes).

Study or subgroup	IM PG		Inject. uterotonics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
13.7.1 Low-risk women						
Egypt 1993	73	2.3 (0.8)	77	3.4 (1.2)		-1.1[-1.42,-0.78]
Holland 1991	22	8.1 (7.5)	28	9.9 (7.4)		-1.8[-5.96,2.36]
India 2006g	100	4 (1)	100	5 (2)		-1[-1.44,-0.56]
India 2008b	108	4 (2)	107	4 (1)		0[-0.42,0.42]
India 2010	100	4 (1)	100	6 (1)		-2[-2.28,-1.72]
13.7.2 High-risk women						
Egypt 1997	45	2.2 (0.7)	43	3.5 (1.5)		-1.3[-1.8,-0.8]
Holland 1995	33	18.2 (32.9)	36	14 (18.9)		4.2[-8.61,17.01]

Analysis 13.8. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 8 Postpartum haemoglobin.

Study or subgroup	IM PG		Inject. uterotonics		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
13.8.1 Low-risk women							
India 2008b	108	11 (1)	107	11 (1)		100%	0[-0.27,0.27]
Subtotal ***	**108**		**107**			**100%**	**0[-0.27,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.8.2 High-risk women							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**108**		**107**			**100%**	**0[-0.27,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Analysis 13.9. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 9 Any side-effect.

Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
13.9.1 Low-risk women					
Holland 1991	0/22	0/28			Not estimable
Subtotal (95% CI)	**22**	**28**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
13.9.2 High-risk women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**22**	**28**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

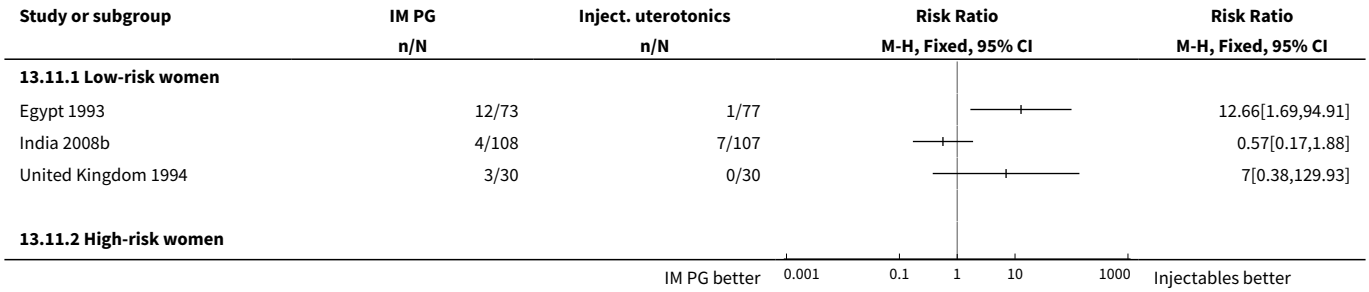
IM PG better — Injectables better

Analysis 13.10. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 10 Nausea.

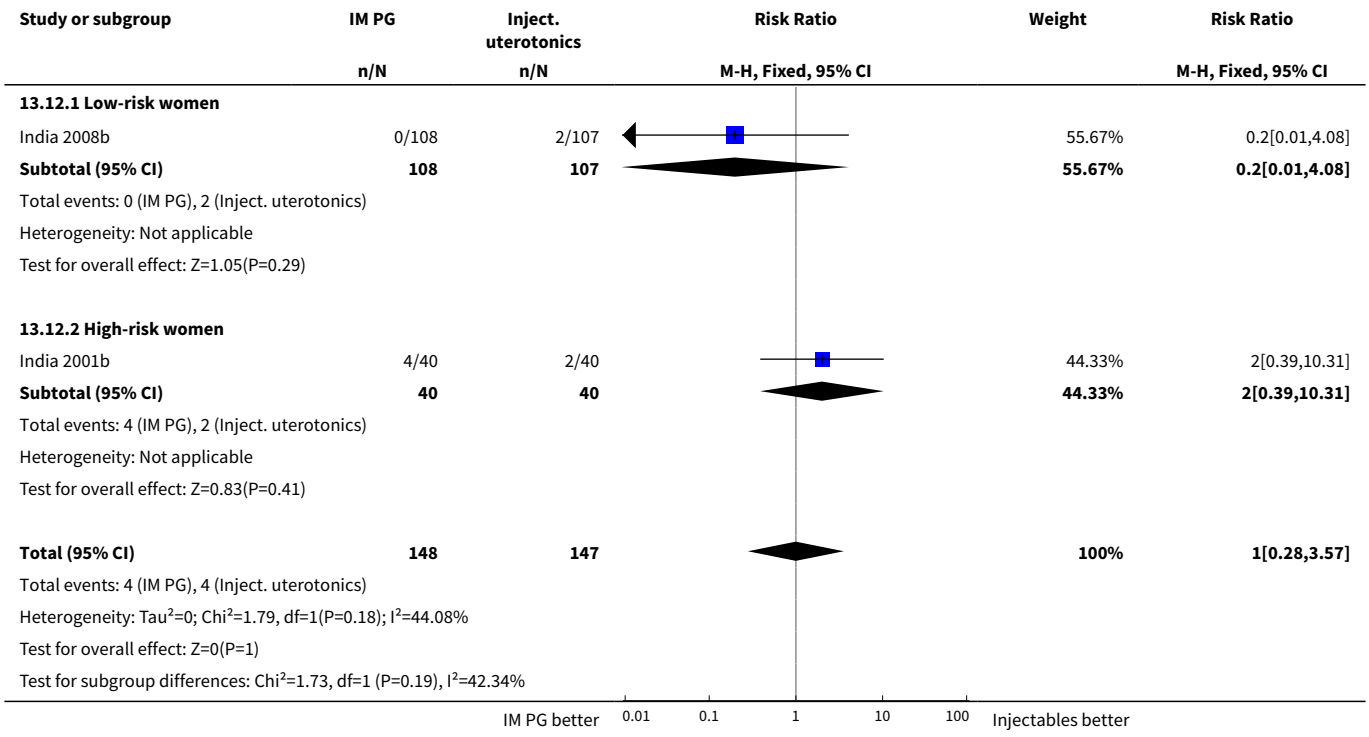
Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
13.10.1 Low-risk women					
Egypt 1993	1/73	1/77		66.06%	1.05[0.07,16.55]
Holland 1991	0/22	0/28			Not estimable
Subtotal (95% CI)	**95**	**105**		**66.06%**	**1.05[0.07,16.55]**
Total events: 1 (IM PG), 1 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
13.10.2 High-risk women					
India 2001b	2/40	0/40		33.94%	5[0.25,100.97]
Subtotal (95% CI)	**40**	**40**		**33.94%**	**5[0.25,100.97]**
Total events: 2 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
Total (95% CI)	**135**	**145**		**100%**	**2.39[0.36,16.09]**
Total events: 3 (IM PG), 1 (Inject. uterotonics)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Chi^2=0.56, df=1 (P=0.45), I^2=0%					

IM PG better — Injectables better

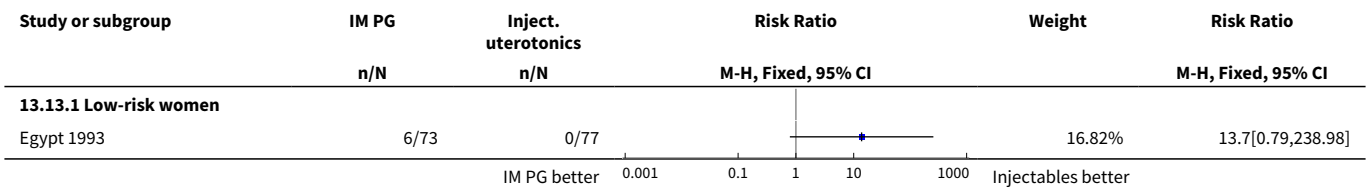
Analysis 13.11. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 11 Vomiting.

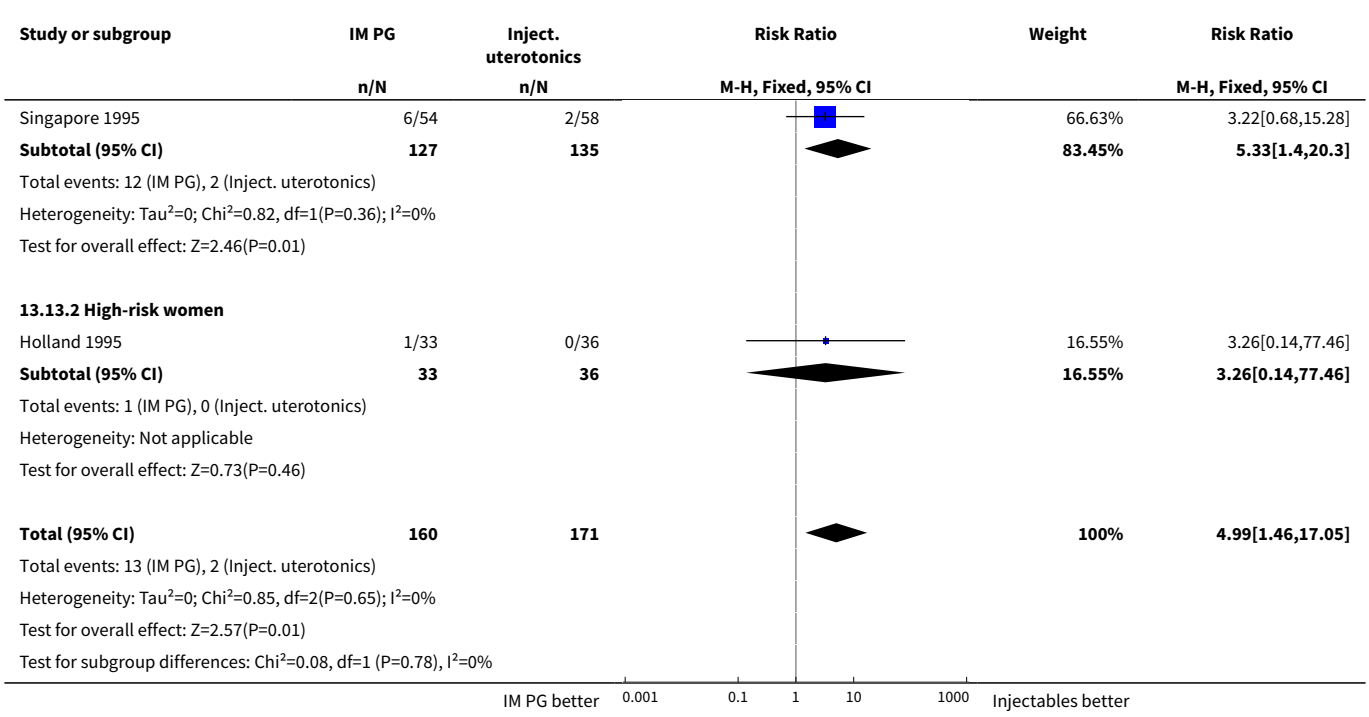


Analysis 13.12. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 12 Headache.

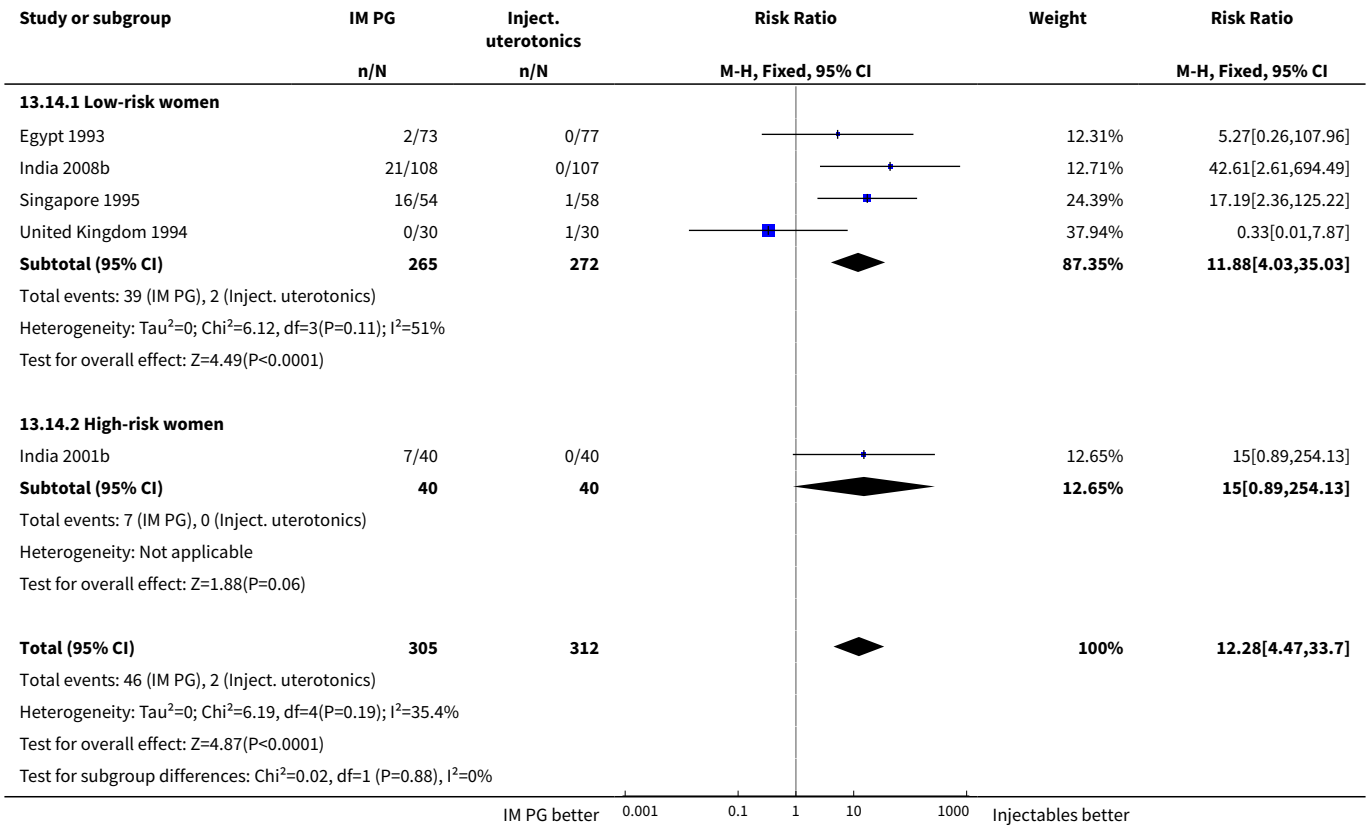


Analysis 13.13. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 13 Abdominal pain.



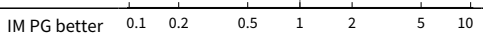


Analysis 13.14. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 14 Diarrhoea.



Analysis 13.15. Comparison 13 Intramuscular prostaglandin versus injectable uterotonics (subgroups by low- and high-risk pregnancy), Outcome 15 Pyrexia (>= 38 degrees C).

