Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
written by Saloni Tanna, Pharm.D; MPH

Background Paper 6.16
Postpartum Haemorrhage

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## Abbreviations

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<th>Description</th>
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<tr>
<td>ACOC</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>AMTSL</td>
<td>Active Management of the Third Stage of Labor</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability Adjusted Life Years</td>
</tr>
<tr>
<td>EML</td>
<td>Essential Medicines List</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecologists and Obstetricians</td>
</tr>
<tr>
<td>ICM</td>
<td>International Confederation of Midwives</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LMICs</td>
<td>Low and Middle Income Countries</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goals</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology</td>
</tr>
<tr>
<td>PPH</td>
<td>Postpartum Haemorrhage</td>
</tr>
<tr>
<td>RCOG</td>
<td>Royal College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>rVIIa</td>
<td>Recombinant Factor VIIa</td>
</tr>
<tr>
<td>TTI</td>
<td>Temperature-Time Indicator</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food and Drugs Administration</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

Introduction
This paper is an update of the 2004 background paper on postpartum haemorrhage (PPH) (http://archives.who.int/prioritymeds/report/index.htm) for the Priority Medicines for Europe and the World report. The paper discusses causes and the burden of PPH, which is the leading cause of maternal mortality, assesses the current treatment options available for PPH, as well as the treatments under development and makes recommendations on future research opportunities.

The burden of postpartum haemorrhage
The World Health Organization (WHO) defines PPH as “blood loss greater than or equal to 500 ml within 24 hours after birth”, and severe primary PPH as “blood loss greater than or equal to 1000 ml within 24 hours.”. Postpartum haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. About 14 million women around the world suffer from PPH every year (26 women every minute). The vast majority of these deaths occur in low and middle-income countries (LMICs). Yet, recent studies have shown increasing incidence of PPH in developed countries as well.

Diagnosis and Management of PPH
The most common symptoms of PPH include uncontrolled bleeding, decreased blood pressure, increased heart rate, decreased red blood cell count, and swelling and pain in tissues in the vaginal and perineal area. Postpartum haemorrhage can be managed by medical, non-medical and surgical interventions. The WHO and other professional bodies recommend active management of the third stage of labor (AMTSL) for all vaginal births. Active management of the third stage of labor involves a prophylactic administration of uterotonics before delivery of the placenta in addition to other non-pharmacological interventions, such as late cord clamping and controlled cord traction of the umbilical cord (in settings where skilled birth attendants are available).

Medicines for managing PPH (uterotonic medicines)
In 2004, oxytocin with or without supplemental ergometrine, ergometrine alone, 15-methyl prostaglandin F2 α, and misoprostol were the uterotonics of choice in AMSTL. In addition to the above medicines, the 2009 and 2012 WHO guidelines for managing PPH mentioned carbetocin, recombinant factor VIIa and tranexamic acid as possible therapeutic interventions for PPH.

Oxytocin and ergometrine are unstable at room temperature and thus require special temperature and light storage conditions to remain effective. Additionally, both medicines must be administered parenterally, requiring trained personnel to administer them. Compared to oxytocin ergometrine has more severe side effects: hypertension, coronary vasospasms, increased systemic vascular resistance, pulmonary edema, intracranial haemorrhage and seizures, and retinal detachment. For these reasons, ergometrine was removed from the WHO Model List of Essential Medicines, making oxytocin is the most
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effective intervention for the prevention or treatment of PPH and therefore the recommended first line treatment. Some studies are on-going to produce heat stable oxytocin formulations.13,14 One example is Uniject, an oxytocin device to ensure safer and accurate dosage of oxytocin, has been developed with a temperature – time – indicator (TTI) to monitor the quality of the product in transit and storage.15 However, this technology is yet to be deployed on a large scale.

As of 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL. Recent studies indicate that where other agents are not available, misoprostol may be effective in preventing and treating PPH without the side effects associated with other uterotonic drugs.16 Furthermore, misoprostol is relatively stable at room temperature, has a long shelf life, and can be given orally – all of which are advantages over currently available uterotonic drugs.16,17 According to the 2012 WHO guidelines, misoprostol may be used in situations where the use of oxytocin is not possible.1

Tranexamic acid is an antifibrinolytic agent used in surgery to reduce blood loss. Based on research studies, the WHO recommended that tranexamic acid may be offered as a treatment for PPH as a fourth alternative or if the bleeding may be partly due to trauma.1,9

Non-medical interventions for management of PPH

The 2012 WHO recommendations for the management of PPH recommends the following non pharmacological interventions for managing PPH: uterine massage, bimanual uterine compression, intrauterine balloon or condom tamponade, external aortic compression, uterine artery embolization, and non-pneumatic anti-shock garments.1,9

Opportunities for further research

While substantial progress has been towards improving on the existing interventions for managing PPH, more research studies are needed to make these improvements and ultimately available for therapeutic use. Areas in which further research studies are needed include: the development of a heat stable oxytocin; scaling up the use of oxytocin-Uniject with the TTI in low resource settings, in tandem with adequate post marketing pharmacovigilance; establishing the standard, safe and effective dose of sublingual misoprostol for treating PPH; exploring the potential of tranexamic acid in treating PPH; exploring the possible benefits of carbetocin in treating PPH in women with pre-eclampsia; and operational research to determine the effectiveness of these interventions at the community level.16,18,19,20

