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

Misoprostol was included in the WHO Model List of Essential Medicines in 2011 for prevention of postpartum haemorrhage (PPH). The WHO Expert committee’s recommendation specifically referred to situations “where oxytocin is not available or cannot be safely used”. Misoprostol is seen as a potential solution to maternal mortality due to PPH in low-resource settings of low- and middle-income countries but the evidence on the use of misoprostol in such settings is very limited and weak. 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 all current published evidence using WHO’s own criteria.

Reasons for the removal:

- 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
- WHO recommendations via EML and treatment guidelines are a critical factor for medicines policy changes in low- and middle-income countries that lack capacities to evaluate the clinical evidence and potential impact of medicines in their particular country context
- In 2011 the Expert Committee rejected the application for addition of misoprostol for PPH treatment to the WHO EML on the grounds that it could divert resources from making oxytocin available. It is not clear why the same reasoning should not be applied to misoprostol for PPH.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

We had several discussions with Dr. Weerasuriya (former secretary of the Expert Committee on Selection and Use of Essential Medicines) and Dr. Richard Laing who encouraged us to apply again.

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

None

4. International Nonproprietary Name (INN, generic name) of the medicine

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

We request the Expert Committee to delete the following clause: “, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used” from the Section 22.1 Oxytocics in the 19th edition of WHO Model List of Essential Medicines.

6. International availability - sources, of possible manufacturers and trade names

Widely available, approved for other indications – not relevant

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Currently listed as an individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Not relevant as the drug has not been shown to be efficacious (see point 10 below).

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. Our recent research in Uganda shows that misoprostol is replacing oxytocin even in settings with fair capacities to enable oxytocin use, health care providers lack training and guidelines on misoprostol use are not available in health care centres (see the attached Uganda case study; the study has not been published so please do not put on the website until it is published).

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

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

1. oxytocin (Strong recommendation, moderate-quality evidence);
2. other injectable uterotonic s (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.

10. Summary of comparative effectiveness in a variety of clinical settings:

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 studies make conclusions about the use of misoprostol for PPH prevention in low resource setting despite focusing on the use of uterotonic s 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)

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 before November 2011 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. Of the 172 studies only six matched the inclusion criteria. The critical review of these studies was published in 2012 (Chu et al. 2012).

We updated the search for the November 2011 – 12 November 2014 period. No further RCTs conducted in low-resource setting of low- and middle-income countries were identified. The search identified five systematic reviews: Tunçalp et al. (2012), Hofmeyr et al. (2013), Olefile et al. (2013), Gizzo et al. (2013), Hundley et al. (2013). The most recent WHO guidelines for prevention and treatment of postpartum haemorrhage were published in 2012 (WHO 2012a). The sources referenced in the identified studies were checked for further clinical studies.

• 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 as no additional RCT conducted in this particular setting have been published recently. In Table 1 we summarise the four RCTs and Table 2 summarises relevant systematic reviews.

Table 1: Summary of identified RCTs in low-resource setting of low- and middle-income countries