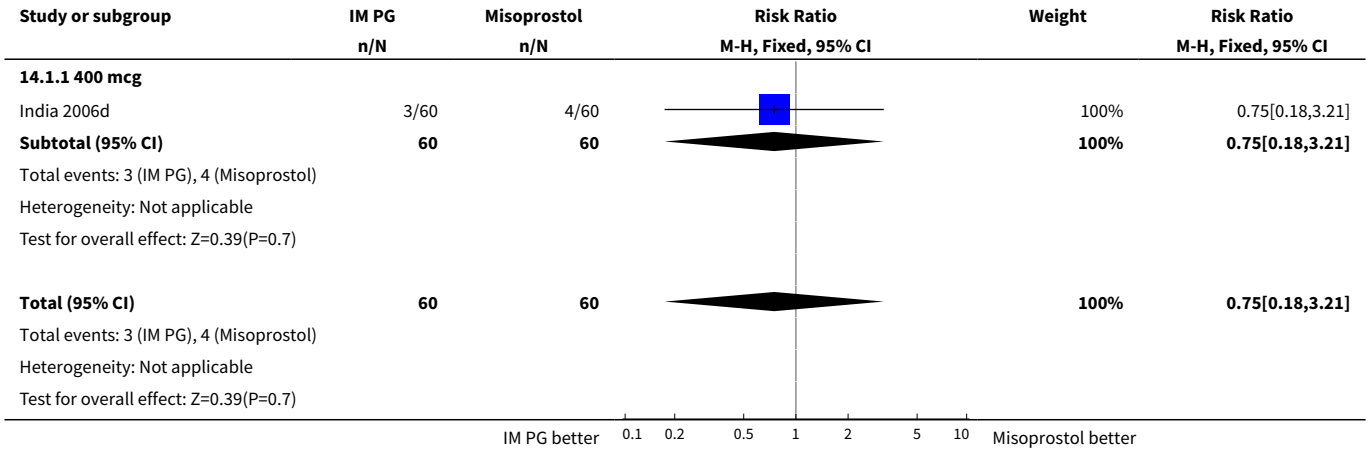
Study or subgroup	IM PG	Inject. uterotonics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
13.15.1 Low-risk women					
Singapore 1995	0/54	0/58			Not estimable
Subtotal (95% CI)	**54**	**58**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
13.15.2 High-risk women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**54**	**58**			**Not estimable**
Total events: 0 (IM PG), 0 (Inject. uterotonics)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



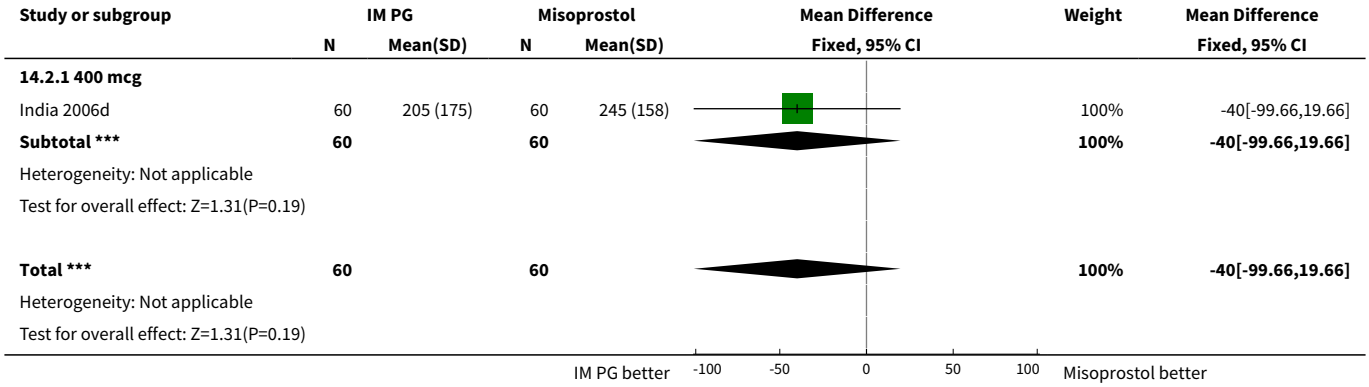
Comparison 14. Intramuscular prostaglandin versus rectal misoprostol

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Postpartum haemorrhage (>= 500 mL)	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.21]
1.1 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.21]
2 Blood loss (mL)	1	120	Mean Difference (IV, Fixed, 95% CI)	-40.0 [-99.66, 19.66]
2.1 400 mcg	1	120	Mean Difference (IV, Fixed, 95% CI)	-40.0 [-99.66, 19.66]
3 Use of additional uterotonics	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.87]
3.1 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.87]
4 Blood transfusion	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
4.1 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
5 Any shivering	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.61]
5.1 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.61]

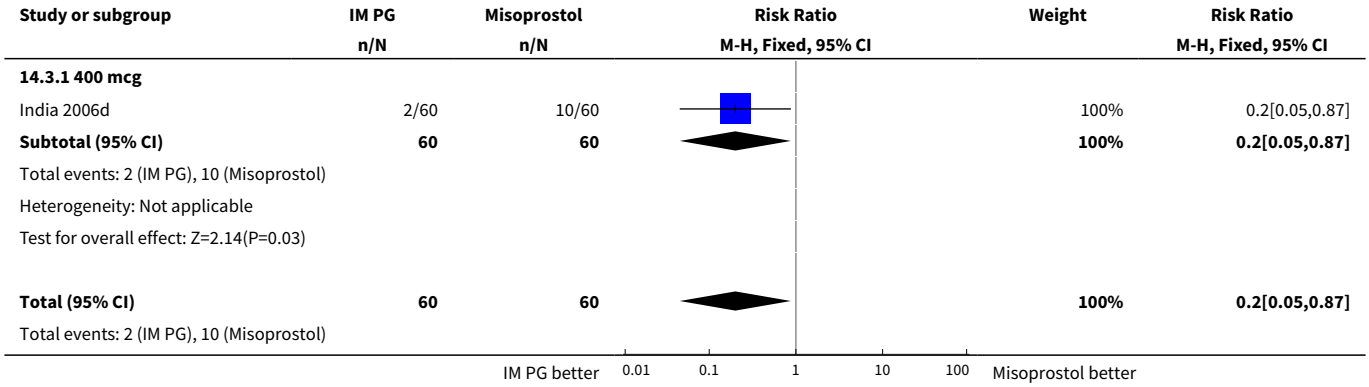
Analysis 14.1. Comparison 14 Intramuscular prostaglandin versus rectal misoprostol, Outcome 1 Postpartum haemorrhage (>= 500 mL).

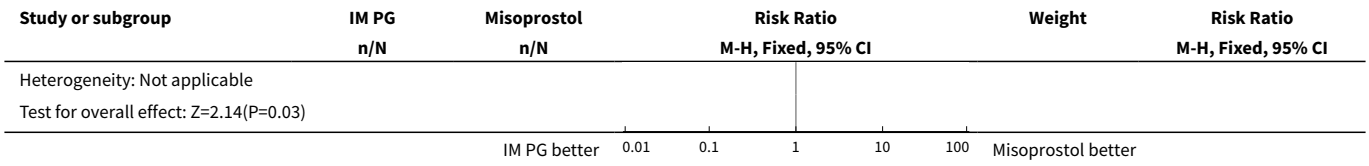


Analysis 14.2. Comparison 14 Intramuscular prostaglandin versus rectal misoprostol, Outcome 2 Blood loss (mL).

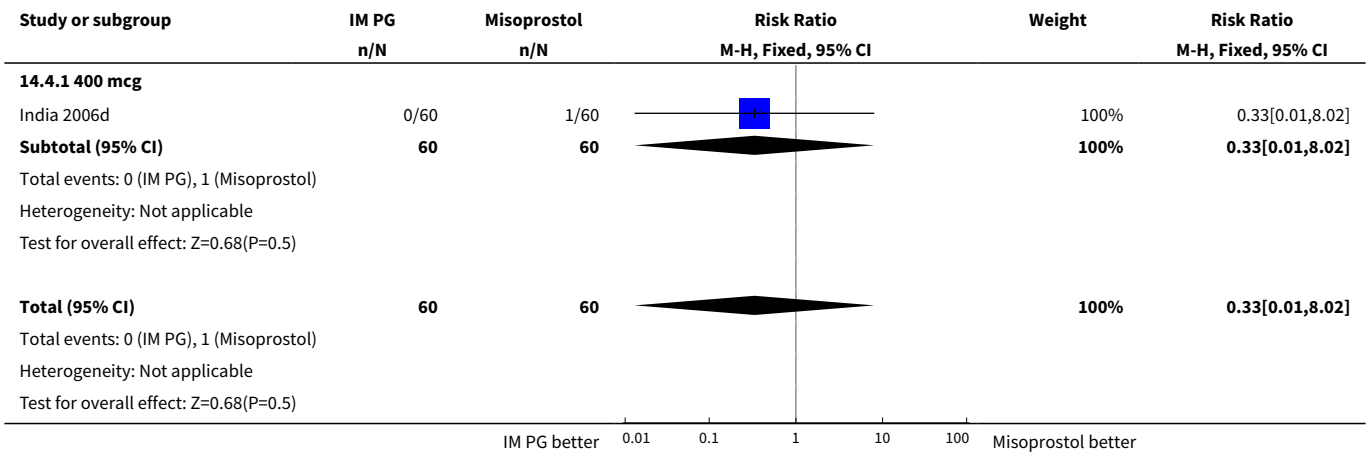


Analysis 14.3. Comparison 14 Intramuscular prostaglandin versus rectal misoprostol, Outcome 3 Use of additional uterotonics.

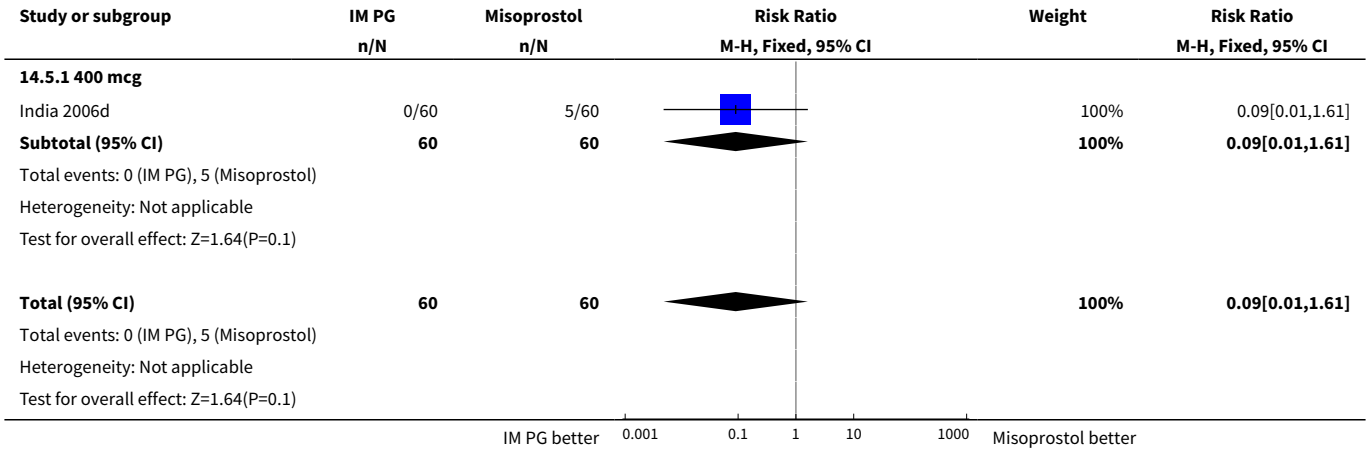




Analysis 14.4. Comparison 14 Intramuscular prostaglandin versus rectal misoprostol, Outcome 4 Blood transfusion.



Analysis 14.5. Comparison 14 Intramuscular prostaglandin versus rectal misoprostol, Outcome 5 Any shivering.

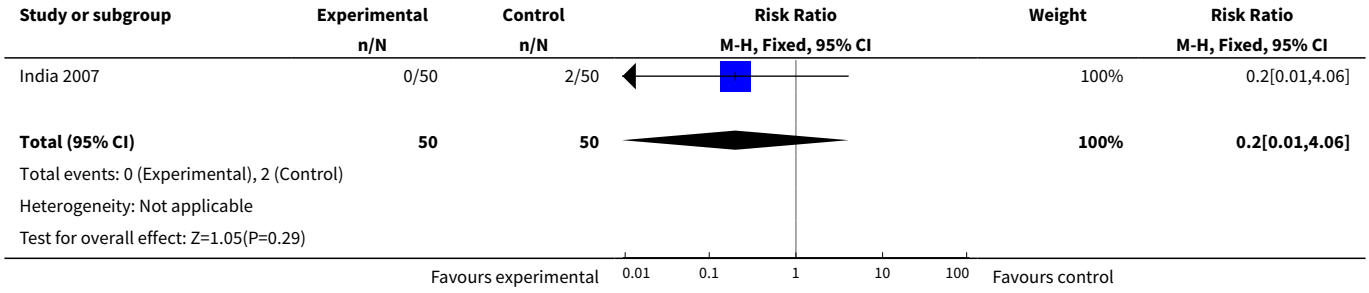


Comparison 15. Intramuscular uterotonics versus another intramuscular uterotonic

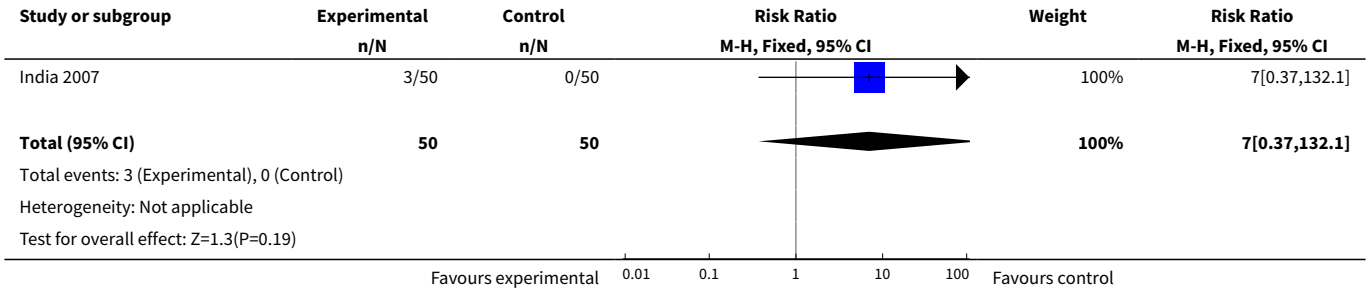
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum haemorrhage (>500 mL)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Nausea	1	100	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 132.10]
3 Vomiting	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.34]
4 Diarrhoea	1	100	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 101.58]
5 High blood pressure	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.60]
6 Pyrexia (>= 38 C)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]

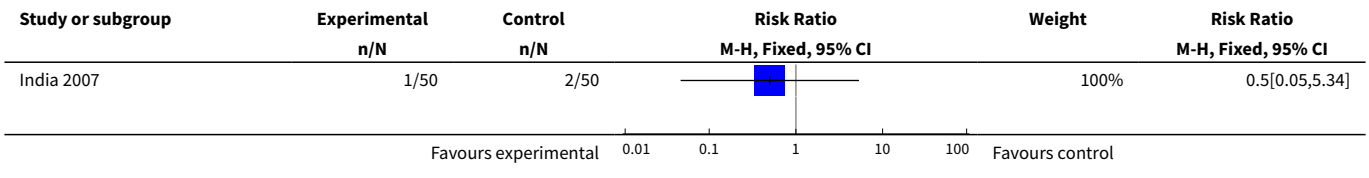
Analysis 15.1. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 1 Postpartum haemorrhage (>500 mL).

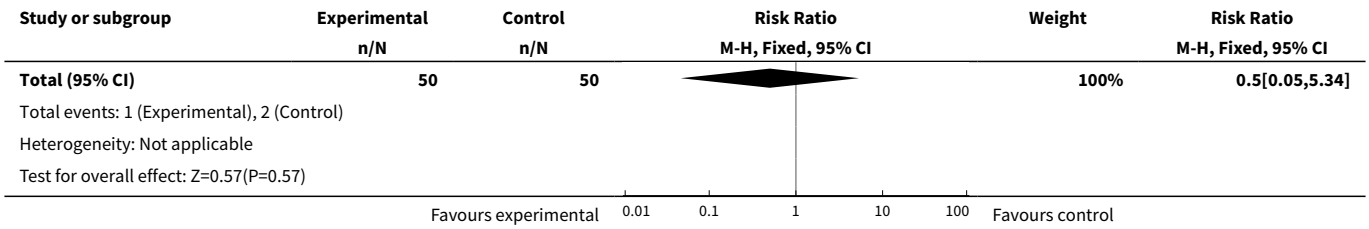


Analysis 15.2. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 2 Nausea.

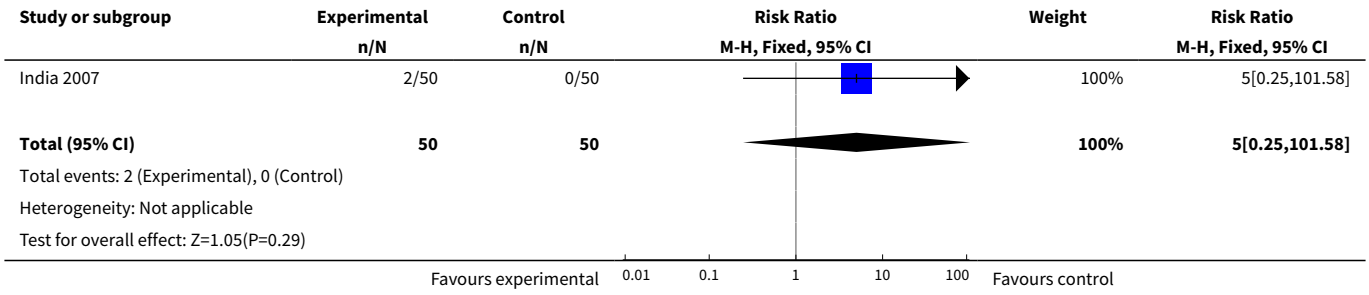


Analysis 15.3. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 3 Vomiting.

