Proposal for the deletion of misoprostol for the prevention of post-partum haemorrhage in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion.

We once again ask the WHO Expert Committee to delete misoprostol for the prevention of post-partum haemorrhage (PPH) from the WHO Model List of Essential Medicines on the following grounds: evidence of efficacy and effectiveness for this indication is still extremely weak at best and conducted studies are deficient in many respects. Misoprostol for prevention of PPH should not be reintroduced until and unless there is strong evidence from a large well-designed RCT.

Misoprostol is promoted as a pragmatic solution to high maternal mortality due to postpartum haemorrhage (PPH) in low-resource settings of low- and middle-income countries. It was included in the WHO Model List of Essential Medicines for prevention of PPH in 2011 and for treatment of PPH in 2015. For both indications the listing refers to situations “where oxytocin is not available or cannot be safely used”. We ask the WHO Expert Committee to revisit the evidence for the use of misoprostol for PPH prevention and consider its removal from the WHO EML on the basis of a detailed reassessment of the currently available evidence.

Reasons for the removal:

- There is no good evidence that misoprostol reduces maternal mortality
- Where skilled birth attendants are present and oxytocin is available, oxytocin is more effective in reducing postpartum bleeding and has fewer side-effects than misoprostol
- For low-resource settings where skilled attendants are not present and/or oxytocin is not available, the evidence of safety, efficacy and effectiveness of misoprostol in preventing PPH is limited, weak, and non-generalisable
- No stringent regulatory agency (e.g. US FDA, MHRA, EMA) has approved misoprostol for the prevention of PPH to date
- The focus should be on skilled birth attendants and remedying the causes of anaemia

2. Name of the WHO technical department and focal point supporting the application (where relevant).

Previously we had discussions with Dr. Weerasuriya and Dr. Richard Laing who encouraged us to apply.

3. Name of the organization(s) consulted and/or supporting the application.

None
4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Misoprostol

G02AD06 uterotonics, prostaglandins

5. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).

The current listing (19th) is as follows:

Tablet: 200 micrograms.
– Management of incomplete abortion and miscarriage;
– Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used

We request the Expert Committee to delete ‘Prevention’ from the Section 22.1 Oxytocics in the 20th edition of WHO Model List of Essential Medicines.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

The most recent WHO guidelines for the prevention and treatment of PPH (WHO 2012a) recommend the universal use of uterotonics during the third stage of labour to prevent PPH. The recommended uterotonics are:

1. oxytocin (Strong recommendation, moderate-quality evidence);
2. other injectable uterotonics (if appropriate ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol in settings where oxytocin is not available (Strong recommendation, moderate quality evidence);
3. misoprostol administered by community health care workers and lay health workers where skilled birth attendants are not present and oxytocin not available (Strong recommendation, moderate quality evidence)

We discuss the evidence behind recommendations 2 and 3 and its quality below.

8. Information supporting the public health relevance.

Not relevant as the drug has not been shown to be efficacious.
Efforts to make misoprostol for PPH prevention widely available divert resources from proven public health measures such as skilled birth attendants and their training, and oxytocin use.


Data on effectiveness are not available. Below we discuss efficacy data. For effectiveness data from phase IV trials and pharmacovigilance data would be needed.

We note that in the literature it is not uncommon that abstracts of RCTs as well as systematic reviews make conclusions about the use of misoprostol for PPH prevention in low resource setting despite focusing on the use of uterotonics in hospital setting, i.e. making recommendations unsupported by the actual study design, data and analysis.

• Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Clinical evidence available up until November 2014 has been reviewed and appraised previously (Chu et al. 2012, Brhlikova & Pollock WHO EML application 2014). To update the previous review, Medline and Embase databases were searched for randomised controlled trials assessing misoprostol use in community and home birth settings in low- and middle-income countries (defined by World Bank classification) published between November 2014 and November 2016 using search terms PPH; bleeding in TSL; misoprostol; RCTs; and prevention. The database search revealed two systematic reviews and further studies were also identified from the sources. Studies were excluded if duplicate, considering injectable prostaglandins, non-RCTs, not reported in English, in high-income and hospital settings.