Conclusion

Postpartum haemorrhage still remains the leading cause of maternal mortality. Though the burden of PPH is highest in developing countries, the incidence of PPH is increasing in developed nations. Current preventive and treatment interventions are inadequate and inequitably distributed. More research is needed to develop new interventions in order to improve on existing interventions and also to ensure that existing and new technologies can be used and are equitably available in rural areas.
1. Introduction

This paper is an update of the 2004 background paper on postpartum haemorrhage (PPH) (http://archives.who.int/prioritymeds/report/index.htm) for the Priority Medicines for Europe and the World report. The paper discusses causes and the burden of PPH, assesses the current treatment options available for PPH as well as the treatments under development, and makes recommendations on future research opportunities. This revised paper serves as a background paper on PPH for the second edition of the Priority Medicines for Europe and the World Report of 2013. While maternal mortality accounted for about 287 000 deaths in 2010, these deaths disproportionately impact the life and health of the affected families.

2. Definition and etiology of PPH

Postpartum haemorrhage (PPH) can be classified as primary (early) or secondary (late). Primary PPH, the most common and severe, occurs within the first 24 hours after delivery. Secondary PPH occurs 24 hours to 12 weeks after delivery. Most cases of morbidity and mortality due to PPH are the result of primary PPH, while secondary PPH results from retained placental fragments, subinvolution of the placental site, infection, and coagulation defects (bleeding diatheses) which cause abnormal excessive bleeding.\textsuperscript{1,7,12} The World Health Organization (WHO) defines PPH as “blood loss greater than or equal to 500 ml within 24 hours after birth”, and severe PPH as “blood loss greater than or equal to 1 000 ml within 24 hours”.\textsuperscript{1,9} This is the most common definition of PPH as the definition for PPH may not be uniform across countries. For example, the United States and Canada define PPH as blood loss of 500 ml for a vaginal delivery and 1 000 ml for a caesarean birth, while in Australia PPH refers to blood loss of 500 ml for a vaginal delivery and 750 ml for a caesarean delivery.\textsuperscript{5} The usefulness in measuring blood loss in managing PPH is not clear. Firstly, it is difficult to accurately estimate blood loss routinely. Secondly, blood loss less than 500 ml in women who are already anaemic may be serious and may require treatment interventions.\textsuperscript{1,7} It has also been shown that many women lose enough blood in otherwise normal deliveries to meet the diagnostic criteria for PPH.\textsuperscript{12,21,22} The 2009 WHO guidelines for the management of PPH conclude that there is not enough evidence to recommend quantification of blood loss over clinical estimation of PPH.\textsuperscript{1}

Bleeding during and after the third stage of labor may result from uterine atony (failure of the uterus to contract properly after delivery), trauma (cervical, vaginal, or perineal lacerations), retained or adherent placental tissue, clotting disorders, and inverted or ruptured uterus.\textsuperscript{7,12} About 75 to 90\% of PPH cases are caused by uterine atony.

The risk factors for PPH are listed in Table 6.16.1. Though some women are at greater risk for postpartum haemorrhage compared to others, two out of three women with PPH had no risk factors before delivery.\textsuperscript{1} Postpartum haemorrhage often comes unexpectedly and caregivers must promptly diagnose and treat it.
Table 6.16.1 Risk Factors for Uterine Atony 17:12

<table>
<thead>
<tr>
<th>Risk factors for postpartum haemorrhage</th>
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<tbody>
<tr>
<td>Prolonged labor</td>
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<tr>
<td>Retained placenta products</td>
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<tr>
<td>Chorioamnionitis</td>
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<tr>
<td>Oxytocin used in labor</td>
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<td>Chorioamnionitis</td>
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<td>Retained placenta products</td>
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<tr>
<td>Oxytocin used in labor</td>
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<tr>
<td>Preeclampsia/eclampsia</td>
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<tr>
<td>Multiple gestation</td>
</tr>
<tr>
<td>Hydroamnios</td>
</tr>
<tr>
<td>Halogenated anesthesia</td>
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<tr>
<td>Previous episode of uterine atony</td>
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<tr>
<td>Increasing maternal</td>
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<tr>
<td>Obesity and raised Body Mass Index</td>
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<tr>
<td>Caesarian delivery and induction of labor</td>
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</table>


3. The burden of PPH

Haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. About 14 million women around the world suffer from PPH every year translating to 26 women every minute. Though maternal deaths and maternal mortality ratio (MMR) have decreased globally from 543 000 and 400 per 100 000 live births to 287 000 and 210 per 100 000 live births respectively between 1990 and 2010, developing countries continue to experience very higher numbers of maternal deaths. In 2010, the MMR in developing countries was 240 per 100 000 (284 000 maternal deaths) compared to 16 (2 200 maternal deaths) in developed countries. Thirty-five countries have been noted as either making insufficient progress or not making any progress at all towards achieving the Fifth Millennium Development Goal (MDG5), which aims to reduce maternal mortality rate by 75% from 2000 to 2015. To reduce MMR and achieve MDG 5, it is important to drastically reduce PPH, the leading cause of maternal mortality.