<table>
<thead>
<tr>
<th>Study Country</th>
<th>Patients number</th>
<th>Risk status</th>
<th>Intervention</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 Ergometrine 2mg PO</td>
<td>TTBA Controlled cord traction, delayed cord cutting</td>
<td>&gt;500mL RR 0.91 (0.67-1.24) NS &gt;1000mL RR 0.48 (0.09-2.59) NS</td>
<td>Shivering RR 2.74 (2.14-3.52) Vomiting RR 0.5 (0.29-0.88) too few outcomes, not powered sufficiently</td>
</tr>
<tr>
<td>Høj et al. (2005) Guinea-Bissau</td>
<td>661 (661)</td>
<td>Low and high risk</td>
<td>Misoprostol 600 µg SL Placebo</td>
<td>ANM Controlled cord traction and cord clamp &amp; cut at delivery</td>
<td>&gt;500mL RR 0.89 (0.76-1.04) NS &gt;1000mL RR 0.66 (0.45-0.98)</td>
<td>Shivering RR 2.43 (1.96-3.01) Fever RR 7.09 (3.84-13.1) Unusually high incidence of severe PPH in a trial with AMTSL; small study, general patient population; effective in reducing incidence of severe blood loss where skilled birth attendants performing AMTSL; health centre</td>
</tr>
<tr>
<td>Derman et al. (2006)</td>
<td>1616</td>
<td>Low risk</td>
<td>Misoprostol 600 µg PO</td>
<td>ANM</td>
<td>&gt;500mL RR 0.53 (0.39-0.72) Shivering, Miso 52.2%</td>
<td>Incidence of PPH decreased in both</td>
</tr>
</tbody>
</table>
Table 2: Summary of identified systematic reviews published in the 2011-2014 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>Tunçalp et al. (2012)</td>
<td>Prostaglandins for preventing PPH</td>
<td>- misoprostol vs placebo (11) or no treatment</td>
<td>Mixed, mainly hospital setting; 4 RCTs in low-resource settings discussed separately</td>
<td>“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)”</td>
<td>Outcomes reported for mixed (hospital and low-resource settings) groups of RCTs; 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>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)</td>
<td>Mixed</td>
<td>“...no statistically significant difference in maternal mortality with misoprostol compared to all control groups (31 studies), or for any of the comparison subgroups; however, point estimates favoured the comparison groups” “a statistically significant difference in the composite outcome ‘maternal death or severe morbidity’ for the comparison of misoprostol versus placebo (12 studies) but not for the comparison of misoprostol versus other uterotonics (17 studies)”</td>
<td>Pooled estimates; Limitations reported: The variety of study designs, populations studied, routes of administration and co-interventions, the exceptionally high incidence of hyperpyrexia in Ecuador”</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Design</td>
<td>Results</td>
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<tr>
<td>Olefile 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>Misoprostol not more effective than placebo in reducing incidence of blood loss ≥ 500ml</td>
<td></td>
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<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>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 uterotonics (1 RCT and 2 non-RCTs; RR = 0.34, 95% CI: 0.16 to 0.73) 60 and referral for PPH (1 RCT and 2 non-RCTs; RR = 0.49, 95% CI: 0.37 to 0.66)</td>
<td></td>
<td></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-randomised and observational studies considered</td>
<td>Efficacy estimate based on one RCT: misoprostol reduced incidence of PPH (RR 0.53; 95% CI 0.39 to 0.74), and severe PPH (RR 0.2; 95% CI 0.04 to 0.91) compared to placebo</td>
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</table>

Note: Gizzo et al. study is not summarised here as it only included misoprostol RCTs conducted in hospitals (see Appendix for details).

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 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.

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).

11. **Summary of comparative evidence on safety:**

- **Estimate of total patient exposure to date** Description of the adverse effects/reactions and estimates of their frequency

- **Identification of variation in safety that may relate to health systems and patient factors**

- **Summary of comparative safety against comparators**

Our concern is with evidence of 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 2010:600SLvs 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 vsU), contributed to by an unusually high rate of hyperpyrexia in one site (58/66 cases occurred in Ecuador).

12. 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.
• range of costs of the proposed medicine

• resource use and comparative cost-effectiveness presented as range of cost per routine outcome

13. Summary of regulatory status of the medicine (in various countries)

Misoprostol is not approved for PPH prevention by stringent regulatory agencies such as US FDA, UK MHRA or 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 November 12, 2014).

UK MHRA: The MHRA register of authorised products lists 25 different products containing misoprostol. Four of these are approved for maternal health indications: Medabon, Mifegyne and Topogyne for medical termination of pregnancy and Mysodelle for labor induction (MHRA website, accessed on November 12, 2014).

EMA: In 2014 EMA approved misoprostol for the treatment of postpartum haemorrhage. 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).

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

15. Proposed (new/adapted) text that could be included in a revised WHO Model Formulary

We request the Committee delete the following clause: “, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used” from the Section 22.1 Oxytocics in the 19th WHO Model List of Essential Medicines.

The adapted formulation of the relevant section:
Section 22.1 Oxytocics

**Tablet:** 200 micrograms.*
* For management of incomplete abortion and miscarriage.

**Vaginal tablet:** 25 micrograms.*
* Only for use for induction of labour where appropriate facilities are available.

References:


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
- 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 Moeen and Derman study not discussed]

**Authors’ conclusion:** “...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.”

**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 uterotonics 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%
confident 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; \( \tau^2 = 0.00, I^2 = 0\% \)) but not for the comparison of misoprostol versus other uterotonic (17 studies; average RR 1.50, 95% CI 0.50 to 4.52; \( \tau^2 = 1.81, I^2 = 69\% \)). 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; \( \tau^2 = 0.47, I^2 = 80\% \)). 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; \( \tau^2 = 0.51, I^2 = 86\% \)) 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; \( \tau^2 = 0.29, I^2 = 58\% \)).

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 uterotonic 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 mg 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 uterotonic agents. 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 Mobeen et al. 2011 graded as high-quality studies; exclusion criteria and temporal trends affecting generalizability were not considered.