The search identified one cluster-randomised trial conducted in community setting in Senegal (Diop et al. 2016) and one systematic review and meta-analysis of RCTs comparing misoprostol versus ergometrine-oxytocin for prevention of PPH (Tan et al. 2016).

• Summary of available data (appraisal of quality, outcome measures, summary of results)

Our critical review of four RCTs conducted in low-resource settings that formed the basis of the Expert Committee’s decision in 2011 remains up-to-date. In Table 1 we summarise the four RCTs and Table 2 summarises relevant systematic reviews.

<table>
<thead>
<tr>
<th>Study Country</th>
<th>Patients number (Numbers screened)</th>
<th>Risk status</th>
<th>Intervention Control</th>
<th>Attendant at birth TSL management</th>
<th>Outcome measures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walraven et al. (2005) Gambia</td>
<td>1229 (1623)</td>
<td>Low risk (some high risk re-entered the study)</td>
<td>Misoprostol 600 µg PO</td>
<td>TTBA Controlled cord traction, delayed cord</td>
<td>&gt;500mL RR 0.91 (0.67-1.24) NS &gt;1000mL RR 0.48 (0.09-2.59)</td>
<td>too few outcomes, not powered sufficiently</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ergometrine 2mg PO</td>
<td></td>
<td>Shivering RR 2.74 (2.14-3.52) Vomiting RR 0.5 (0.29-0.88)</td>
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The most recent study conducted in 28 maternity huts in three districts in Senegal was an unmasked cluster-randomised controlled trial comparing oxytocin administered i.m. via Uniject with oral misoprostol and the effect on haemoglobin levels (Diop et al. 2016). Of 1820 women recruited during pregnancy or at the time of delivery 1412 women delivered in the study huts. 1049 women received the study drugs and recorded haemoglobin concentrations prior and post delivery; 647 women received misoprostol (600 µg orally) and 402 women received oxytocin (10 IU oxytocin intramuscularly). The study found no significant difference in haemoglobin decrease between the two groups when adjusted for cluster design (0.3 g/L, 95% CI –8.26 to 8.92, p=0.71) and reported shivering as more common in the misoprostol group and nausea in the oxytocin group.

We note that there were 18 unexplained stillbirths in the studied population which have not been accounted for.

Table 2: Summary of identified systematic reviews published in the 2011-2016 period