Table 6.16.2 summarizes the statistics on the global burden of PPH. The incidence of PPH among countries ranges from 0.55% to 17.5% of deliveries with 60% of all maternal deaths occurring during the postpartum period of which 45% in the first 24 hours after delivery. According to the 2005 World Health Report which focused on maternal and child health, the incidence of PPH was 10.5% of live births with about 13.8 million PPH cases per year. The case fatality rate of PPH was 1% with a DALY (Disability Adjusted Life Years) of 4.4 million. Table 6.16.1 above shows the major obstetric complications and their contributions to maternal deaths.
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<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (% of live births)</th>
<th>Cases</th>
<th>Case fatality rate</th>
<th>Maternal deaths (2000)</th>
<th>Main sequelae</th>
<th>DALYs lost (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH</td>
<td>10.5</td>
<td>13 795 000</td>
<td>1.0</td>
<td>132 000</td>
<td>Severe anemia</td>
<td>4,418</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4.4</td>
<td>5 768 000</td>
<td>1.3</td>
<td>79 000</td>
<td>Infertility</td>
<td>6,901</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia</td>
<td>3.2</td>
<td>4 152 000</td>
<td>1.7</td>
<td>63 000</td>
<td>Eclampsia</td>
<td>2,231</td>
</tr>
<tr>
<td>Obstructed labor</td>
<td>4.6</td>
<td>6 038 000</td>
<td>0.7</td>
<td>42 000</td>
<td>Urinary incontinence, Fistula</td>
<td>2,951</td>
</tr>
<tr>
<td>Abortion</td>
<td>14.8</td>
<td>19 340 000</td>
<td>0.3</td>
<td>63 000</td>
<td>Infertility</td>
<td></td>
</tr>
</tbody>
</table>


About 99% of deaths from PPH occur in low and middle income countries (LMICs) compared with 1% in industrialized nations.12 The risk of maternal mortality from haemorrhage is 100 per 100 000 live births in developing countries accounting for one-third of all maternal deaths in Africa and Asia. The risk of maternal mortality in developed countries is 1 per 100 000 live births, or 100 times less compared to the risk in LMICs.12 Women who survive severe PPH are more likely to die in the year following PPH.7,26 Kaye et al. conducted a systematic review of the magnitude and case fatality ratio for severe maternal morbidity in sub-Saharan Africa between 1995 and 2010 using twelve studies with sample sizes ranging from 557 to 23 026 participants. The review found that the incidence of haemorrhage ranged from 0.06% to 3.05%, while the case fatality ratio for haemorrhage ranged from 2.8% to 27.3%.27

While PPH seems to be most devastating in developing countries, recent studies have shown increasing incidence of PPH in developed countries. A population based retrospective cohort study among 650 000 childbirth hospitalizations between 1999 and 2009 in Ireland showed that the overall rate of PPH increased from 1.5% to about 4% during that time period.28 Atonic PPH increased from 1% to 3.4%. Another review by the International Postpartum Haemorrhage Collaborative Group found an increase in the incidence and the severity of adverse outcomes of PPH in Australia, Canada, the UK, and the United States.5 The increase in incidence of PPH in Australia, Canada and the USA were mainly limited to atonic PPH. These findings are consistent with findings from a population-based study in the USA by Callaghan et al. The study showed that PPH increased 26% between 1994 and 2006 from about 2% (n = 85,954) to almost 3% (n = 124,708; p< 0.001) primarily due to an increase in uterine atony.4 This increase observed in PPH could not be explained by changes in rates of cesarean delivery, vaginal birth after cesarean delivery, maternal age, multiple birth, hypertension, or diabetes mellitus. The risk of death from obstetric haemorrhage in the USA has remained at 7.7 per 100 000 deliveries, with haemorrhage as the lethal cause in 13%-30% of all cases.29
4. Diagnosis and Management of PPH

The symptoms and signs of PPH may vary from women to women including uncontrolled bleeding, decreased blood pressure, increased heart rate, decreased red blood cell count (hematocrit), and swelling and pain in tissues in the vaginal and perineal area.

Postpartum haemorrhage is managed by medical, non-medical and surgical interventions. There are two approaches to the clinical management of the third stage labor (the period from the birth of the child until the placenta is delivered): expectant and active management. Expectant management involves allowing the placenta to deliver spontaneously or aiding by gravity, maternal effort or nipple stimulation. Uterotonic agents are given only if there is excessive bleeding, and the cord is clamped later. Active management of third stage of labor involves a prophylactic administration of uterotonics before delivery of the placenta, late cord clamping, and controlled cord traction (in settings where skilled birth attendants are available). These procedures enable the uterus to contract immediately, decreasing the amount of time necessary to deliver the placenta. More recently, Begley et al. discussed a third method of clinical management of the third stage of labor called the mixed management (also known as ‘combined’ or ‘piecemeal’ management). This consists of the use of some of the components of both active and expectant management.