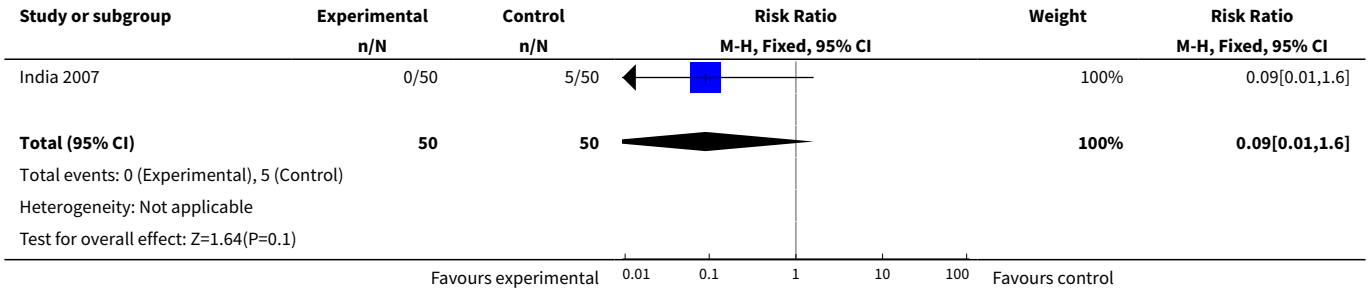




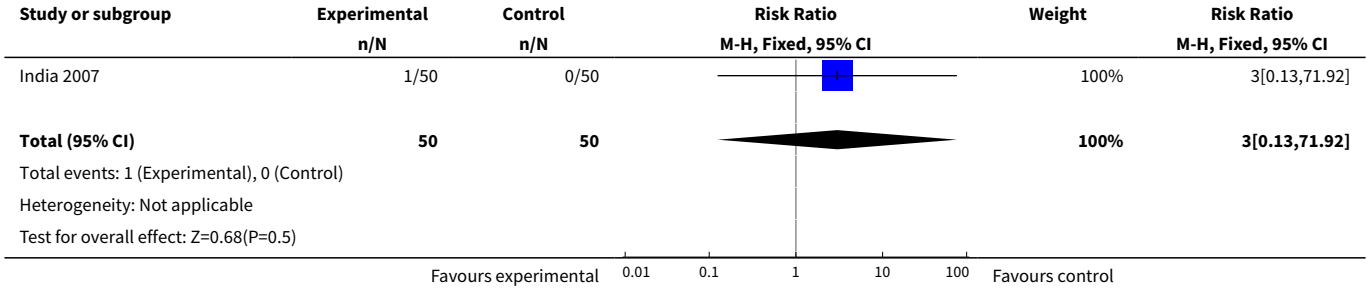
Analysis 15.4. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 4 Diarrhoea.



Analysis 15.5. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 5 High blood pressure.



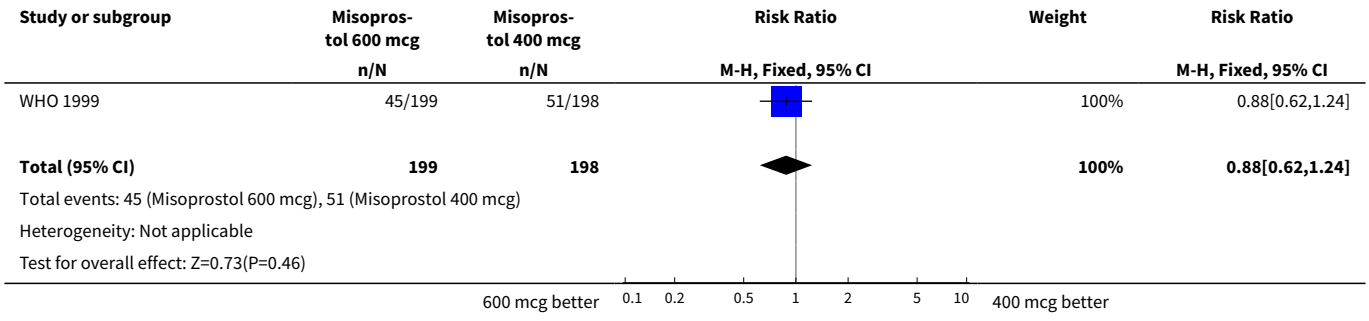
Analysis 15.6. Comparison 15 Intramuscular uterotonics versus another intramuscular uterotonic, Outcome 6 Pyrexia (>= 38 C).



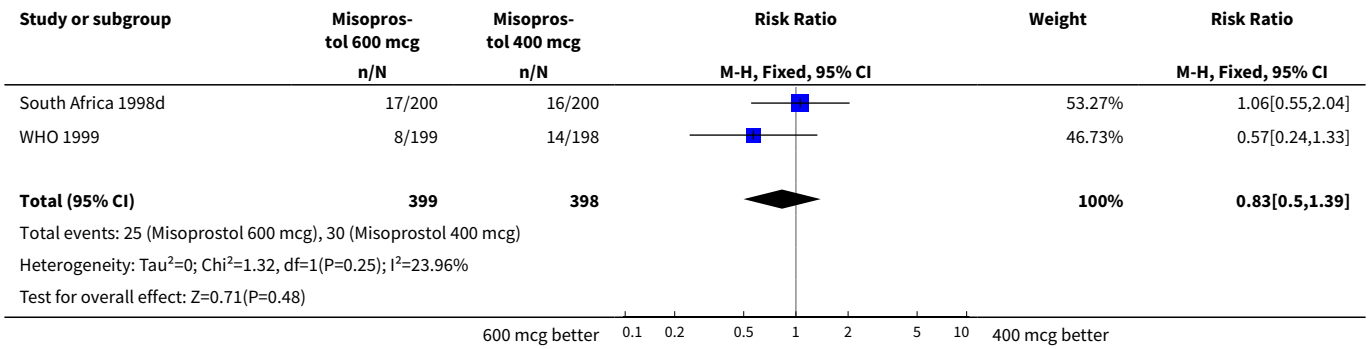
Comparison 16. Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum haemorrhage (>= 500 mL)	1	397	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.62, 1.24]
2 Severe postpartum haemorrhage (>= 1000 mL)	2	797	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.39]
3 Blood loss (mL)	2	547	Mean Difference (IV, Fixed, 95% CI)	-30.00 [-41.84, -18.16]
4 Use of additional uterotonics	3	947	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.35]
5 Blood transfusion	2	797	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Manual removal of placenta	2	797	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.35, 4.20]
7 Duration of third stage (minutes)	2	547	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.36, 0.27]
8 Third stage >= 30 minutes	1	400	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.31, 28.60]
9 Nausea	2	792	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.22, 12.48]
10 Vomiting	2	792	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.88]
11 Headache	1	398	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.25, 8.88]
12 Abdominal pain	1	398	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.63, 3.59]
13 Diarrhoea	1	397	Risk Ratio (M-H, Fixed, 95% CI)	8.96 [0.49, 165.23]
14 Shivering	3	945	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.12, 1.69]
15 Pyrexia (>= 38 degrees C)	3	944	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.45, 2.88]

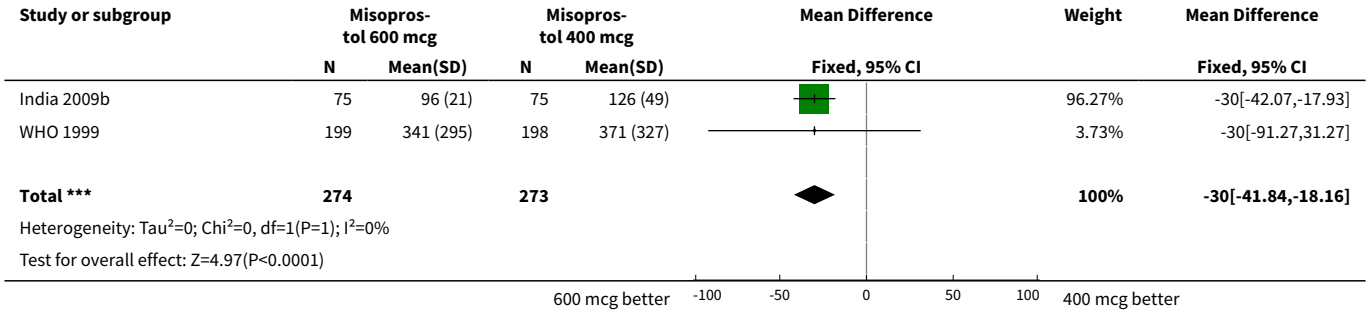
Analysis 16.1. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 1 Postpartum haemorrhage (>= 500 mL).



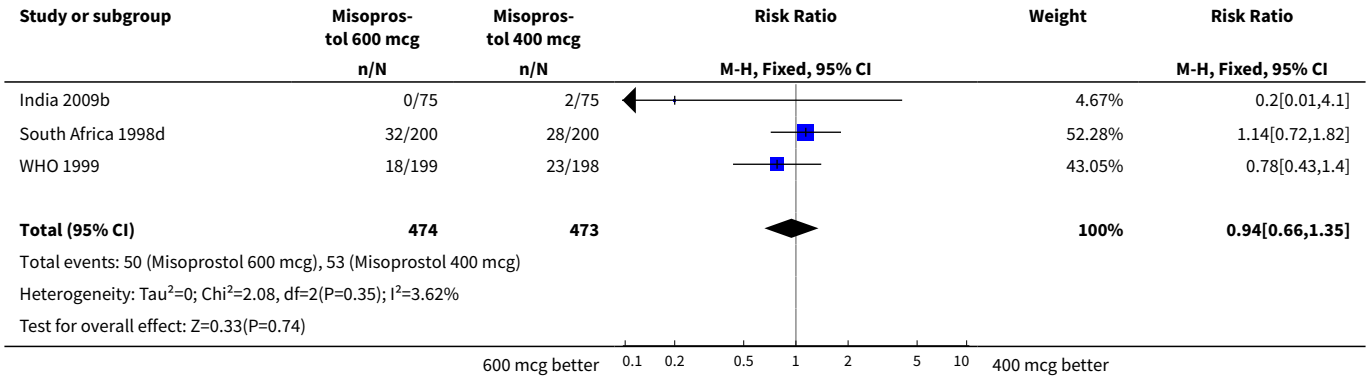
Analysis 16.2. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 2 Severe postpartum haemorrhage (>= 1000 mL).



Analysis 16.3. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 3 Blood loss (mL).

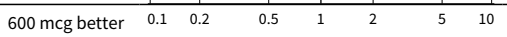


Analysis 16.4. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 4 Use of additional uterotonics.



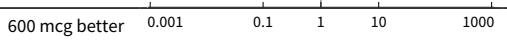
Analysis 16.5. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 5 Blood transfusion.

Study or subgroup	Misoprostol 600 mcg n/N	Misoprostol 400 mcg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
South Africa 1998d	0/200	0/200			Not estimable
WHO 1999	0/199	0/198			Not estimable
Total (95% CI)	**399**	**398**			**Not estimable**
Total events: 0 (Misoprostol 600 mcg), 0 (Misoprostol 400 mcg)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



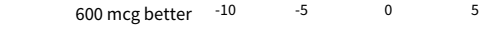
Analysis 16.6. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 6 Manual removal of placenta.

Study or subgroup	Misoprostol 600 mcg n/N	Misoprostol 400 mcg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
South Africa 1998d	2/200	0/200		11.09%	5[0.24,103.49]
WHO 1999	3/199	4/198		88.91%	0.75[0.17,3.29]
Total (95% CI)	**399**	**398**		**100%**	**1.22[0.35,4.2]**
Total events: 5 (Misoprostol 600 mcg), 4 (Misoprostol 400 mcg)					
Heterogeneity: Tau^2=0; Chi^2=1.25, df=1(P=0.26); I^2=20.2%					
Test for overall effect: Z=0.31(P=0.75)					

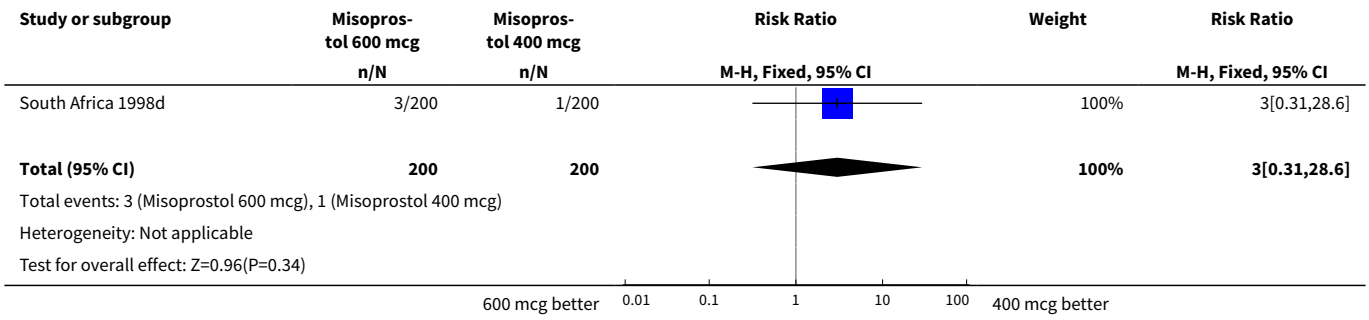


Analysis 16.7. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 7 Duration of third stage (minutes).

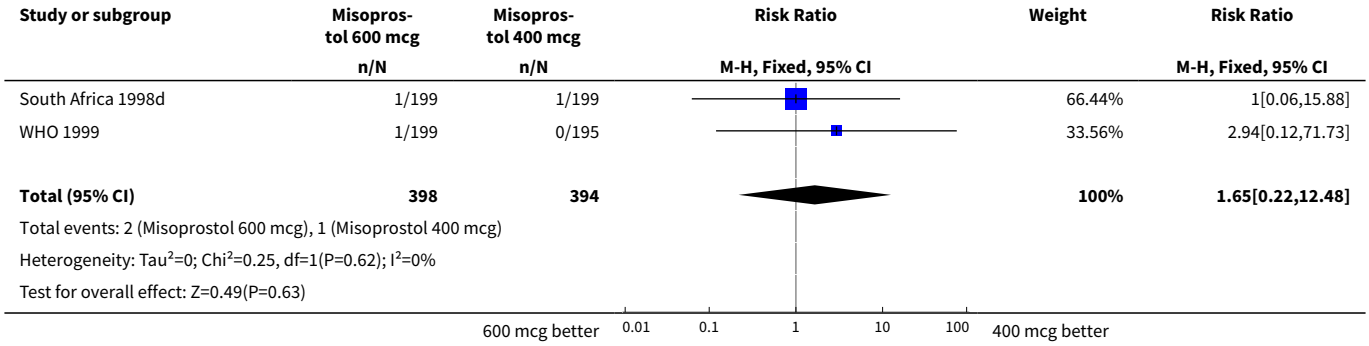
Study or subgroup	Misoprostol 600 mcg N	Misoprostol 600 mcg Mean(SD)	Misoprostol 400 mcg N	Misoprostol 400 mcg Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
India 2009b	75	6 (1)	75	6 (1)		97.97%	0[-0.32,0.32]
WHO 1999	199	6.4 (6.6)	198	8.6 (14.5)		2.03%	-2.2[-4.42,0.02]
Total ***	**274**		**273**			**100%**	**-0.04[-0.36,0.27]**
Heterogeneity: Tau^2=0; Chi^2=3.69, df=1(P=0.05); I^2=72.87%							
Test for overall effect: Z=0.28(P=0.78)							



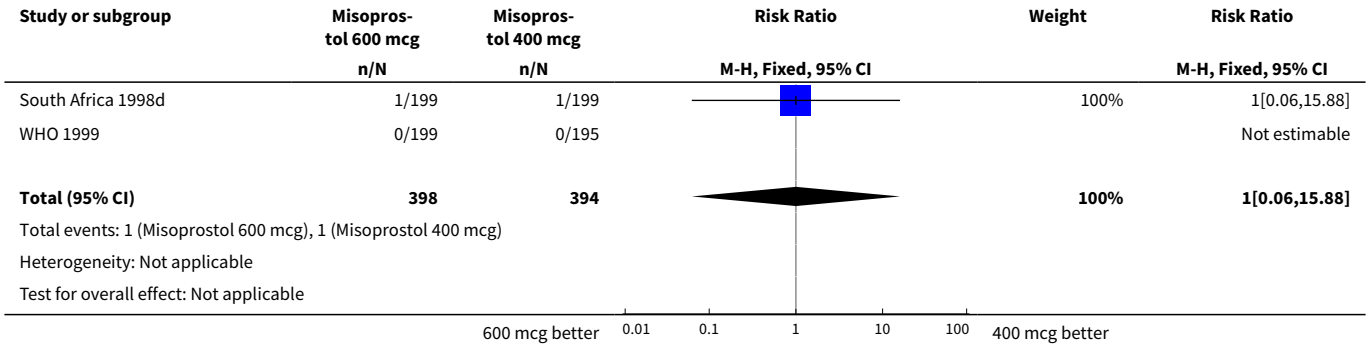
Analysis 16.8. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 8 Third stage >= 30 minutes.



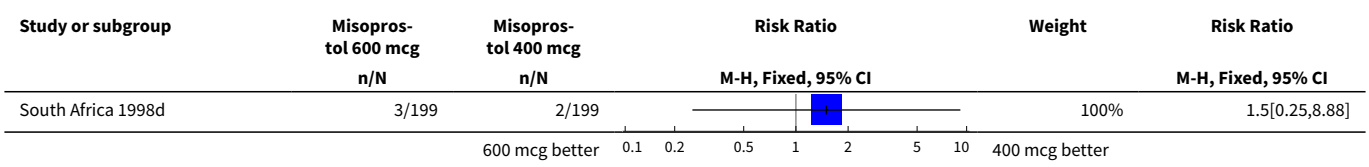
Analysis 16.9. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 9 Nausea.