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Title</th>
<th>Misoprostol RCTs included (Number of studies)</th>
<th>Setting</th>
<th>Reported Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuncalp et al. (2012)</td>
<td>Prostaglandins for preventing PPH</td>
<td>- misoprostol vs placebo (11) or no treatment - oral (21) and sublingual (8) misoprostol vs</td>
<td>Mixed, mainly hospital setting; 4 RCTS in low-resource settings</td>
<td>*Oral or sublingual misoprostol compared with placebo is effective in</td>
<td>Outcomes reported for mixed (hospital and low-resource setting) groups of</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Title</td>
<td>Study Design</td>
<td>Study Details</td>
<td>Results</td>
<td>Limitations</td>
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<tr>
<td>Hofmeyr et al. (2013)</td>
<td>Postpartum misoprostol for preventing maternal mortality and morbidity</td>
<td>78 studies (59,216 women): PPH prevention (71) and PPH treatment (8) - misoprostol vs placebo (23), no additional treatment (2), other uterotonic agents (51) or uterotonic and placebo (2)</td>
<td>Mixed</td>
<td>Understanding the effectiveness of misoprostol 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) is complex due to the variety of study designs, populations studied, routes of administration and co-interventions, the exceptionally high incidence of hyperpyrexia in Ecuador.</td>
<td>Pooled estimates; Important differences in the four low-resource trials discussed; exclusion criteria and temporal trends not discussed; importance of side-effects noted.</td>
</tr>
<tr>
<td>Olefie et al. (2013)</td>
<td>Misoprostol for prevention and treatment of postpartum haemorrhage: A systematic review</td>
<td>3 RCTs comparing misoprostol to placebo or no treatment for the prevention of PPH in the population of low-risk women</td>
<td>Mixed; low-resource setting (2), hospital (1)</td>
<td>Misoprostol not more effective than placebo in reducing incidence of blood loss ≥ 500ml</td>
<td>Pooled estimates; High level of heterogeneity.</td>
</tr>
<tr>
<td>Hundley et al. (2013)</td>
<td>Should oral misoprostol be used to prevent postpartum haemorrhage in home birth settings in low resource countries? A systematic review of the evidence.</td>
<td>Misoprostol vs placebo RCTs (2); 4 non-RCTs also included in the meta-analysis</td>
<td>Home and village sub centres</td>
<td>With misoprostol a significant reduction in the incidence of PPH (2 RCTs and 2 non-RCTs; RR = 0.58, 95% CI: 0.38 to 0.87), additional uterotonic (1 RCT and 2 non-RCTs; RR = 0.34, 95% CI: 0.16 to 0.73) and referral for PPH (1 RCT and 2 non-RCTs; RR = 0.49, 95% CI: 0.37 to 0.66) was observed.</td>
<td>Pooled estimates; Heterogeneous studies.</td>
</tr>
<tr>
<td>WHO (2012a)</td>
<td>WHO recommendations for the prevention and treatment of postpartum haemorrhage:</td>
<td>The recommendation on the use of misoprostol by community/lay health workers: No direct evidence available; 12 RCTs, non-</td>
<td>Low resource setting</td>
<td>Efficacy estimate based on one RCT: misoprostol reduced incidence of PPH (RR 0.53; 95% CI 0.39 to 0.66)</td>
<td>The evidence of efficacy based on one RCT assessed as moderate quality; the</td>
</tr>
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</table>
The four key trials used 600μg misoprostol in the intervention arm; three assessed misoprostol alongside components of active management of the third-stage labour (AMTSL), two used expectant management of labour and one allowed birth attendants to choose management practice. The three AMTSL studies showed no significant differences in PPH incidence or referral to higher centres and only one study showed significant decrease in severe PPH using misoprostol. One expectant management study and the choice of management by birth attendants study found significant decreases in PPH incidence with misoprostol. All studies showed significantly increased risk of shivering with misoprostol.

All studies have important shortcomings either due to use of alternative uterotonics in the control arm, confounding management practices, and subjective assessment or, with one exception (Høj et al.; the numbers were very small), exclusion of high-risk women. PPH incidence fell in both the control and intervention groups in both the landmark papers that informed the WHO decision to admit misoprostol to the 17th Essential Medicines List. This suggests factors other than misoprostol use are crucial in determining outcomes. Current evidence does not support misoprostol use in home and community settings in low- and middle-income countries for PPH prevention.

- **Quality of available evidence**

Our assessment of the four low-resource setting RCTs is in line with the quality grading by the WHO Guideline Development Group (GDG)(WHO 2012a). The GDG considered these four RCTs, together with other seven non-randomised and observational studies, as evidence for the use of misoprostol by community or lay health workers. The estimate of misoprostol efficacy was based on one RCT (Derman et al. 2006) graded as moderate quality. The GDG noted that this study “reported too few events related to the impact of misoprostol in severe health outcomes, including severe PPH” and therefore “firm conclusions cannot be drawn from this evidence” (p.14). In addition, misoprostol was administered and deliveries attended by auxiliary nurse-midwives and the results might not be transferable to settings where skilled birth attendants are not available. Thus the evidence to support the administration by community or lay health workers based on this and other studies was graded as very-low quality (WHO 2012b).

The systematic reviews (Table 2) provide additional evidence on the use of misoprostol for PPH prevention. The extrapolation of their estimates of efficacy to low-resource settings where skilled birth attendants and/or oxytocin are not available is however problematic. The systematic reviews typically combine studies with different settings and patient populations, variable designs, and different co-interventions. Reviews considering RCTs conducted in low-resource setting separately reveal important limitations in the evidence in support of misoprostol use (Tunçalp et al. 2012, Hundley et al. 2013, WHO 2012 guidelines). Moreover, none of these systematic reviews paid
attention to exclusion criteria and temporal trends, two critical factors for generalisability of findings to general population in low resource settings.