In a paper by Prendiville et al. in 2000 the advantages of AMSTL were described as substantially decreasing the following signs and symptoms:

- Incidence of PPH due to an atonic uterus by about 60%
- Length of the third stage of labor
- Need for additional drugs to treat excessive bleeding by about 70%
- Need for a blood transfusion
- Need for surgical intervention
- Incidence of anaemia and other problems associated with excessive blood loss

The Prendiville study has since been withdrawn. However, a 2011 systemic review of Cochrane Pregnancy and Childbirth Group Trials Register by Begley et al confirmed most of the above advantages of AMSTL. The review which compared the effectiveness of active and expectant management of third stage labor in women expecting vaginal delivery in hospitals yielded seven randomized and quasi-randomized controlled trials (RCTs), six in high-income countries and one in low-income countries, all involving 8247 women. Four studies compared active with expectant management, while three compared active management with a mixed management. The findings of this review are:

1. Among women at mixed levels of risk of bleeding, active management showed a reduction in the average risk of maternal primary haemorrhage of more than 1000 ml at time of birth (risk ratio (RR): 0.34, 95% confidence interval (CI): 0.14 to 0.87). The risk of maternal hemoglobin falling below 9 g/dl after birth was also reduced (average RR 0.50, 95% CI: 0.30 to 0.83, two studies, 1 572 women).

2. There were significant decreases in primary blood loss greater than 500 ml and mean maternal blood loss at birth, as well as the need for maternal blood transfusion and the use of uterotonics during the third stage or within the first 24 hours or both.
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3. Significant increases in maternal diastolic blood pressure, vomiting after birth, after-pains, and use of analgesia from birth up to discharge from the labor ward were observed with active management. Also, the number of women returning to hospital with bleeding increased.

4. There was a decrease in the baby’s birth weight with active management, which the authors attributed to lower blood volume as a result of interference with placental transfusion due to early cord clamping.

5. There was no significant difference in the length of the third stage of labor compared to AMTSL and expectant management.

6. Among women at low risk of excessive bleeding, there were similar findings, except that at 24 to 72 hours, there was no significant difference between groups for severe haemorrhage or maternal haemorrhage less than 9 g/dl.

7. The authors could not draw any firm conclusions about the differences in outcome between mixed management and active management of the third stage of labor.

The WHO, International Federation of Gynecologists and Obstetricians (FIGO) and the International Confederation of Midwives (ICM) recommend that skilled birth attendants provide AMTSL for all vaginal births. Where skilled birth attendants are not available to provide all of the components of AMTSL, FIGO and ICM recommend that oxytocin (10 IU) or misoprostol (400-600 µg orally) should be given by a trained health worker. Oxytocin is preferred to other uterotonic drugs because it is effective 2–3 minutes after injection with relatively minimal secondary effects. It is important to note that although AMTSL reduces postpartum blood loss, about 3 to 16.5% of women will still go on to experience PPH and will require treatment.

5. Medicines for managing PPH

Active management using standard uterotonic drugs can reduce both PPH incidence and maternal mortality by 40%. In 2004, oxytocin with or without supplemental ergometrine (methergine), ergometrine alone, 15-methyl prostaglandin F2α, and misoprostol were the uterotonics of choice in AMTSL. In addition to the above medicines, the 2009 and the 2012 WHO guidelines for managing PPH mentioned carbetocin, recombinant factor VIIa and tranexamic acid as possible therapeutic interventions for PPH.

The following sections discuss the effectiveness and limitations of each of these medicines as well as recent research studies to overcome their limitations.

5.1 Oxytocin

Oxytocin is a hormone used to help start or continue labor and to control bleeding after delivery. It is also sometimes used to help milk secretion in breast feeding. Other indications for oxytocin include diabetes insipidus and vasodilatory shock.
Oxytocin is therapeutically available in the following dosage forms:

- **Nasal** solution which is indicated for increasing milk production in breast feeding (not indicated for PPH)
- **Parenteral** injection which is indicated for preventing and treating PPH. There is limited evidence on the comparative effectiveness of intravenous (IV) and intramuscular (IM) oxytocin. In a systemic review of the December 2011 Cochrane Pregnancy and Childbirth Group’s Trials Register by Oladapo et al., no RCTs were found on the comparative effectiveness and safety of IV and IM oxytocin in the prevention of PPH after vaginal delivery.

Administering oxytocin immediately after childbirth is the single most important intervention used to prevent PPH. Women given oxytocin lose less blood, resulting in a decreased incidence of PPH and anaemia. Oxytocin also allows for a faster delivery of placenta minimizing the need for manual removal of the placenta and the associated pain and risks of infections. The timing of oxytocin administration is critical; it is most effective when administered within one minute after the birth of the baby. Waiting to give oxytocin until after the placenta is delivered may increase the woman’s risk of uncontrolled bleeding.

Despite the usefulness of oxytocin in both preventing and treating PPH, the medicine has some limitations. First as a neuropeptide, oxytocin is unstable at room temperature when kept for more than three months. Parenteral and solid formulations degrade rapidly during storage under tropical conditions (of temperature above 30°C) and high humidity. A WHO study published in 1994 evaluated the stability of oral formulations of oxytocics in tropical climates. The medicines (oral ergometrine, oral methylergometrine, buccal oxytocin and buccal desamino-oxytocin) were exposed to artificially-regulated tropical conditions of temperature ranging between 6-40°C and relative humidity between 20-85%. None of the oral oxytocics including oxytocin were found to be stable under the simulated conditions. Oxytocin thus requires special temperature and light storage conditions to remain effective. Additionally, oxytocin preparations must be administered parenterally to prevent PPH. This requires trained personnel. In many settings, lack of trained personnel undermines the potential for implementing the active management of third-stage labor using oxytocin.