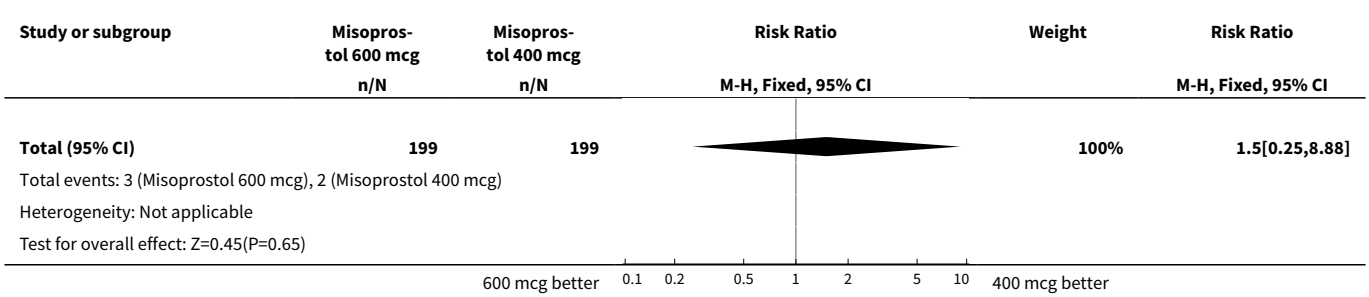


Analysis 16.10. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 10 Vomiting.

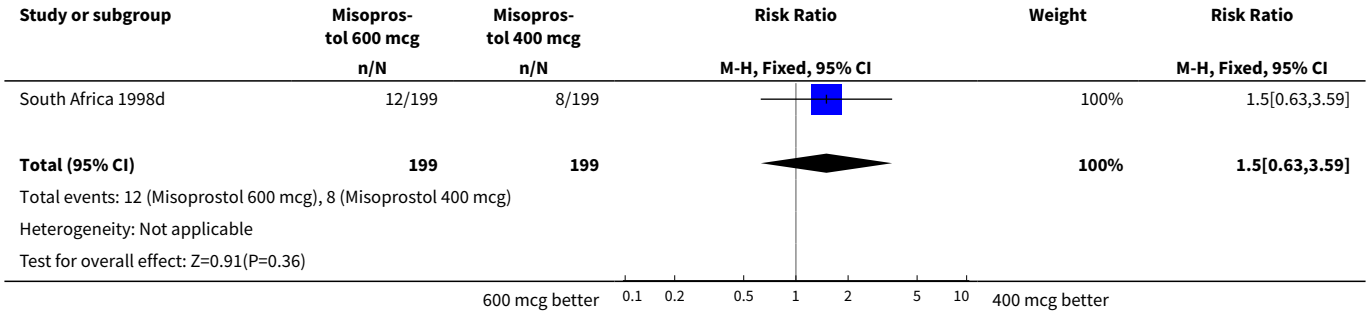


Analysis 16.11. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 11 Headache.

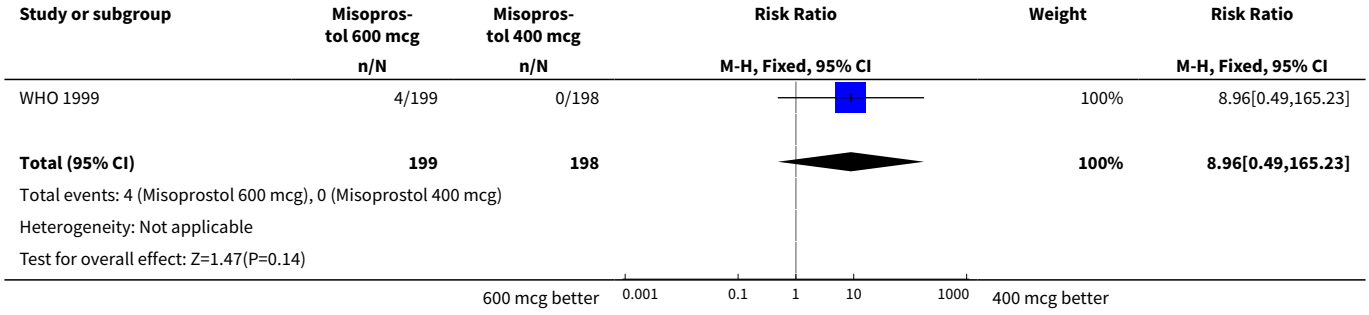




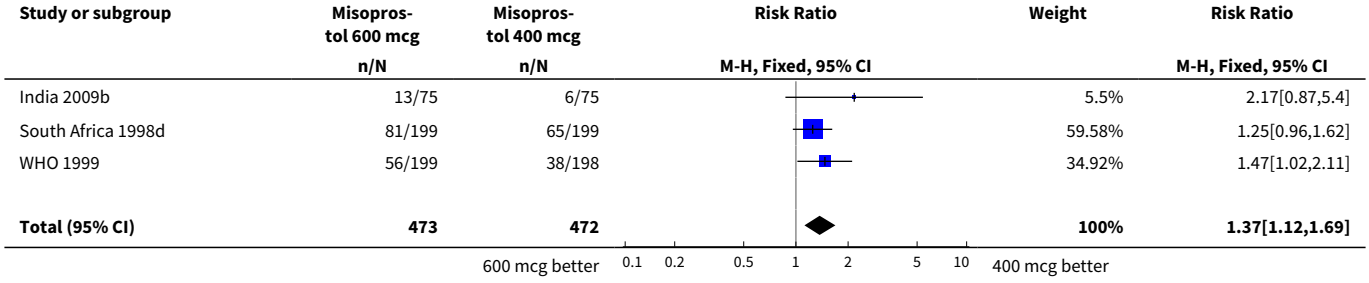
Analysis 16.12. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 12 Abdominal pain.

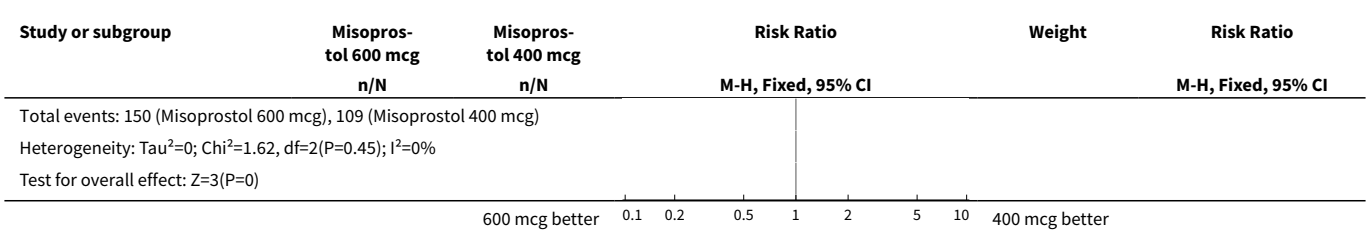


Analysis 16.13. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 13 Diarrhoea.

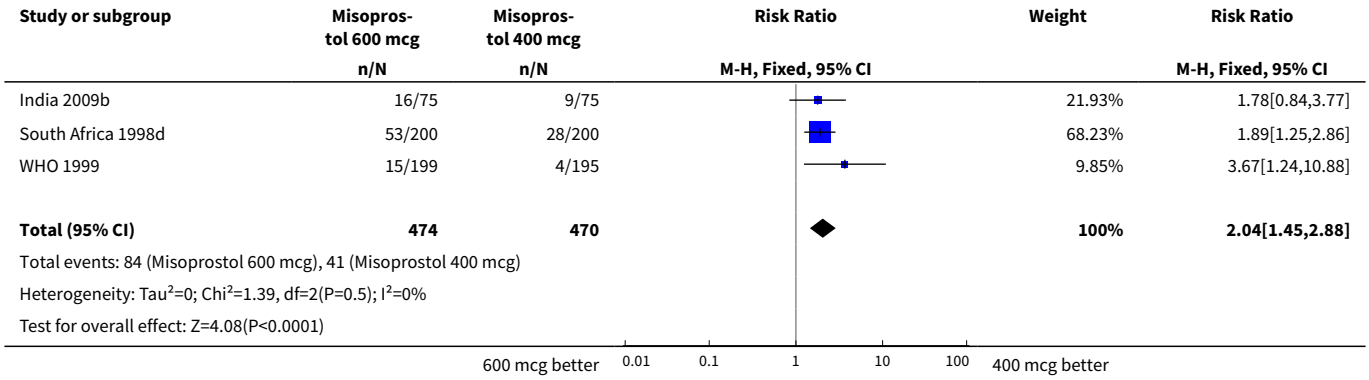


Analysis 16.14. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 14 Shivering.





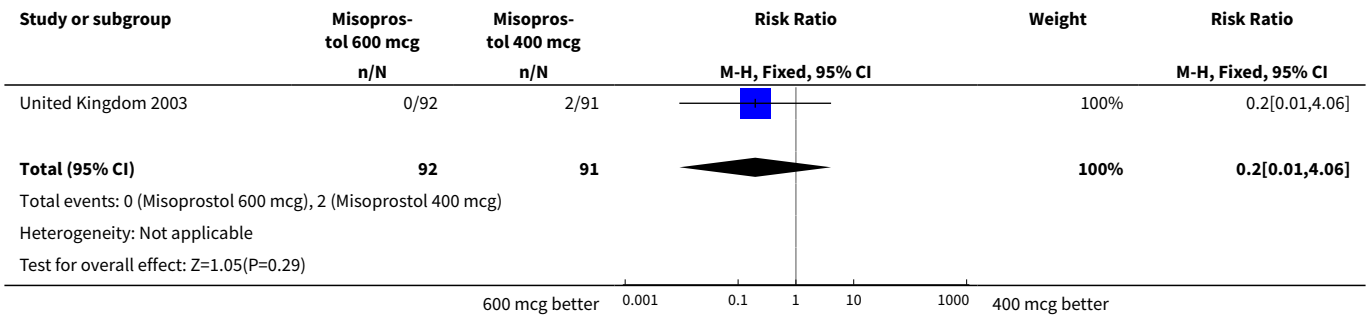
Analysis 16.15. Comparison 16 Drug/dose: misoprostol 600 mcg oral versus 400 mcg oral, Outcome 15 Pyrexia (>= 38 degrees C).



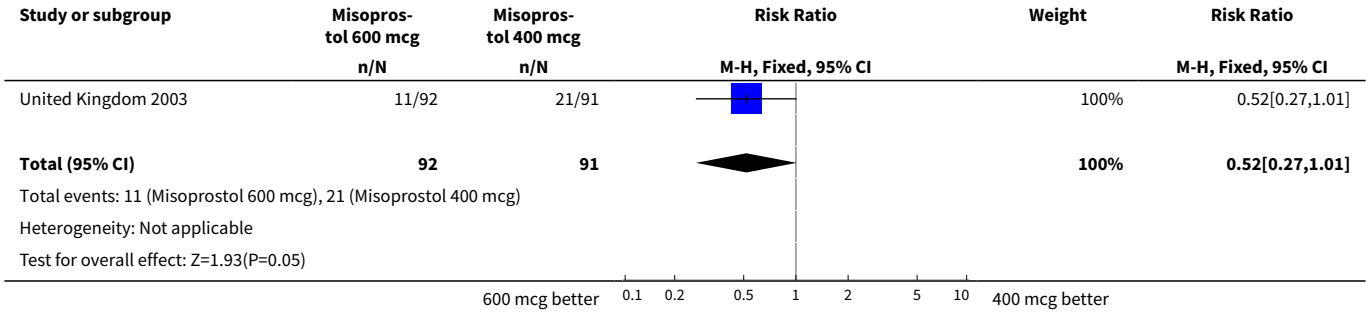
Comparison 17. Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Manual removal of placenta	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.06]
2 Nausea	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.27, 1.01]
3 Vomiting	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.33, 1.91]
4 Headache	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.29, 1.39]
5 Abdominal pain	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.12]
6 Diarrhoea	1	183	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 71.91]
7 Any shivering	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.56]
8 Severe shivering	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.45]
9 Pyrexia	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]

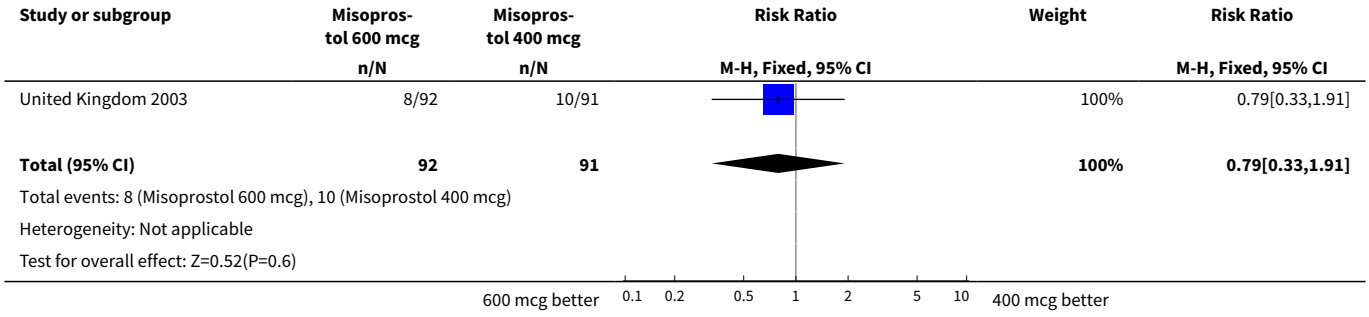
Analysis 17.1. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 1 Manual removal of placenta.



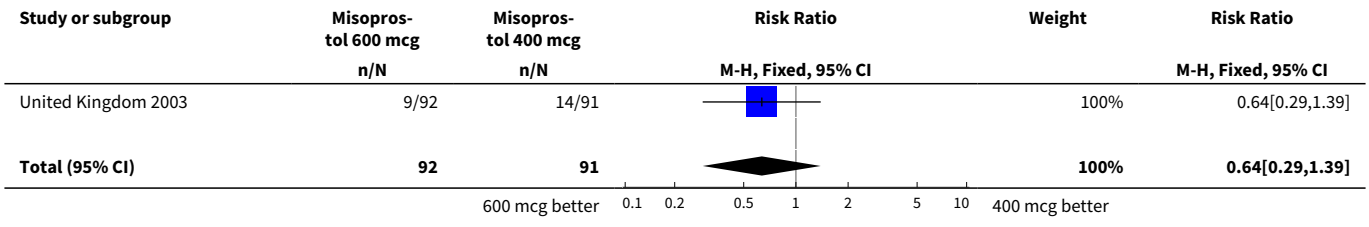
Analysis 17.2. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 2 Nausea.

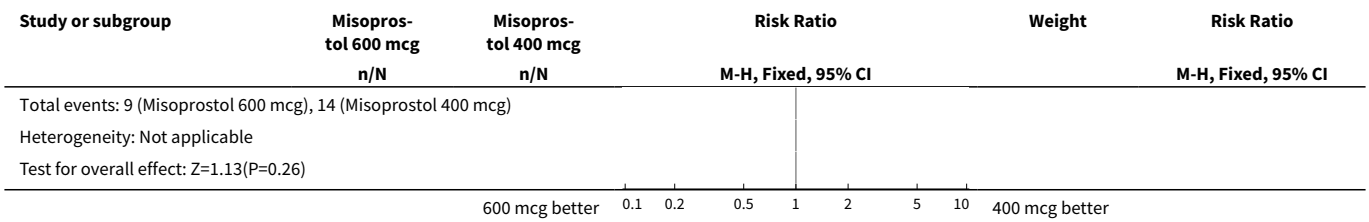


Analysis 17.3. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 3 Vomiting.

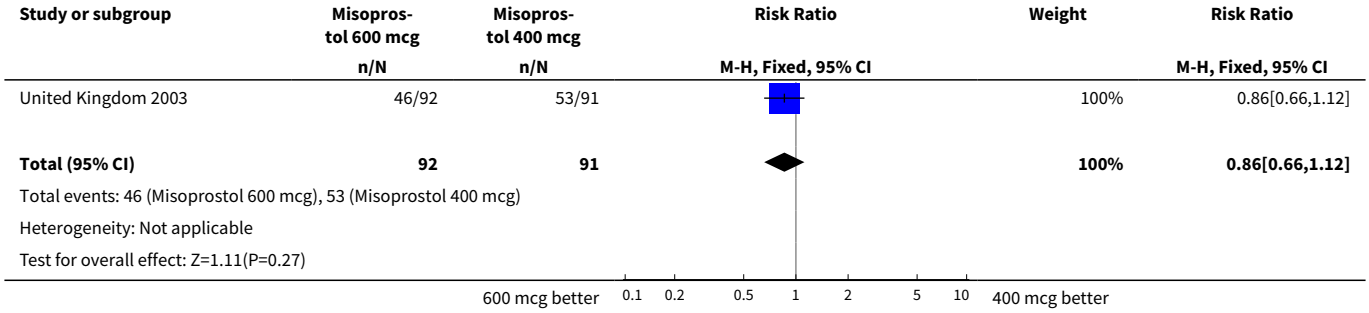


Analysis 17.4. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 4 Headache.