Exclusion criteria: Most studies excluded women at risk. This requires an effective antenatal screening to assess eligibility for misoprostol. The cost-benefit ratio for low-risk women is however different from the ratio for the general population and the use of misoprostol might not be recommendable.

Temporal trends: Temporal trends were apparent in two low-resource setting RCTs (Derman et al. 2006, Moeen et al. 2011). Authors of both studies concluded that there are important factors other than misoprostol such as training of birth attendants and comprehensiveness of care.

- **Summary of available estimates of comparative effectiveness**

It is not possible to estimate overall efficacy of misoprostol, or it comparative efficacy, due to significant heterogeneity in the study design of existing studies (data on effectiveness are not available).

### 10. Review of harms and toxicity: summary of evidence on safety.

Our concern is with evidence of efficacy and effectiveness but some data on safety and side effects are available from systematic reviews (Tunçalp et al. 2012, Hofmeyr et al. 2013).

**Tunçalp et al.:**

"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.”

(pp.12-13)

"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.” (p.14)

**Hofmeyr et al.:**

(p.12) **Summary of main results**

The number of maternal deaths is too small for meaningful statistical analysis. The range of plausible effects lies between a small (18%) reduction and a large (5.28 times) increase with misoprostol. The outcome ‘death or severe morbidity’ was increased with misoprostol, due to a large increase in hyperpyrexia in dosages of 600 μg or more. When hyperpyrexia was excluded from the definition, there was no difference between groups. As most of these hyperpyrexia events occurred in Ecuador, this may indicate a genetic predisposition. Pyrexia was, as expected, increased with misoprostol and this effect was dose-related.

(pp.11-12) **Primary outcome: Maternal mortality**
There was no statistically significant difference in maternal mortality with misoprostol compared to all control groups (31 studies; 11/19,715 (56/100,000) versus 4/20,076 deaths (20/100,000); risk ratio (RR) 2.08, 95% confidence interval (CI) 0.82 to 5.28; Analysis 1.1), or for any of the comparison subgroups; however, point estimates favoured the comparison groups:

- Misoprostol versus placebo: 10 studies, 6/4626 (130/100,000) versus 1/4707 (21/100,000); RR 2.70; 95% CI 0.72 to 10.11; Analysis 1.1. Most of these deaths occurred in trials of treatment (three studies; 5/851 versus 0/870; RR 6.16; 95% CI 0.75 to 50.85; Analysis 2.1).
- Misoprostol versus other uterotonics: 21 studies, 5/15,089 (3/100,000) versus 3/15,369 (19/100,000); RR 1.54; 95% CI 0.40 to 5.92; Analysis 1.1.

All maternal deaths occurred in studies evaluating misoprostol doses 600 μg versus controls (Analysis 3.1).

Secondary outcomes:

**Maternal death or severe morbidity**

‘Maternal death or severe morbidity’ was significantly higher with misoprostol compared with placebo: 12 studies; 43/5003 (0.86%) versus 24/5082 (0.47%); average RR 1.70, 95% CI 1.02 to 2.81; Tau² = 0, I² = 0%; Analysis 1.2. One study (SATAEV 2010:600SL vs P), contributed most of the morbidity events (41/67 events). When we excluded this study in a sensitivity analysis, there was no longer a statistically significant difference between the misoprostol and placebo groups (11 studies; average RR 1.15, 95% CI 0.51 to 2.57; I² = 0%; Analysis 1.3). There was no statistically significant difference between misoprostol and other uterotonics: 17 studies; average RR 1.50, 95% CI 0.50, 4.52; Tau² = 1.81, I² = 69%, Analysis 1.2; however, there was significant heterogeneity in this subgroup. This was due to the very large effect in one study (EEV 2010:800SL vs U), contributed to by an unusually high rate of hyperpyrexia in one site (58/66 cases occurred in Ecuador).