Moreover, there are some adverse reactions associated with the use of oxytocin. Oxytocin causes contractions of the uterus. In women who are unusually sensitive to its effects, these contractions may become too strong. In rare cases, this may lead to tearing of the uterus. Oxytocin has been reported to cause irregular heartbeat and increase bleeding after delivery in some women. It has also been reported to cause jaundice in some newborn infants. Other side effects include: confusion, convulsions (seizures), difficulty in breathing; dizziness, fast or irregular heartbeat, headache (continuing or severe), hives, severe pelvic or abdominal pain, skin rash or itching, vaginal bleeding (increased or continuing), weakness, rapid weight gain, nausea, and vomiting. However, some of these side effects are rare and do not happen when oxytocin is used for PPH prevention and treatment.

The expertise and extensive monitoring required to administer oxytocin parenterally, the adverse effects associated with the medicine, and the specific storage requirements of oxytocic agents are barriers to the effective use of these drugs in many countries. Some studies are on-going to produce heat stable oxytocin formulations. The oxytocin-Uniject, a device to ensure safer and accurate dosage of oxytocin has also been developed with a
Temperature Time Indicator (TTI) to monitor the quality of the product in transit and storage. These strategies are discussed in detail below.\textsuperscript{15,34}

The development of heat stable oxytocin

Avanti et al. demonstrated that divalent metal ions Calcium (Ca$^{2+}$), Magnesium (Mg$^{2+}$), or Zinc (Zn$^{2+}$) in combination with a citrate buffer greatly improved the stability of oxytocin in aqueous solutions.\textsuperscript{14} Their study showed the recovery and remaining percentage of oxytocin increased by 80\% in the presence of 50 mM Ca$^{2+}$ and 90\% in the presence of 50 mM Mg$^{2+}$ when these preparations were kept for six months at 40$^\circ$C. Zinc ions were found to have higher impact on improving the stability of oxytocin at lower concentrations compared to Mg$^{2+}$ and Ca$^{2+}$ ions. A 10 mM Zn$^{2+}$ ions in citrate buffer exerted the same effect on oxytocin stability as combinations of citrate buffer and 50 mM magnesium ions, indicating that zinc ion is a better stabilizer of oxytocin.

Avanti et al. are conducting follow-up studies to identify various degradation products and understand the degradation pathways of oxytocin.\textsuperscript{13} The aim of these follow-up studies is to develop oxytocin formulations that will be stable (yield greater than 90\% recovery) after one year. Though some progress has been made towards a heat stable oxytocin formulation, the fact still remains that there is currently no heat stable oxytocin formulation for therapeutic use. Further research is needed to make these discoveries useful to patients.

Oxytocin in Uniject

Intramuscular or intravenous oxytocin is the preferred uterotonic for AMTSL, in order to prevent postpartum haemorrhage.\textsuperscript{1,7} However, in many low-resource settings, safe injection is not always possible due to the need for injection skills and training, lack of sterile equipment, and difficulty measuring the correct dose of oxytocin. To overcome these barriers to safe injection, the Program for Appropriate Technology in Health (PATH) developed the Uniject device for safer oxytocin administration.\textsuperscript{15} The device comes as a single dose, individually packed prefilled, non-refillable, sterile injection, which is easy to use, with a fixed needle that can be "activated" for use after opening the sterile packet. The Uniject device is not new to public health interventions. It has been used to administer tetanus toxoid to pregnant women in Bolivia, Indonesia, and Mali and to deliver Cyclofem (a monthly injectable contraceptive) to women in Brazil.\textsuperscript{3,35,36,37}

The oxytocin-Uniject has the following advantages\textsuperscript{3}:

- Routine prophylactic use in deliveries by skilled birth attendants
- Improved injection safety
- Improved dose accuracy and convenience
- Selected or emergency use by specially trained providers at community level to prevent or treat PPH
- Potential use in areas with high rates of postpartum haemorrhage and areas with limited access to referral care.

The 2004 background paper used studies conducted in Indonesia to illustrate the above advantages of the oxytocin-Uniject.\textsuperscript{38} The experiences of 140 midwives who attended 2 200 home births using prophylactic oxytocin in Uniject were compared with the midwives’ previous experiences with oxytocin in standard syringes. The authors found that unsafe
Reuse of syringes was reduced from 33% to zero once the midwives were supplied with the Uniject. Dosage accuracy increased slightly, and the Uniject was found by mothers to be less painful than regular syringe injections. Additionally, 98% of midwives preferred the Uniject and were willing to pay a small additional amount (over standard syringes) for the convenience of using it.

Since 2004 the oxytocin-Uniject has been produced with a time temperature exposure indicator device (TTI). PATH, in conjunction with BIOL Pharmaceuticals, incorporated the TTI technology in which one of small colored stickers placed on the medicine becomes darker in relation to the cumulative exposure of the medicine to heat. Like the Uniject technology, the TTI technology is not new to public health interventions. It has been used as an efficient way of monitoring the stability of vaccines as they move out of the cold chain. Stability studies on the oxytocin-Uniject conducted by PATH and BIOL have shown similarities between the different lengths of time the oxytocin remained fully potent at different storage temperatures and the existing TTI developed for the most stable group of vaccines.