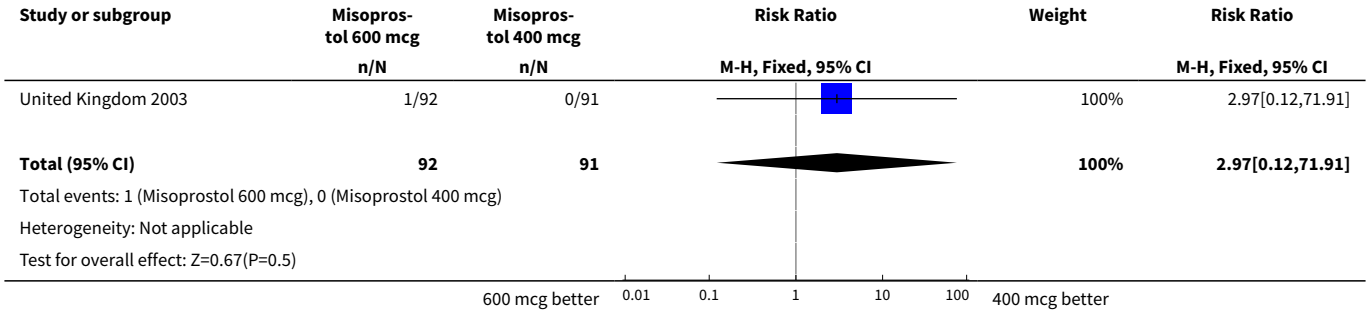




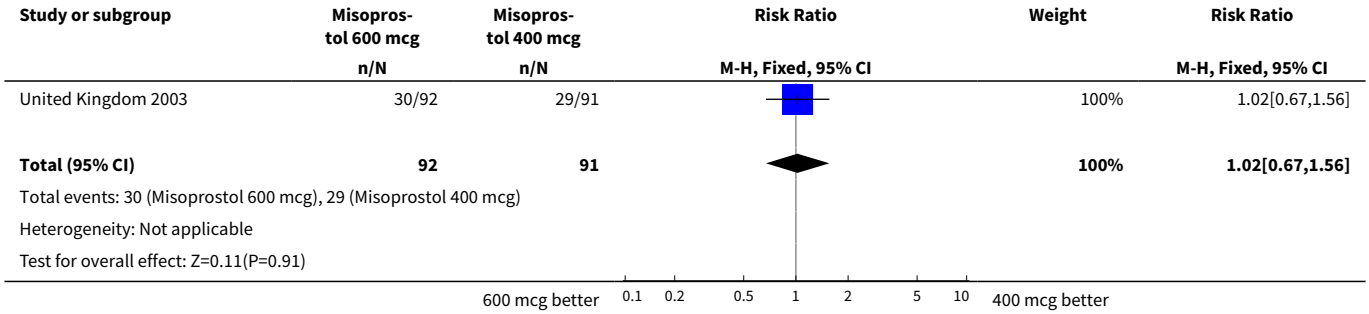
Analysis 17.5. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 5 Abdominal pain.



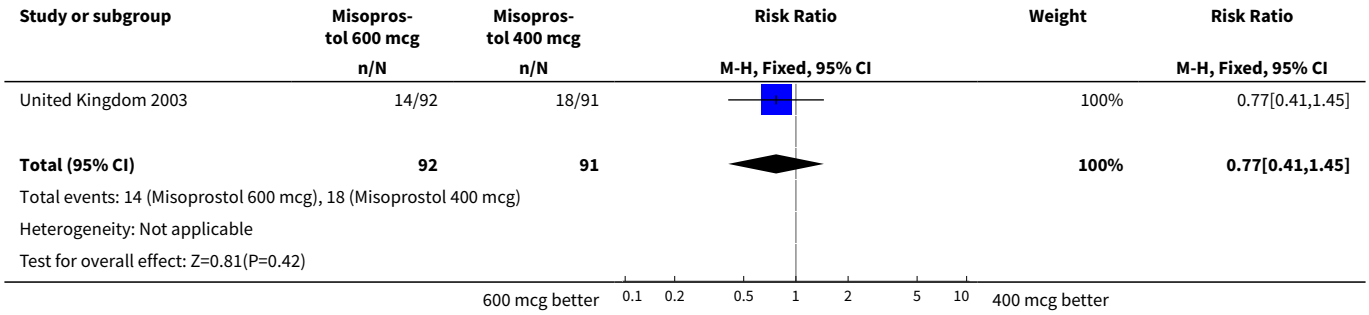
Analysis 17.6. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 6 Diarrhoea.



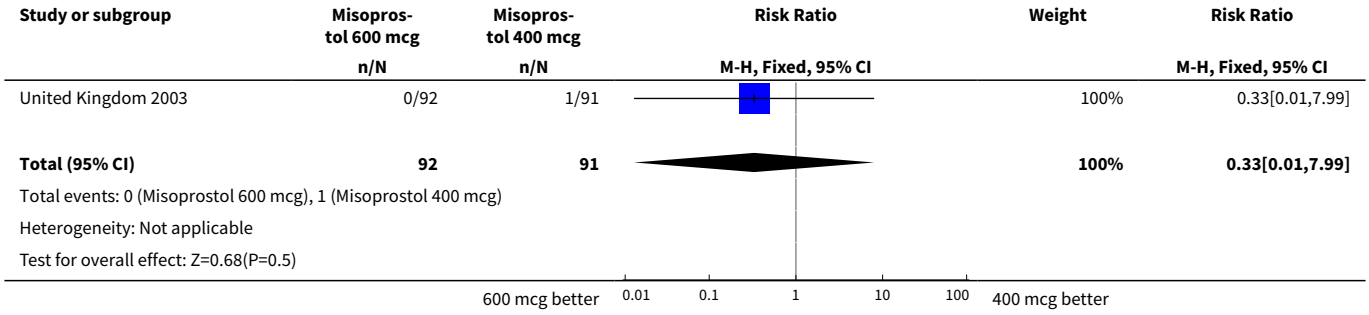
Analysis 17.7. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 7 Any shivering.



Analysis 17.8. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 8 Severe shivering.



Analysis 17.9. Comparison 17 Drug/dose: misoprostol 600 mcg rectal versus 400 mcg rectal, Outcome 9 Pyrexia.



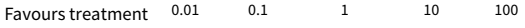
Comparison 18. Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Manual removal of placenta	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.08]
2 Nausea	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.28, 1.08]
3 Vomiting	1	184	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.73, 9.74]
4 Headache	1	184	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.56, 4.04]
5 Abdominal pain	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.74, 1.30]
6 Diarrhoea	1	184	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.70]
7 Any shivering	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.33, 0.64]
8 Severe shivering	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.16, 0.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Pyrexia	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.00]

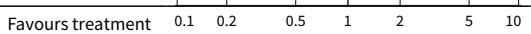
Analysis 18.1. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 1 Manual removal of placenta.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
United Kingdom 2003	0/92	1/92		100%	0.33[0.01,8.08]
Total (95% CI)	**92**	**92**		**100%**	**0.33[0.01,8.08]**
Total events: 0 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					



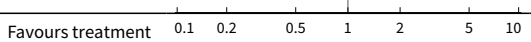
Analysis 18.2. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 2 Nausea.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
United Kingdom 2003	11/92	20/92		100%	0.55[0.28,1.08]
Total (95% CI)	**92**	**92**		**100%**	**0.55[0.28,1.08]**
Total events: 11 (Treatment), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.73(P=0.08)					

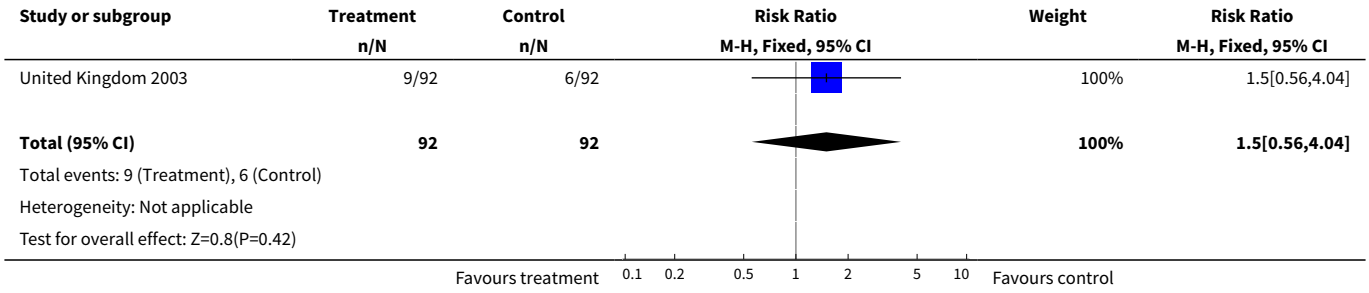


Analysis 18.3. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 3 Vomiting.

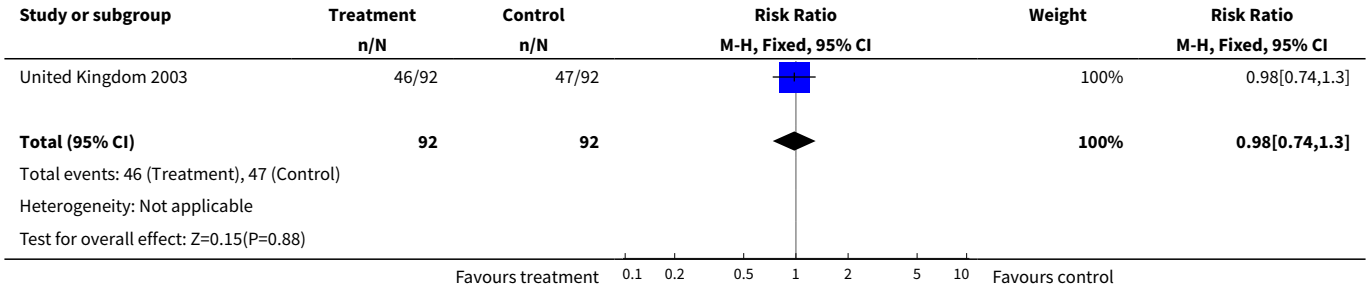
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
United Kingdom 2003	8/92	3/92		100%	2.67[0.73,9.74]
Total (95% CI)	**92**	**92**		**100%**	**2.67[0.73,9.74]**
Total events: 8 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



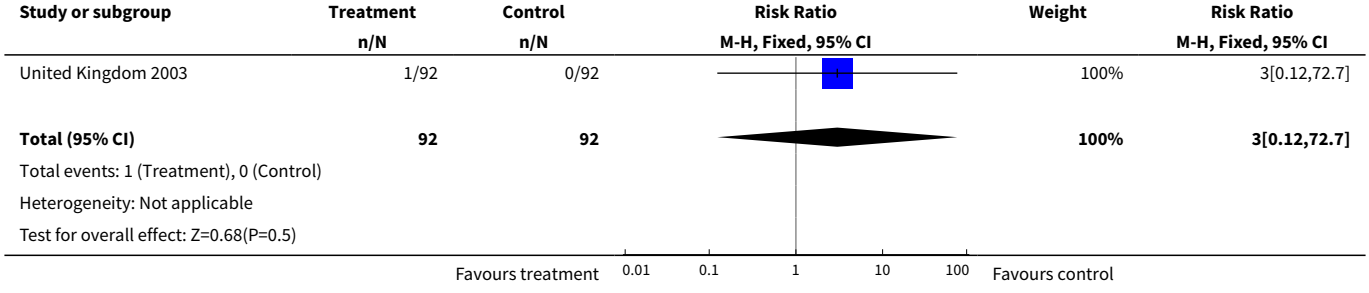
Analysis 18.4. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 4 Headache.



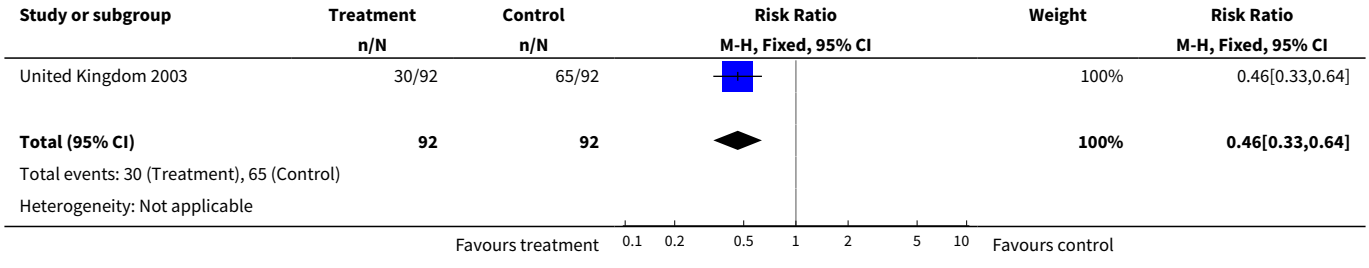
Analysis 18.5. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 5 Abdominal pain.

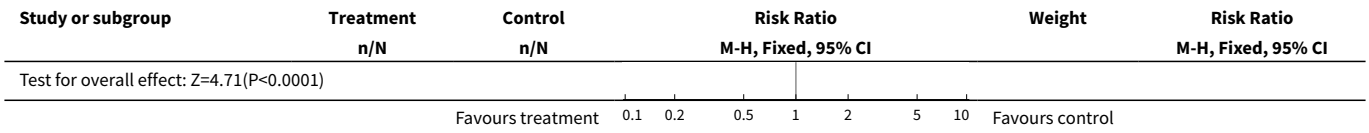


Analysis 18.6. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 6 Diarrhoea.

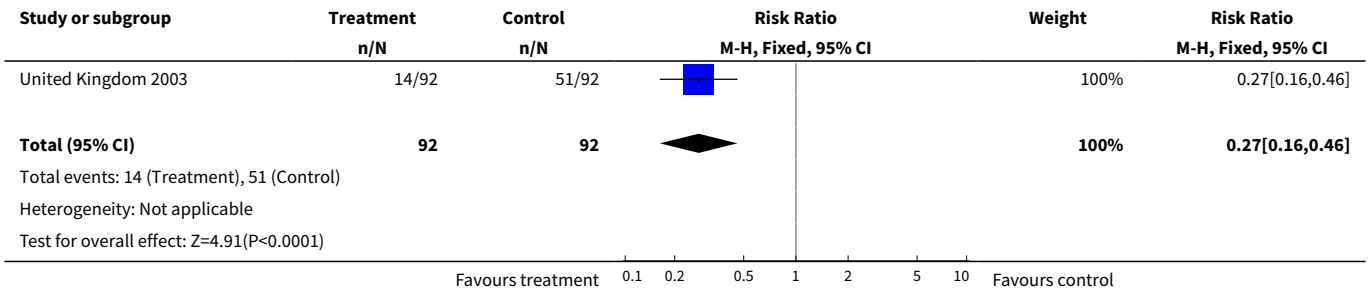


Analysis 18.7. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 7 Any shivering.

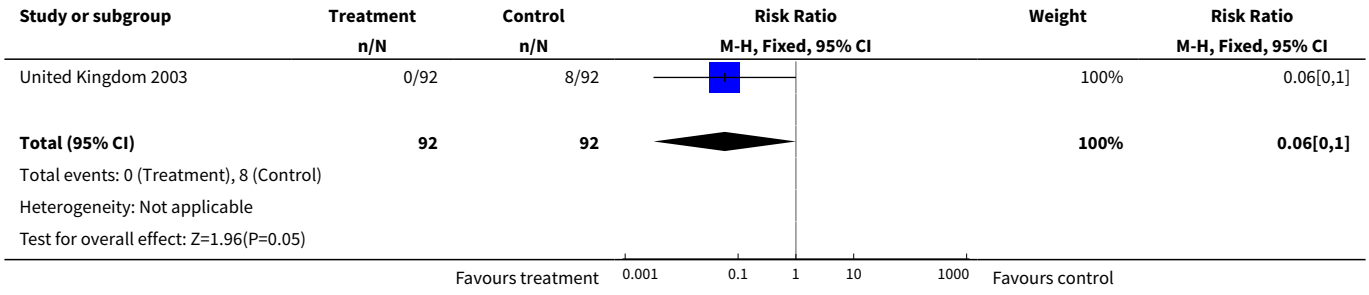




Analysis 18.8. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 8 Severe shivering.



Analysis 18.9. Comparison 18 Drug/route: misoprostol 600 mcg rectal versus 600 mcg oral, Outcome 9 Pyrexia.