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

Not relevant, efficacy and effectiveness are the key concern.

Regulatory information

12. Summary of regulatory status of the medicine.

Misoprostol is not approved for PPH prevention by stringent regulatory agencies such as US FDA, EMA.

**US FDA:** Several different products containing misoprostol are registered with the US FDA – Arthrotec, Cytotec, and their generic equivalents; neither of them have regulatory approval for prevention of post-partum haemorrhage or any other maternal health indication (US FDA website, accessed on Dec 2, 2016).

**EMA:** Three products containing misoprostol are currently listed in the EMA register, one in combination with mifepristone approved for medical abortion an two approved for induction of labour (EMA website, accessed on Dec 2, 2016).

In 2014 EMA approved one misoprostol product (Hemoprostol) for the treatment of postpartum haemorrhage for use in countries outside the EU through Article 58. It should be noted that “[t]he company originally presented the results of a study intended to show that Hemoprostol was also
useful in preventing post-partum haemorrhage from developing in the first place, but as the study failed to show benefit the company withdrew its application for this use during the assessment.”

The positive scientific opinion for Hemoprostol [misoprostol], 200 µg, tablet, for the treatment of PPH due to uterine atony in situations where intravenous oxytocin is not available was in accordance with Article 58 of Regulation (EC) No 726/2004 and part of the cooperation between the European Medicines Agency and WHO to evaluate “medicines that are not intended for use in the EU but are needed to prevent or treat diseases of major public health importance around the world” (EMA 2014).

Health Canada: Several misoprostol products registered; none of these for PPH prevention or treatment (Health Canada website, accessed on Dec 2, 2016).

WHO Prequalified products: There are three WHO prequalified misoprostol products (Tablets 200µg); one approved in 2014 and two in 2016 (WHO List of Prequalified Products accessed on Dec 2, 2016).

Developing countries: Misoprostol for prevention and treatment of post-partum haemorrhage has been licensed in several developing countries (Holden 2009). The evidence base of safety and efficacy used for these approvals has not been evaluated to date. In Uganda, the dossier submitted to the National Drug Authority provided evidence on toxicological, quality and stability tests; no pharmacological or clinical trials relevant to the safety and efficacy of misoprostol in management of postpartum haemorrhage were submitted (please see the attached case study). Misoprostol has been added to the National Essential Medicines List of Uganda following the WHO decision.


Not relevant to this application

14. Reference list.


Reviewers’ commentary by Pollock et al.


Appendix: Notes on available systematic reviews

Olefile et al. (2013) – systematic review of RCTs comparing misoprostol to placebo or no treatment for the prevention of PPH in the population of low-risk women. Three RCTs were included in the meta-analysis, two oral misoprostol studies and one sublingual misoprostol; high level of
heterogeneity; the review concluded that “misoprostol does not appear to be more effective than placebo” (the primary outcome was incidence of PPH – blood loss greater or equal to 500ml).

**Tunçalp et al. (2012)** – Cochrane systematic review ‘Prostaglandins for preventing PPH’

misoprostol vs placebo or no treatment – 11 RCTs included (authors concluded: 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).)

- oral (21 RCTs) and sublingual (8 RCTs) misoprostol vs injectable uterotonic
- plus a section on the concurrent use of misoprostol and oxytocin vs conventional uterotonic
- four low-resource setting trials discussed separately (Gambia 2005; Guinea-Bissau 2005; India 2006c; Pakistan 2011), their setting and limitations summarised [BUT temporal trends in Mboeen and Derman study not discussed]

**Authors’ conclusion:** “…Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonic 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.”

**Hofmeyr et al. (2013)** – Cochrane systematic review ‘Postpartum misoprostol for preventing maternal mortality and morbidity’

Reviewed maternal deaths and severe morbidity in all randomised trials of misoprostol for prevention or treatment of PPH: 78 studies (59,216 women) included [71 postpartum haemorrhage (PPH) prevention studies and seven PPH treatment studies; 68 studies were conducted in women who underwent vaginal birth and 10 were conducted in women who underwent caesarean section. Misoprostol was compared to placebo (23), no additional treatment (2), other uterotonic agents (51) or uterotonic and placebo (2), at doses ranging from 50 μg to 1000 μg, via oral (35), sublingual (22), buccal (2), rectal (19), vaginal (1) and intrauterine routes (1).]