The Uniject with TTI is expected to ensure that only effective oxytocin is administered, improving the overall quality assurance of programs, to improve the ability of programs to flexibly transport and store oxytocin (oxytocin could move in and out of cold chain, cool chain, room temperature, and allow for longer “out of cold chain” periods compared with other approaches). A pilot study on the effectiveness of the oxytocin-Uniject with TTI was carried out from August 2007 to January 2008 in 45 sites in Mali. In addition to documenting the experience with the TTI in the desert heat of Mali, the study also sought to evaluate the feasibility and safety of the oxytocin-Uniject, its acceptability to providers, pharmacy managers, and management staff, and its impact on the coverage of AMTSL in the Malian context. The safety of the Uniject was evaluated in terms of two outcomes: selected obstetric complications (ruptured uterus, retained placenta, PPH, and uterine inversion) and needle-stick injuries. The results of the study showed no unusual safety problems associated with the use of the Uniject. Other specific observations from the study include the following:

**Safety:** Only five of the 140 (4%) providers interviewed had needle-stick injuries with the oxytocin-Uniject device. The rates of retained placenta and PPH were not significantly different when oxytocin in ampoules or oxytocin in the Uniject device was used. However, the rates of retained placenta and PPH were significantly lower when AMTSL was applied using the oxytocin-Uniject device with TTI compared to vaginal births without AMTSL. Rates of uterine rupture remained constant and occurred only in women referred from peripheral facilities and were not associated with introduction of the oxytocin-Uniject device with TTI. One case of uterine inversion was diagnosed in a referral health center in Bamako in a woman who presented at the health center after home delivery.

**Feasibility:** About 77% (108/140) felt the training they received was adequate to prepare them to use the oxytocin-Uniject device while 97% of providers (136/140) felt competent to manipulate the oxytocin-Uniject devices after training activities. Only 127 (91%) of the providers trained actually gave an injection with the oxytocin-Uniject device. Of these, 92% (117/127) felt confident after only one injection, and about 8% (10/127) felt confident after two or more injections. Through formal or informal training, providers quickly learned how to use the Uniject device, interpret the TTI and determine if oxytocin had been exposed to high temperatures over a period of time that would compromise its effectiveness.
Impact on AMTSL coverage: AMTSL coverage was already high and the introduction of the oxytocin-Unject device with TTI did not increase coverage significantly.

Acceptability: Providers preferred the oxytocin-Unject device with TTI to a standard or auto-disable syringe. About 99% (139/140) of providers indicated they preferred the oxytocin-Unject while 68% of health care facility managers felt there were no disadvantages to use of the oxytocin-Unject device. However, 17% (7) of managers felt that storage of the units was a disadvantage and 5% (2) noted that the need to cut the foil wrapper with a sharp object was a disadvantage.

A community based cluster randomized trial is currently on-going to assess the effectiveness, safety, and feasibility of expanding the use of prophylactic intramuscular oxytocin in Unject with TTI in peripheral health care providers at home births in four rural districts in Ghana. The intervention group consists of community health officers randomized to provide an injection of oxytocin 10 IU via the Unject injection system within one minute of delivery of the baby to women who request their presence at home at the onset of labor. The primary outcomes of this study is to determine if administration of prophylactic oxytocin via Unject by this cadre will reduce the risk of postpartum haemorrhage by 50% compared to deliveries which do not receive the prophylactic intervention. For the purpose of this study, postpartum haemorrhage will be examined under the following definitions: blood loss of at least 500 ml; treatment for bleeding and/or blood loss of at least 500 ml; hospital referral for bleeding and/or treatment for bleeding; and hospital referral for bleeding and/or blood loss of at least 500 ml. Secondary outcomes included safety (adverse maternal and fetal outcomes) and feasibility of the intervention (logistical concerns regarding assistance at home births and the storage and handling of oxytocin). The results of this trial are expected in mid-2013.

It is evident from the above discussions, that much progress has been made towards the improving the management of PPH with the use of the oxytocin-Unject. However, this technology is yet to be deployed on a large scale. Scaling up this technology should be associated with extensive evaluation and pharmacovigilance.

5.2 Carbetocin

Carbetocin is a synthetic oxytocin agonist with longer duration of action compared to oxytocin. It has an average lifespan four times that of oxytocin and a pharmacological effect that lasts for two hours. Carbetocin binds to oxytocin receptors on the smooth muscles of the uterus, resulting in rhythmic contractions of the uterus and increased uterine tone. It has a better gastrointestinal and cardiovascular side effects profile compared to oxytocin, syntometrine and other ergot alkaloids. Carbetocin has not been approved by the United States Food and Drugs Administration (USFDA) for use in vaginal births. However, it is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anesthesia in 23 countries. Carbetocin remains more expensive than oxytocin, and the 2009 WHO guidelines on managing PPH conclude that there is no evidence of significant advantage of carbetocin over oxytocin.
5.3 Ergometrine

According to WHO recommendations, in the case of treatment failure or unavailability of oxytocin, the second line treatment of choice are ergometrine or ergometrine and oxytocin fixed dose combination. Ergometrine and methylergometrine are more unstable at room temperature compared to oxytocin. It is also photosensitive and thus requires special temperature and light storage conditions to remain effective. A skilled personnel is required to administer ergometrine. However, compared to oxytocin ergometrine has more severe side effects, which includes hypertension, coronary vasospasms, increased systemic vascular resistance, pulmonary edema, intracranial haemorrhage and seizures, and retinal detachment. These side effects make ergometrine inferior to oxytocin and for this reason ergometrine has been removed from the WHO EML.