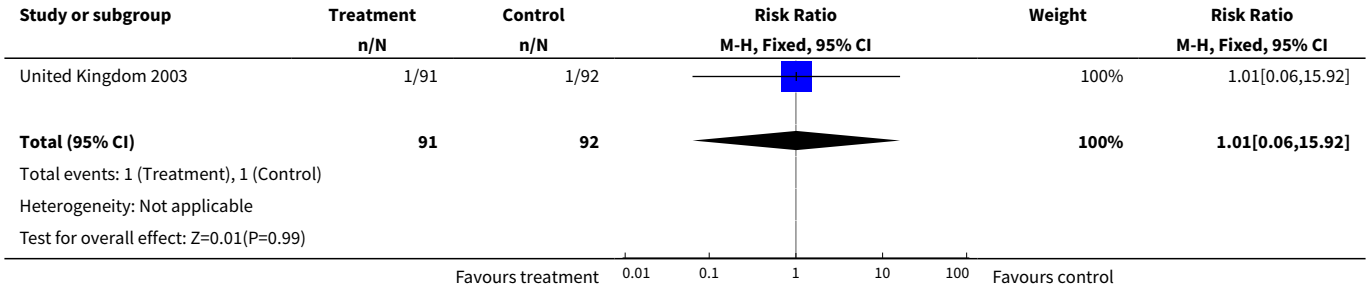


Comparison 19. Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral

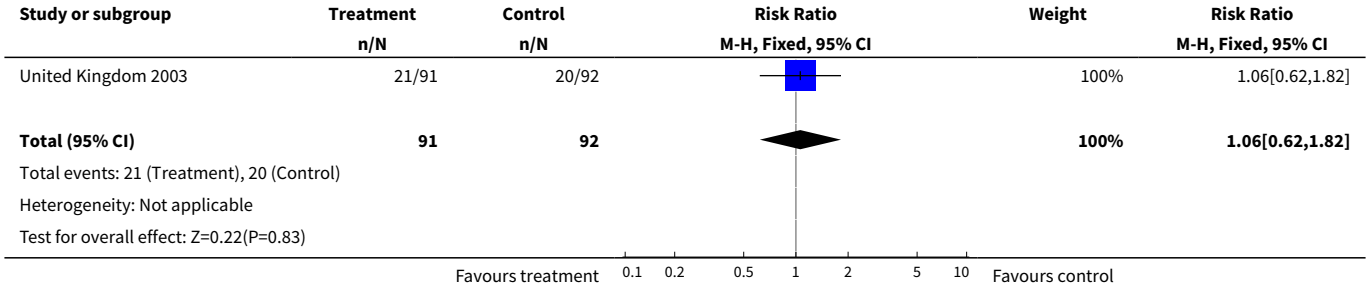
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Manual removal of placenta	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.92]
2 Nausea	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.62, 1.82]
3 Vomiting	1	183	Risk Ratio (M-H, Fixed, 95% CI)	3.37 [0.96, 11.85]
4 Headache	1	183	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [0.95, 5.87]
5 Abdominal pain	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.87, 1.49]
6 Diarrhoea	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Any shivering	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.32, 0.63]
8 Severe shivering	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.56]
9 Pyrexia	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.92]

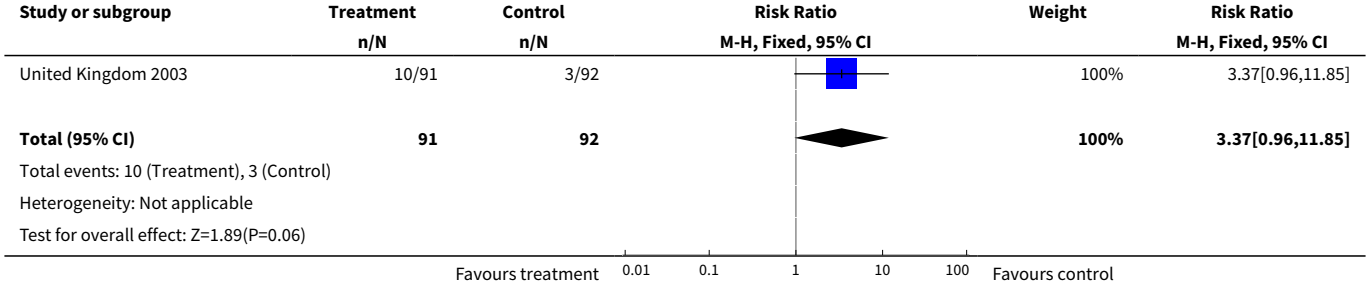
Analysis 19.1. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 1 Manual removal of placenta.



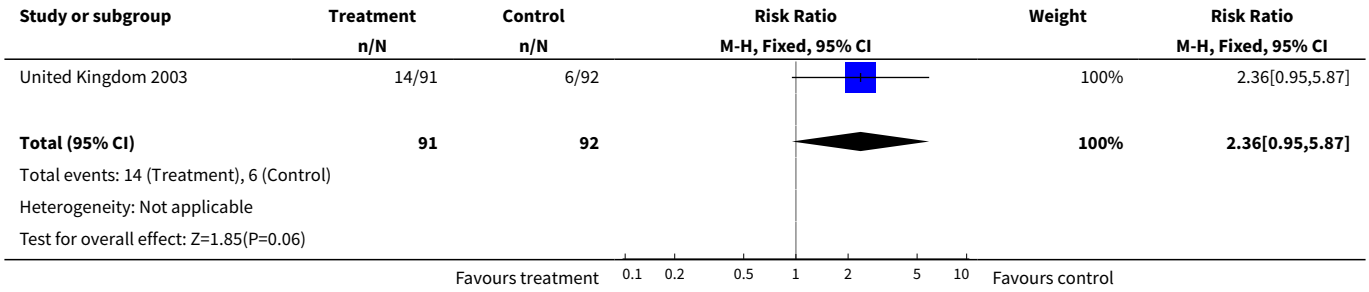
Analysis 19.2. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 2 Nausea.



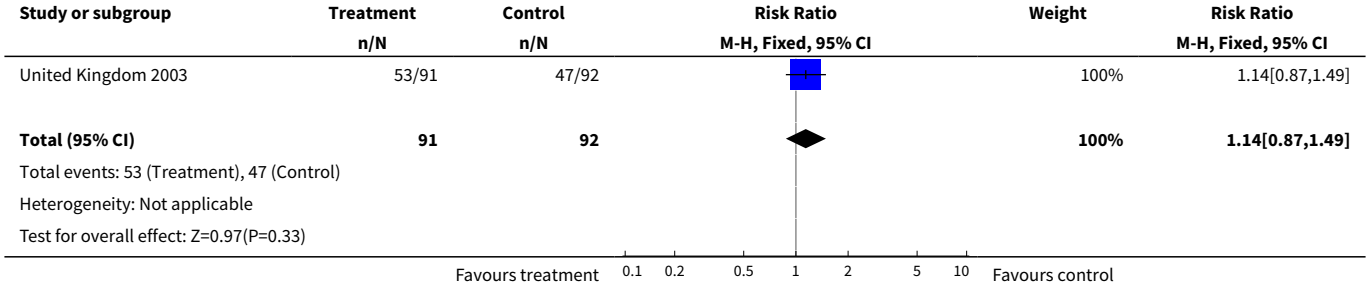
Analysis 19.3. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 3 Vomiting.



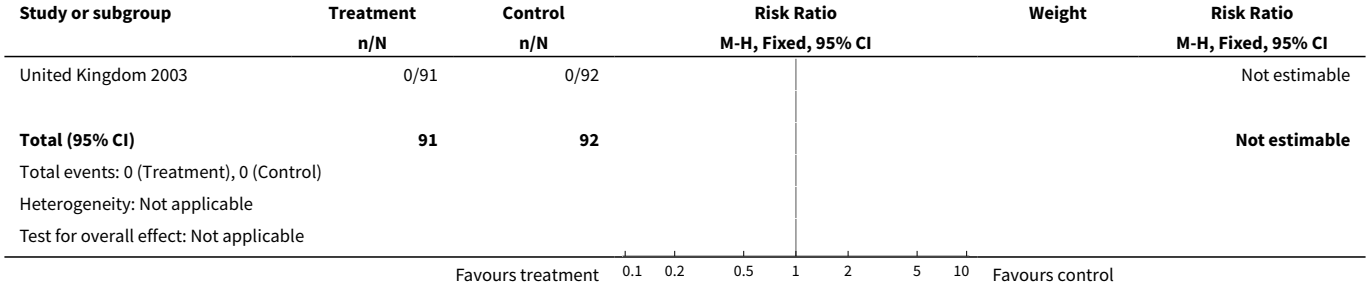
Analysis 19.4. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 4 Headache.



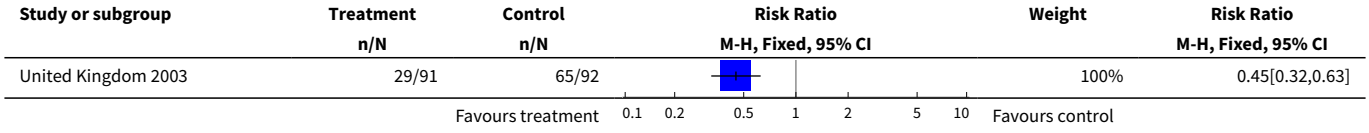
Analysis 19.5. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 5 Abdominal pain.

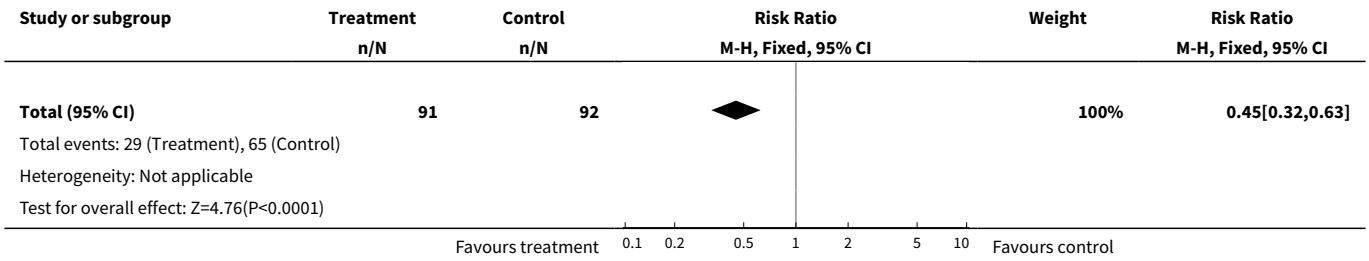


Analysis 19.6. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 6 Diarrhoea.

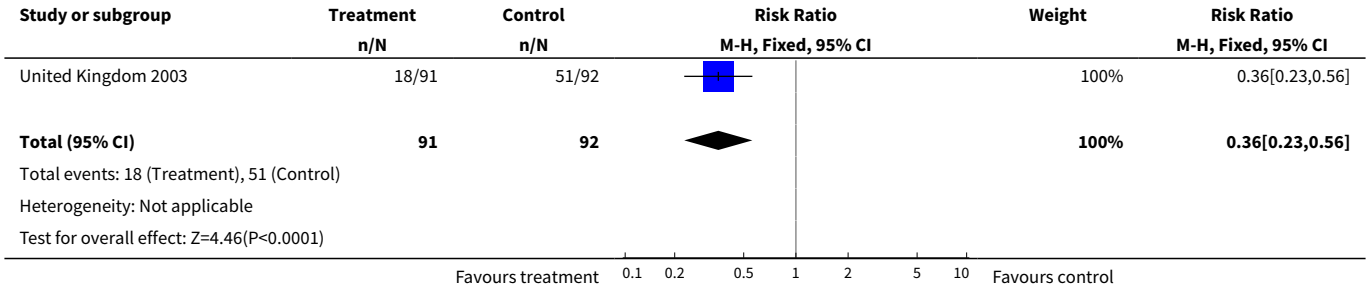


Analysis 19.7. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 7 Any shivering.

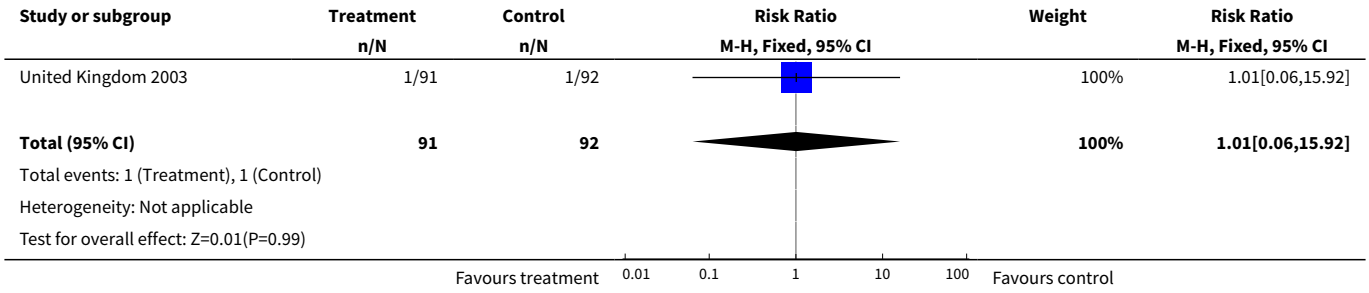




Analysis 19.8. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 8 Severe shivering.



Analysis 19.9. Comparison 19 Drug/dose/route: misoprostol 400 mcg rectal versus 600 mcg oral, Outcome 9 Pyrexia.

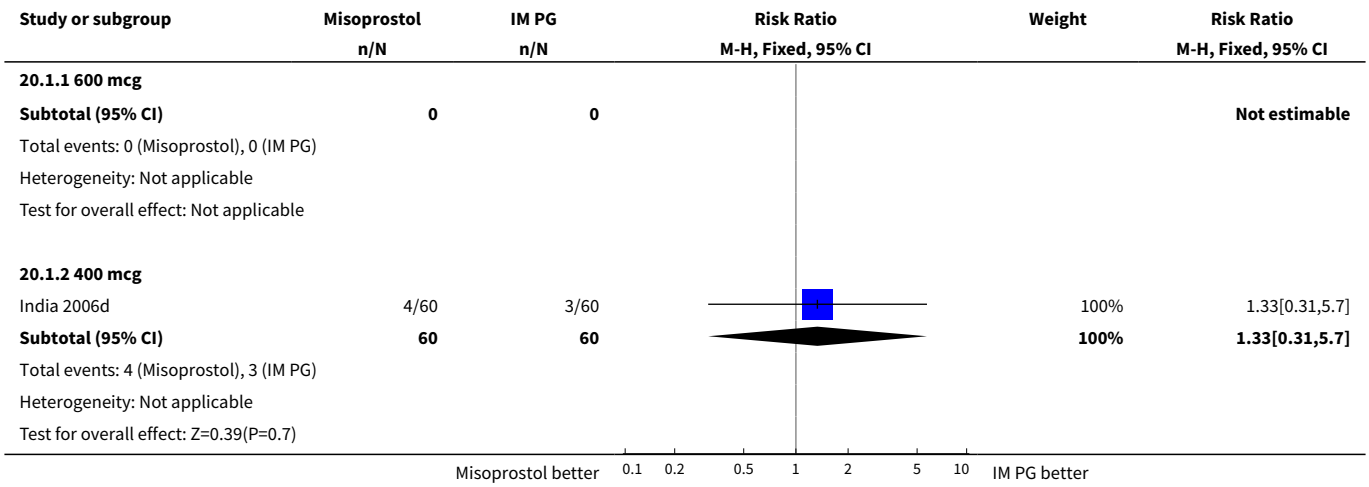


Comparison 20. Rectal misoprostol versus intramuscular prostaglandin (subgroups by dose)

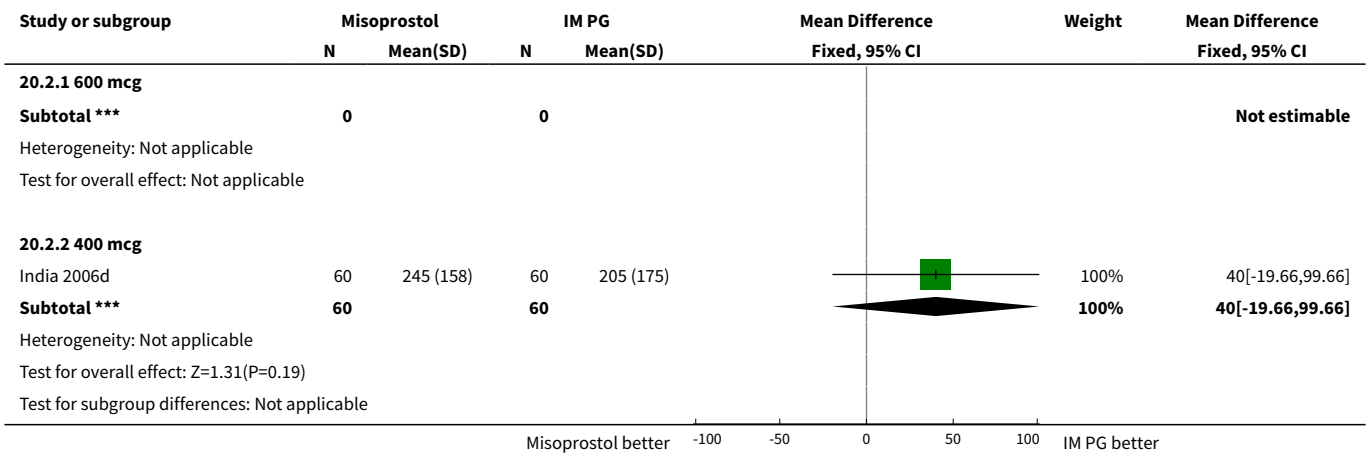
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum haemorrhage (>= 500 mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.70]
2 Blood loss (mL)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 600 mcg	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 400 mcg	1	120	Mean Difference (IV, Fixed, 95% CI)	40.0 [-19.66, 99.66]
3 Use of additional uterotonics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 600 mcg	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 400 mcg	1	120	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [1.14, 21.86]

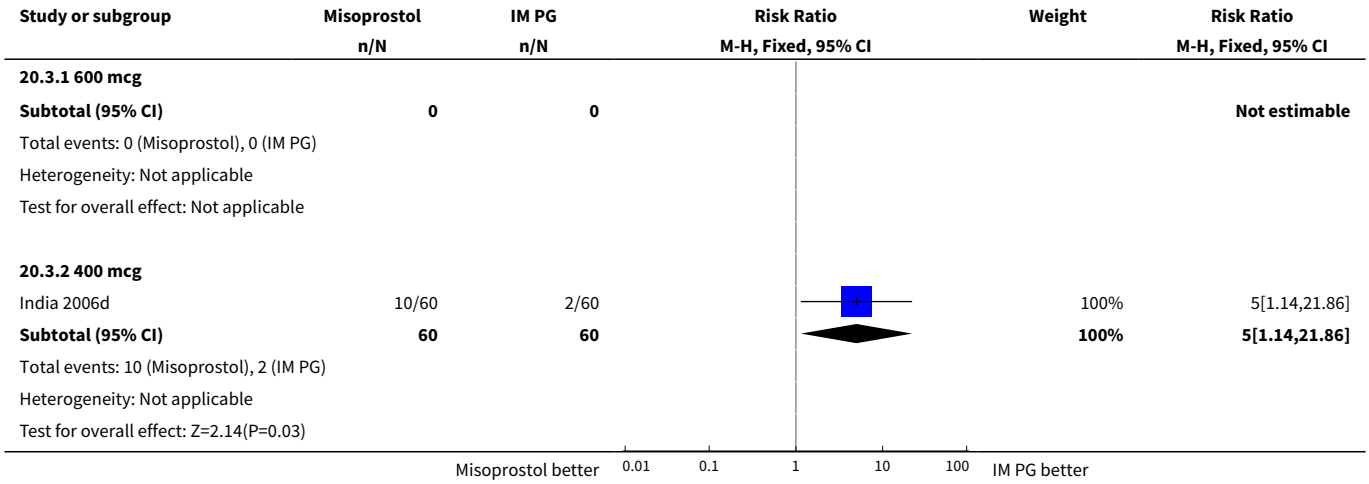
Analysis 20.1. Comparison 20 Rectal misoprostol versus intramuscular prostaglandin (subgroups by dose), Outcome 1 Postpartum haemorrhage (>= 500 mL).