“There was no statistically significant difference in maternal mortality for misoprostol compared with control groups overall (31 studies; 11/19,715 versus 4/20,076 deaths; risk ratio (RR) 2.08, 95% confidence interval (CI) 0.82 to 5.28); or for the trials of misoprostol versus placebo: 10 studies, 6/4626 versus 1/4707 ; RR 2.70; 95% CI 0.72 to 10.11; or for misoprostol versus other uterotonic: 21 studies, 5/15,089 versus 3/15,369 (19/100,000); RR 1.54; 95% CI 0.40 to 5.92. All 11 deaths in the misoprostol arms occurred in studies of misoprostol _600 μg.

There was a statistically significant difference in the composite outcome ‘maternal death or severe morbidity’ for the comparison of misoprostol versus placebo (12 studies; average RR 1.70, 95% CI 1.02 to 2.81; Tau² = 0.00, I² = 0%) but not for the comparison of misoprostol versus other uterotonic (17 studies; average RR 1.50, 95% CI 0.50 to 4.52; Tau² = 1.81, I² = 69%). When we excluded hyperpyrexia from the composite outcome in exploratory analyses, there was no significant difference in either of these comparisons.

Pyrexia > 38°C was increased with misoprostol compared with controls (56 studies, 2776/25,647 (10.8%) versus 614/26,800 (2.3%); average RR 3.97, 95% CI 3.13 to 5.04; Tau² = 0.47, I² = 80%). The
The effect was greater for trials using misoprostol 600 μg or more (27 studies; 2197/17,864 (12.3%) versus 422/18,161 (2.3%); average RR 4.64; 95% CI 3.33 to 6.46; Tau² = 0.51, I² = 86%) than for those using misoprostol 400 μg or less (31 studies; 525/6751 (7.8%) versus 185/7668 (2.4%); average RR 3.07; 95% CI 2.25 to 4.18; Tau² = 0.29, I² = 58%).

Limitations: “The variety of study designs, populations studied, routes of administration and co-interventions, as well as the exceptionally high incidence of hyperpyrexia in Ecuador were limiting factors. “

Gizzo et al. (2013) – systematic review to provide an “Overview on all available uterotonics for PPH prevention to clarify indications and contraindications in choice among drugs”
- search limited to the 2007-2012 period; 9 studies included (three of these compared misoprostol to other uterotonics or placebo: one study found 400 and 600 mcg misoprostol more effective in reducing blood loss (less than 200ml in all arms) than 5 IU oxytocin; one study showed sublingual 400 mcg misoprostol as effective as 10 IU oxytocin IM (blood loss less than 200ml); one study showed small but insignificant improvement in PPH (blood loss more than 500 and 1000ml) with 400mcg sublingual misoprostol compared to placebo
- none of misoprostol studies conducted in low-resource setting included; despite this the authors stated in the abstract that “Oxytocin is the first choice for PPH prophylaxis. Ergot alkaloids, syntometrine, and prostaglandins are second-line uterotonics. Misoprostol is not effective as oxytocin but it may be used when the latter is not available.”

Hundley et al. (2013) ‘Should oral misoprostol be used to prevent postpartum haemorrhage in home birth settings in low resource countries? A systematic review of the evidence’
Systematic review and meta-analysis of placebo controlled misoprostol RCTs and non-RCTs conducted in low resource settings. Two RCTs (Derman et al. 2006 and Moeeen et al. 2011 graded as high-quality studies; exclusion criteria and temporal trends affecting generalizability were not considered.

Tan et al. (2016) ‘Misoprostol versus ergometrine-oxytocin for preventing postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials’
Six RCTs conducted in hospital setting between 1998 and 2009 were included