5.4 Misoprostol

Prostaglandins are effective in controlling haemorrhage but most have disadvantages of being more expensive and having increased side effects. One notable exception is misoprostol, which has a uterotonic property for use in active management of the third stage of labor. Misoprostol is an inexpensive (less than US$ 1 per dose) prostaglandin E1 analogue and has been suggested as an alternative for routine management of the third stage of labor. Studies to date indicate that where other agents are not available, misoprostol may be effective in reducing the incidence of PPH without the side effects associated with other uterotonic drugs. Though misoprostol is relatively stable at room temperature and has a long shelf life, it is sensitive to moisture and may degrade in areas of high humidity. Misoprostol can be given orally, which has a big advantage over oxytocin and ergometrine. According to the WHO misoprostol may be considered third line treatment (after oxytocin and ergometrine) because of its slightly lower potency, which is partly offset by its ease of administration and low cost. An additional practical problem is that misoprostol can be (mis)used for carrying out abortions and is therefore not marketed or approved in many countries.

Adverse effects of misoprostol: A number of adverse effects are associated with misoprostol including frequent transient fever and shivering, which are dose and route dependent. Other adverse effects of misoprostol include nausea, vomiting, and diarrhoea. Though lower doses have lower side effects, there is not enough evidence on the efficacy of lower doses of misoprostol. Breastfeeding is not contraindicated when misoprostol is used for PPH prevention.

5.4.1 Misoprostol in the prevention of PPH

In 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL as the results of trials conducted in the late 1990s and early 2000s were discordant on the benefits of misoprostol in the prevention of PPH. Over the past decade however, the efficacy of misoprostol for PPH prevention has been well documented. The evidence-based misoprostol regimen for prophylaxis against PPH is a single 600 µg dose administered orally to women immediately after vaginal delivery of the baby (or babies, in the case of multiple births). There is also substantial evidence in support of the beneficial effects of oral misoprostol for PPH prevention in the community level. This evidence is summarized below.
Derman et al. demonstrated the effectiveness of misoprostol in preventing haemorrhage in a placebo-controlled trial in 2002-2005. A total of 1,620 women in four primary-health centers in rural India were randomized to receive oral misoprostol (n=812) or a placebo (n=808) after delivery. The drug was administered by auxiliary nurse midwives, who took care of the deliveries and measured blood loss. The intervention group received a single oral dose of 600 μg misoprostol administered after the delivery of the baby and within five minutes of clamping and cutting the umbilical cord. Compared to the placebo, oral misoprostol significantly reduced the rate of acute PPH (12% versus 6.4%, p<0.0001; RR = 0.53, 95% CI: 0.39 to 0.74). Oral misoprostol also significantly reduced the rate of acute severe postpartum haemorrhage (1.2% to 0.2%, p<0.0001; RR = 0.20, 95% CI: 0.04 to 0.91). For every 18 women treated, one case of postpartum haemorrhage was prevented. However, women in the misoprostol group experienced higher rate of transitory symptoms of chills and fever compared to women in the control group.

In another randomized placebo controlled trial in Pakistan in 2006-2008, Mobeen et al studied whether misoprostol reduced the incidence of PPH (blood loss of 500 ml or more) in a total of 1,119 women giving birth at home. A total of 534 women were randomized to receive 600 μg oral misoprostol after delivery while 585 received a placebo. Oral misoprostol was associated with a significant reduction in the rate of PPH (16.5 versus 21.9%; RR = 0.76, 95% CI: 0.59 to 0.97). Compared to a placebo, significantly fewer women who received misoprostol had a drop in hemoglobin less than 3 g/dl (5.1 versus 9.6%; RR = 0.53, 95% CI: 0.34 to 0.83). In this study, cord traction was carried out according to provider preference, in contrast to the Derman study in which there was no controlled cord traction.

Sublingual misoprostol has also been shown to reduce the incidence of severe PPH. Hoje et al conducted a randomized double blind placebo controlled trial in a primary health center in Bissau, Guinea-Bissau, involving 661 women undergoing vaginal delivery. The women were randomized to sublingual misoprostol 600 μg or a placebo also administered sublingually immediately after delivery. The results of this study showed no statistically significant difference in incidence of postpartum haemorrhage (defined as blood loss of more than 500 ml) between the two groups, RR = 0.89 (95% CI: 0.76 to 1.04). Mean blood loss was 10.5% lower in the misoprostol group compared to the placebo group. The rates of severe postpartum haemorrhage of 1000 ml or 1500 ml were respectively 17% (56) and 8% (25) in the placebo group and 11% (37) and 2% (7) in the misoprostol group. Significantly fewer women in the misoprostol group experienced blood loss of 1000 ml or more (RR = 0.66, 95% CI: 0.45 to 0.98) or more than 1500 ml (RR = 0.28, 95% CI: 0.12 to 0.64). There was also less decrease in hemoglobin concentration in the misoprostol group, the mean difference between the two groups being 0.16 mmol/l.