Analysis 20.2. Comparison 20 Rectal misoprostol versus intramuscular prostaglandin (subgroups by dose), Outcome 2 Blood loss (mL).



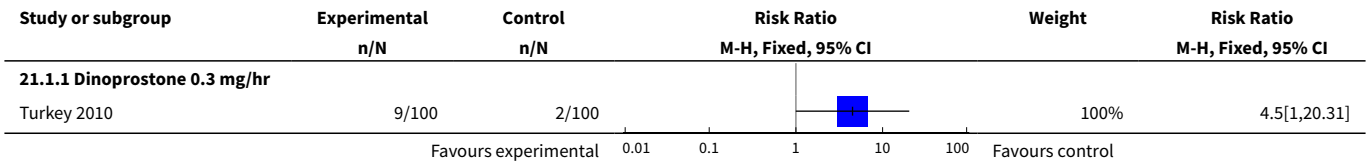
Analysis 20.3. Comparison 20 Rectal misoprostol versus intramuscular prostaglandin (subgroups by dose), Outcome 3 Use of additional uterotonics.

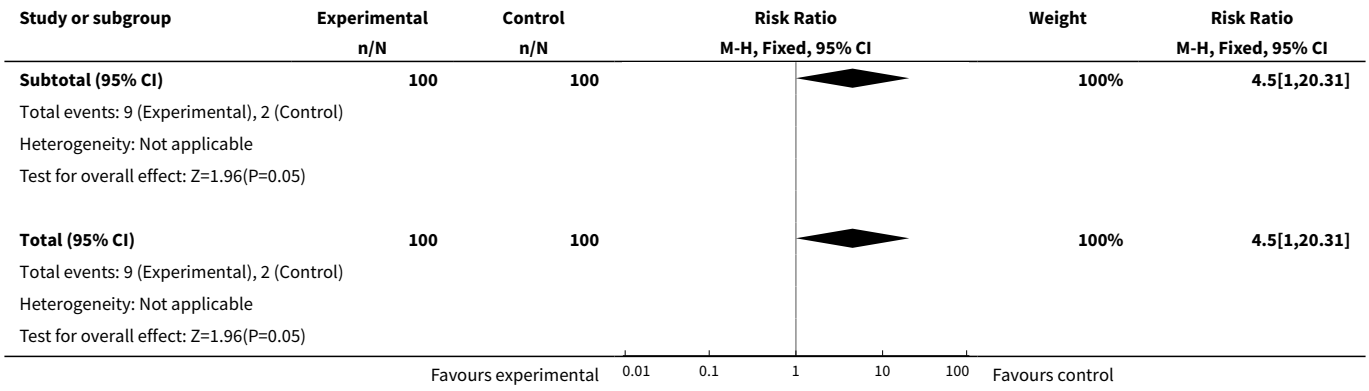


Comparison 21. Controlled release prostaglandins (vaginal insert) versus injectable uterotonics

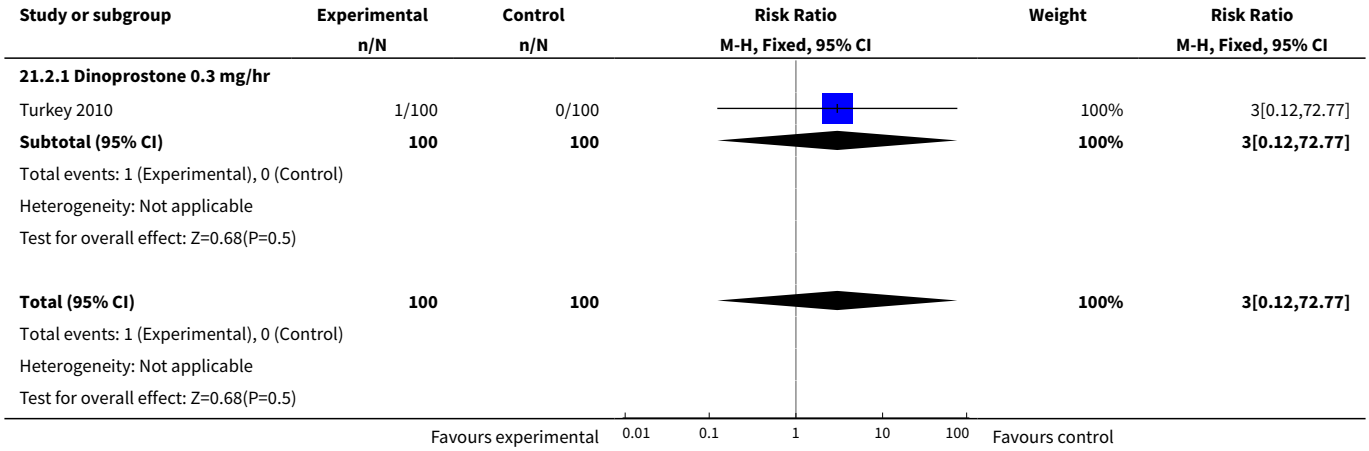
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Nausea	1	200	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [1.00, 20.31]
1.1 Dinoprostone 0.3 mg/hr	1	200	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [1.00, 20.31]
2 Diarrhoea	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]
2.1 Dinoprostone 0.3 mg/hr	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]
3 Pyrexia (>= 38 C)	1	200	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.28]
3.1 Dinoprostone 0.3 mg/hr	1	200	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.28]
4 Shivering	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]
4.1 Dinoprostone 0.3 mg/hr	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]

Analysis 21.1. Comparison 21 Controlled release prostaglandins (vaginal insert) versus injectable uterotonics, Outcome 1 Nausea.

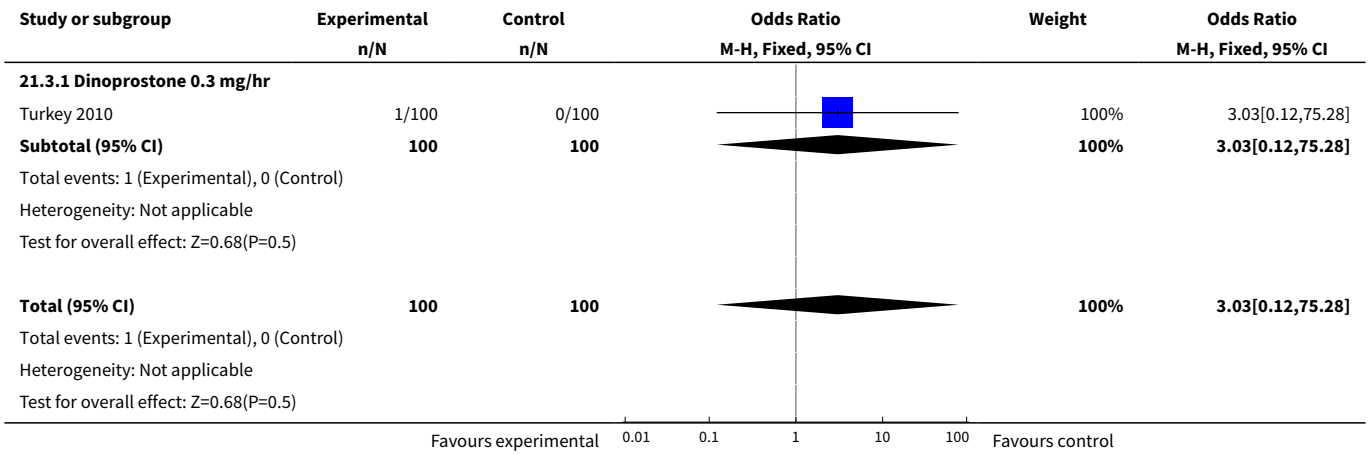




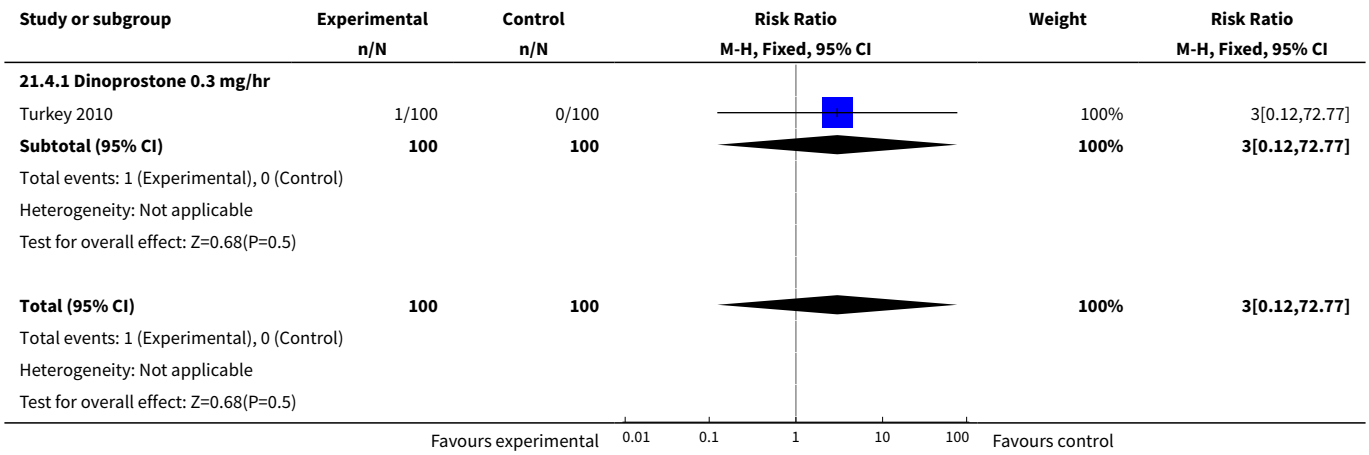
Analysis 21.2. Comparison 21 Controlled release prostaglandins (vaginal insert) versus injectable uterotonics, Outcome 2 Diarrhoea.



Analysis 21.3. Comparison 21 Controlled release prostaglandins (vaginal insert) versus injectable uterotonics, Outcome 3 Pyrexia (>= 38 C).



Analysis 21.4. Comparison 21 Controlled release prostaglandins (vaginal insert) versus injectable uterotonics, Outcome 4 Shivering.



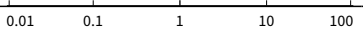
Comparison 22. Oral misoprostol versus traditional ZB11

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 600 mcg	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Postpartum haemorrhage (>=500 mL)	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.03, 1.91]
2.1 600 mcg	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.03, 1.91]
3 Severe postpartum hemorrhage (>=1000 mL)	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.69, 3.36]
3.1 600 mcg	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.69, 3.36]
4 Use of additional uterotonics	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.91, 1.68]
4.1 600 mcg	1	960	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.91, 1.68]
5 Nausea	1	958	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.49, 2.11]
5.1 600 mcg	1	958	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.49, 2.11]
6 Vomiting	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.22, 3.01]
6.1 600 mcg	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.22, 3.01]
7 Diarrhoea	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.12, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 600 mcg	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.12, 1.15]
8 Any shivering	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
8.1 600 mcg	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
9 Pyrexia (>= 38 C)	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.95]
9.1 600 mcg	1	958	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.95]

Analysis 22.1. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 1 Maternal death.

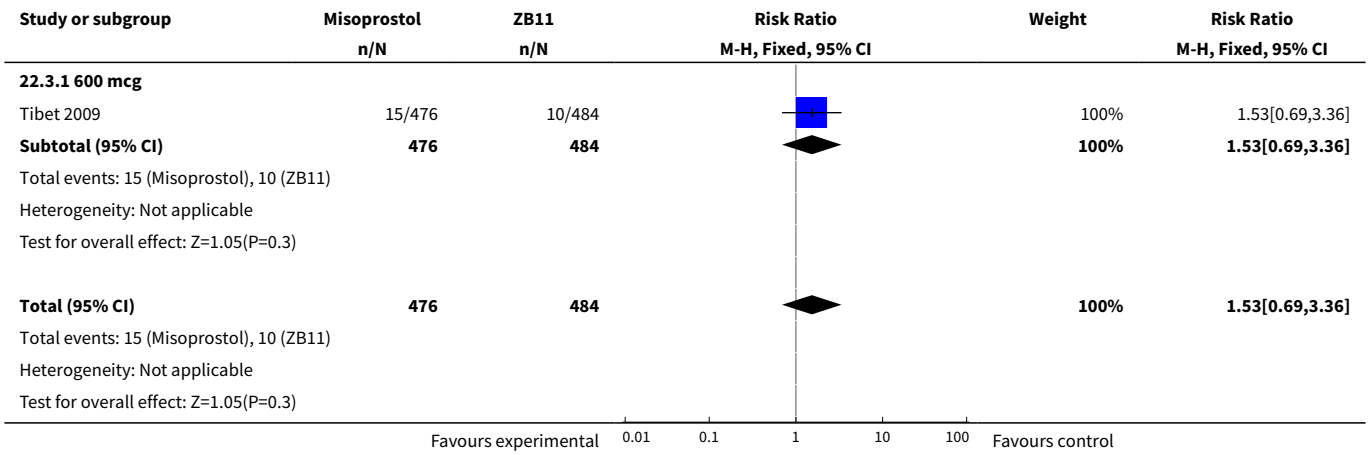
Study or subgroup	Misoprostol n/N	ZB11 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
22.1.1 600 mcg					
Tibet 2009	0/476	0/484			Not estimable
Subtotal (95% CI)	**476**	**484**			**Not estimable**
Total events: 0 (Misoprostol), 0 (ZB11)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**476**	**484**			**Not estimable**
Total events: 0 (Misoprostol), 0 (ZB11)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



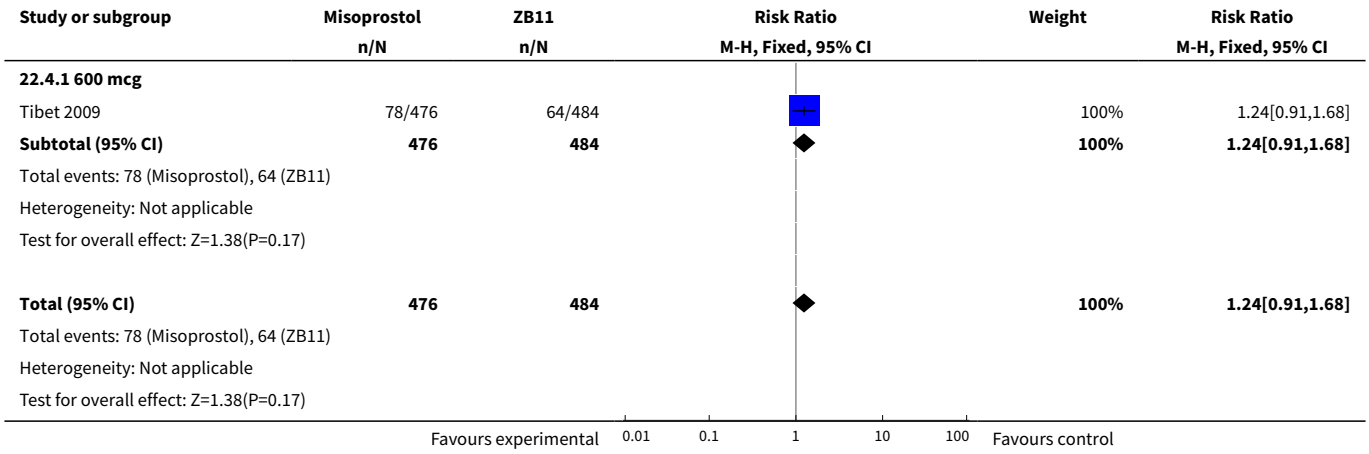
Analysis 22.2. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 2 Postpartum haemorrhage (>=500 mL).

Study or subgroup	Misoprostol n/N	ZB11 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
22.2.1 600 mcg					
Tibet 2009	83/476	60/484		100%	1.41[1.03,1.91]
Subtotal (95% CI)	**476**	**484**		**100%**	**1.41[1.03,1.91]**
Total events: 83 (Misoprostol), 60 (ZB11)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.18(P=0.03)					
Total (95% CI)	**476**	**484**		**100%**	**1.41[1.03,1.91]**
Total events: 83 (Misoprostol), 60 (ZB11)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.18(P=0.03)					

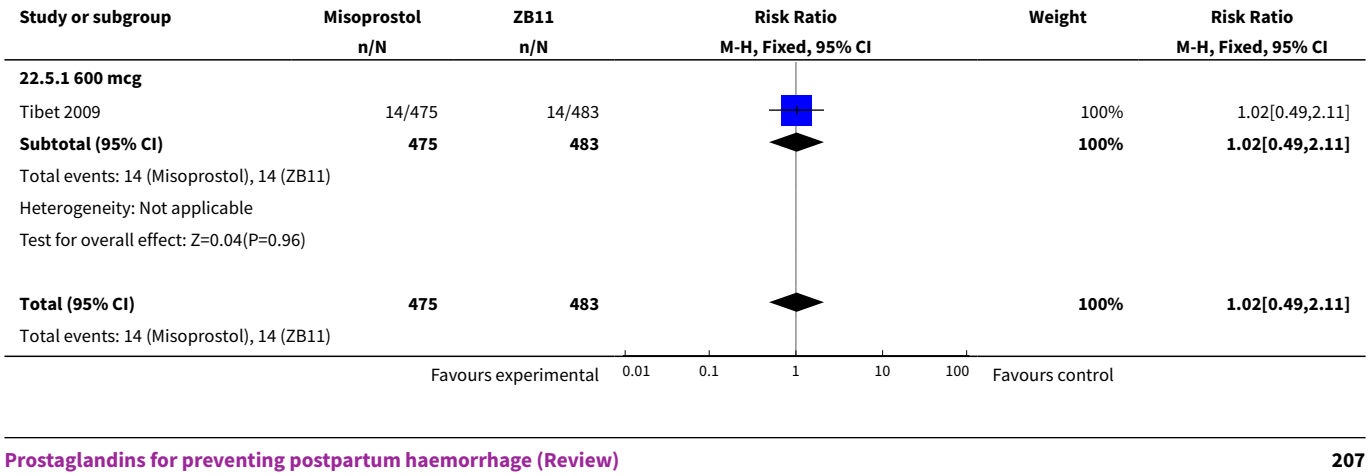
Analysis 22.3. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 3 Severe postpartum hemorrhage (>=1000 mL).

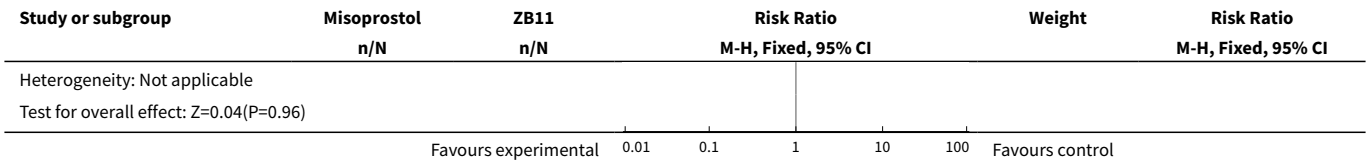


Analysis 22.4. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 4 Use of additional uterotonics.

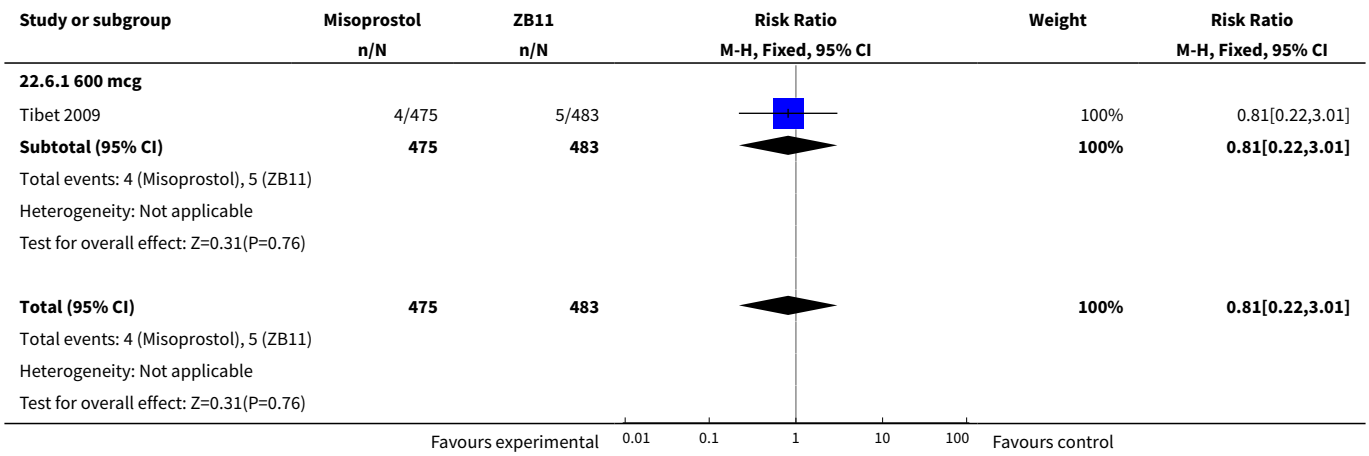


Analysis 22.5. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 5 Nausea.

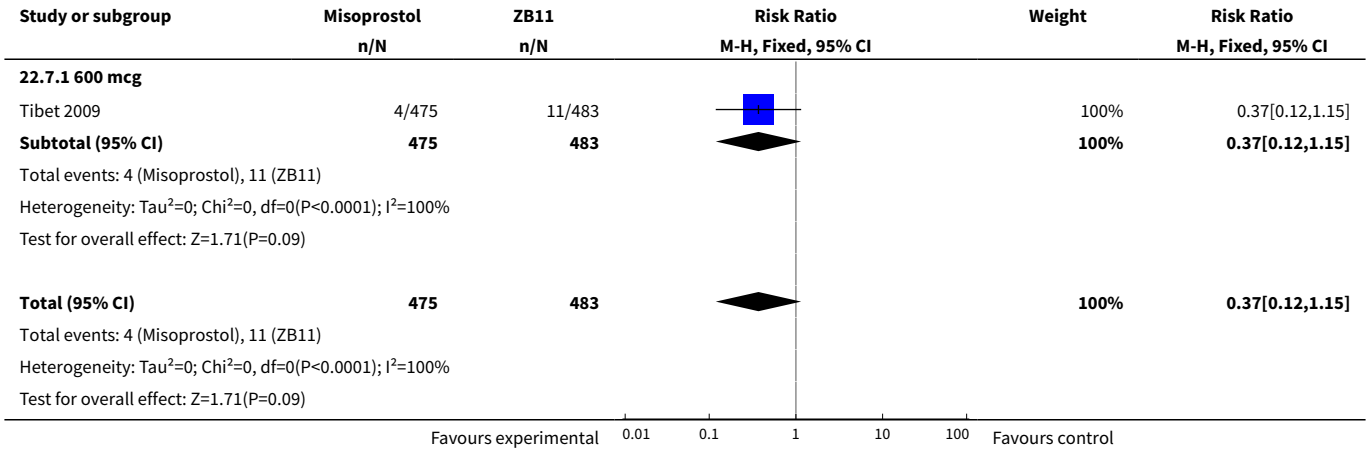




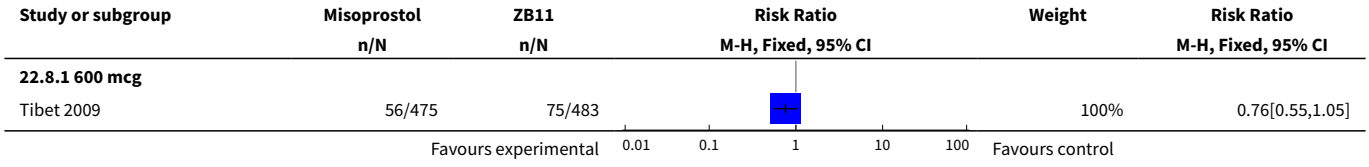
Analysis 22.6. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 6 Vomiting.

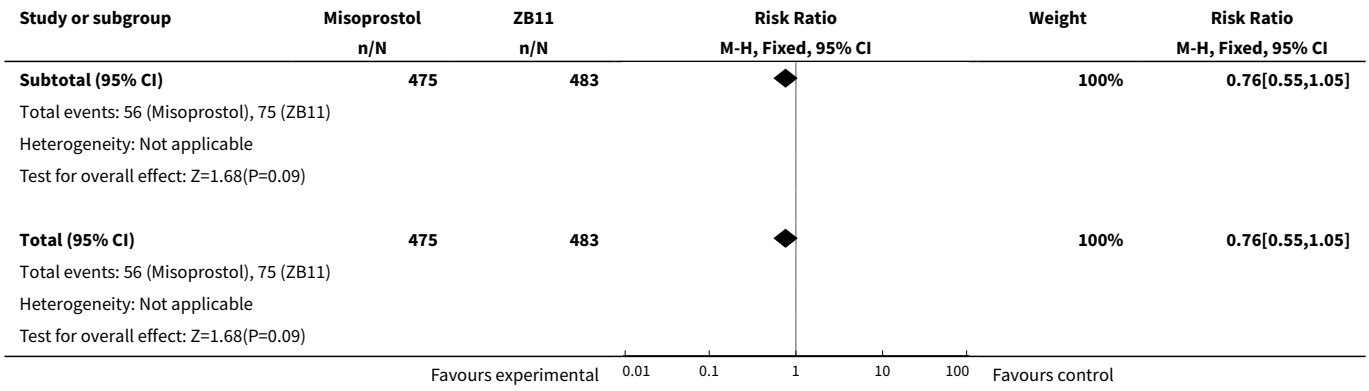


Analysis 22.7. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 7 Diarrhoea.

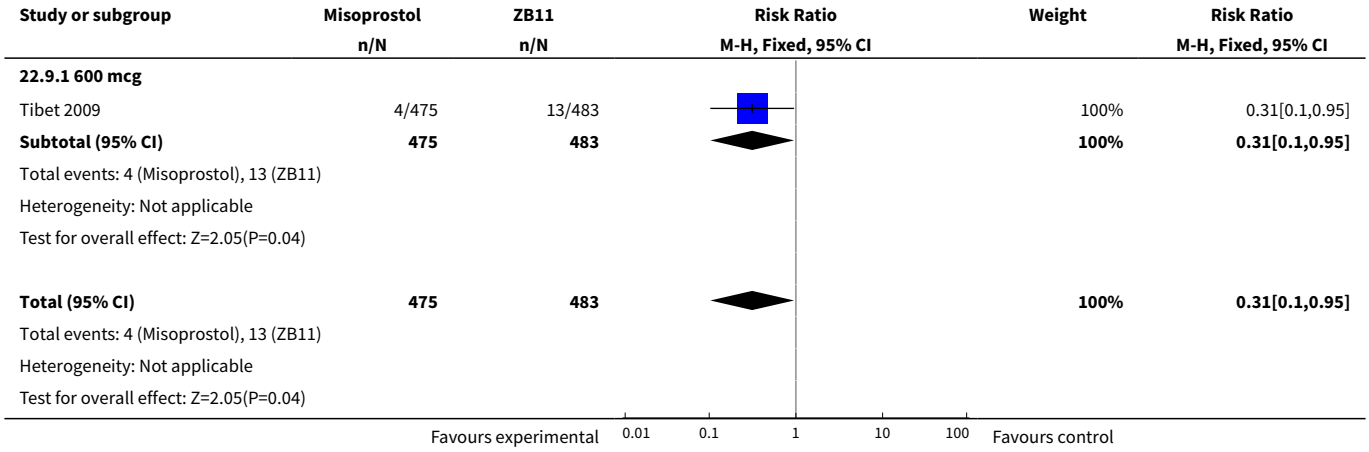


Analysis 22.8. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 8 Any shivering.





Analysis 22.9. Comparison 22 Oral misoprostol versus traditional ZB11, Outcome 9 Pyrexia (>= 38 C).



APPENDICES

Appendix 1. Methods used to assess trials included in previous versions of this review

Two review authors independently evaluated trials under consideration for methodological quality and appropriateness for inclusion without consideration of their results. No language preferences were applied either during the search or selection of trials. Two authors independently extracted data regardless of whether they participated in a particular included trial or not.

We assessed methodological quality in terms of adequacy of allocation concealment as described in Higgins 2005.

In addition to the main outcomes, we systematically extracted the following data for each study:

1. trial entry criteria (high versus low risk, other specific exclusion criteria);
2. exclusions and missing data after randomization;
3. management of the third stage of labour;
4. the duration and technique of assessment of blood loss.

We evaluated statistical heterogeneity across trial results using the chi-square test as calculated in MetaView. Whenever statistical ($P < 0.1$) or visual heterogeneity was encountered, we explored the possible reasons. In meta-analyses with significant heterogeneity (statistical or visual), we discuss the trials individually (i.e. without totals).

It is not clear how components of third stage management, other than the uterotonic, affect the blood loss. While the comparison of the uterotonic might be valid, if other components of active management are effective, then the scope for any difference between a prostaglandin and a placebo or another uterotonic could be minimized if those components are used.

These factors are assessed as possible sources of heterogeneity where appropriate and if there are adequate numbers of studies to allow such assessments.

Because of the significant differences in pharmacokinetics and possibly other properties, we analysed oral, rectal, sublingual and buccal misoprostol and intramuscular prostaglandins (PGF2alpha and synthetic E2) separately.

We did not exclude trials on the basis of a predetermined cut-off value for loss to follow-ups and postrandomization exclusions. We systematically extracted this information and discussed as appropriate for each trial.

WHAT'S NEW

Date	Event	Description
20 June 2011	New search has been performed	Search updated in January 2011. Number of included studies has increased from 46 to 72 studies. We updated the search in May 2012 and have added the results to Studies awaiting classification for consideration at the next update.
20 June 2011	New citation required but conclusions have not changed	Main conclusions remain unchanged. More evidence has accumulated on oral misoprostol versus placebo comparison in community-based settings and misoprostol versus conventional oxytocics in facilities. New review author helped to prepare this update.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 4, 1997

Date	Event	Description
7 January 2011	Amended	Search updated. Forty-five new reports added to Studies awaiting classification.
19 June 2008	Amended	Converted to new review format.
23 May 2007	New search has been performed	Search updated on 28 February 2007. The current update includes 14 new trials bringing the total to 46 trials. The review now includes more evidence on misoprostol compared to placebo at non-hospital, peripheral settings. The conclusions related to misoprostol comparison to conventional injectable uterotonics and that of intramuscular prostaglandins remain unchanged. Three papers from China are in the awaiting assessment section pending their translation.
23 May 2007	New citation required but conclusions have not changed	The statistics editor noticed some discrepancies in standard deviation figures of continuous data in some trials. In Switzerland 1999 the data were actually reported as standard error and this has been corrected. Continuous data from India 1988c, Nigeria

Date	Event	Description
		2003 and Ghana 2000 have ben excluded because they could not be reconciled by looking at the paper again.
21 November 2003	New search has been performed	The current update includes 5104 additional women from seven misoprostol trials (Canada 2002; Colombia 2002; France 2001; Nigeria 2003; Turkey 2002; Turkey 2003; United Kingdom 2003) and some excluded trials. The conclusions of the review have not changed.

CONTRIBUTIONS OF AUTHORS

Özge Tunçalp prepared the 2011 update, including completing the 'Risk of bias' tables for the studies included in earlier versions of the review. All other review authors contributed by assisting with the data extraction, analysis advice, writing and final approval of the text. Özge Tunçalp is the guarantor of the review.

DECLARATIONS OF INTEREST

Two review authors (AM Gülmezoglu, GJ Hofmeyr) participated in the WHO 1999 and WHO 2001 trials and one review author (GJ Hofmeyr) participated in Africa 2011; South Africa 1998a; South Africa 1998b; South Africa 1998c; South Africa 1998d. GJ Hofmeyr did not assess the trials or extract the data for the trials in which he was involved. AM Gülmezoglu extracted the data but these were independently checked by Fatu Forna, an author on the earlier version of the review.

SOURCES OF SUPPORT

Internal sources

- UK Cochrane Centre, NHS R&D Programme, Oxford, UK.
- HRP-UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.
- Duke University School of Medicine, North Carolina, USA.
- Department of Maternal and Child Health, University of North Carolina-Chapel Hill, USA.
- Effective Care Research Unit, University of the Witwatersrand, East London/Johannesburg, South Africa.
- Department of Obstetrics and Gynecology, Emory University, Atlanta, USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Labor Stage, Third; Administration, Oral; Administration, Sublingual; Fever [chemically induced]; Misoprostol [adverse effects] [*therapeutic use]; Oxytocics [adverse effects] [*therapeutic use]; Postpartum Hemorrhage [*prevention & control]; Prostaglandins [*therapeutic use]; Randomized Controlled Trials as Topic; Shivering

MeSH check words

Female; Humans; Pregnancy