A meta-analysis of the findings of these three studies showed that compared to a placebo, misoprostol resulted in 24% and 41% reductions in the incidence of PPH and severe PPH respectively. However, these trials lack the power to detect an association between the reductions in PPH observed and a reduced risk of maternal death.

In 2011 the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines recommended the addition of 600 μg dose of oral misoprostol to the WHO Model List of Essential Medicines for the prevention of PPH. In addition to WHO, FIGO, and ICM, the Royal College of Obstetricians and Gynaecologists (RCOG) also supports the use of
misoprostol for PPH prevention and recommend that misoprostol can be used to prevent PPH where oxytocin is not available or where birth attendants’ skills are limited.\textsuperscript{16}

### 5.4.2 Misoprostol in the treatment of PPH

An expert panel set up by FIGO recommended that misoprostol can be used for the primary treatment of PPH in the absence of standard uterotonics.\textsuperscript{16} This recommendation was based on published results from seven case reports and three RCTs on the use of misoprostol in treating PPH. Following this recommendation, two large-scale double-blind placebo-controlled randomized trials that compared 800 μg of sublingual misoprostol with 40IU of intravenous oxytocin were conducted. These non-inferiority trials showed PPH due to suspected uterine atony in 9 out of 10 women was controlled successfully within 20 minutes of treatment with either drug.\textsuperscript{16,52,53} Though adverse effects such as shivering and fever were significantly more common in the misoprostol group compared with the oxytocin group, the authors concluded that in settings in which use of oxytocin is not feasible, misoprostol might be a suitable first line treatment alternative for postpartum haemorrhage. Details of these trials are outlined in Annex 1.

There is little evidence to support the benefits of adjunct treatment of PPH with misoprostol and oxytocin. Two RCTs, one undertaken by Hofmeyr et al. in 2002-2003 and the other by Walraven et al. in 2002-2003 showed that compared to a placebo, adjunct administration of misoprostol with standard PPH treatment using oxytocin led to a significant reduction in blood loss greater than or equal to 500 ml.\textsuperscript{54,55} However both studies had small sample sizes (238 and 160 respectively) and had limited power to only detect large differences.\textsuperscript{16,56} However, a recently conducted large multi-center double-blind placebo controlled trial showed no clinical advantage of adjunct use of 600 μg misoprostol (given sublingually) with standard treatment.\textsuperscript{16,57}

The sublingual route is recommended for treating PPH because of the following reasons\textsuperscript{16}:

- The sublingual route is the only treatment route tested in RCTs. Though published studies and case reports on the treatment of PPH using misoprostol have reported on rectal or sublingual route, no double-blind RCT has evaluated the efficacy of administering misoprostol via the rectal route. This was also noted in the 2004 report.
- The sublingual route has the advantage of rapid onset of action compared to the rectal route.
- Compared to other routes, the sublingual route is easy to administer, has the fastest absorption, highest serum levels, greatest bioavailability, and more sustained effect.

In addition to FIGO, the WHO, and RCOG, the American College of Obstetricians and Gynecologists (ACOG) acknowledge that misoprostol is effective in treating PPH and recommend that it be used for treatment in situations where standard uterotonics are unavailable or unfeasible to use. Questions still remain on whether the same therapeutic efficacy of 800 μg misoprostol can be achieved with a lower dose (600 μg) to minimize adverse effects. However, Raghavan et al. argued that while a reduced dose might benefit only a small number of special populations, unjustifiably huge resources would be needed to compare the efficacy of 600 μg and 800 μg misoprostol.\textsuperscript{16} According to the 2009 WHO guidelines on managing PPH, a further review of the safety and effective doses and dosage forms of misoprostol was going to be commissioned by the WHO.\textsuperscript{1}
5.5 Tranexamic acid

Tranexamic acid is an antifibrinolytic agent used in surgery to reduce blood loss. A systematic review of randomized controlled trials of antifibrinolytic agents in elective surgery showed that tranexamic acid reduced the risk of blood transfusion by 39%. According to the WHO, tranexamic acid may be offered as a treatment for PPH if: (i) administration of oxytocin, followed by second-line treatment options and prostaglandins, has failed to stop the bleeding; or (ii) it is thought that the bleeding may be partly due to trauma. The usefulness of tranexamic acid in PPH treatment is worth exploring through further research studies.

Gungorduk et al. in 2011 conducted a double-blind RCT to estimate the effects of adding intravenous tranexamic acid to the standard AMTSL in reducing vaginal blood loss. About 288 women were given intravenous tranexamic acid infusion in addition to standard AMTSL (prophylactic oxytocin 10 IU within two minutes of birth, early clamping of the umbilical cord, and controlled cord traction) while 226 women in the control group received 5% glucose in addition to standard AMTSL. The study results showed significantly lower mean blood loss at the third and fourth stages of labor in the intervention group than that in the placebo group (261.5 ml versus 349.98 ml respectively; p < 0.001). The frequency of PPH greater than 500 ml was also significantly lower in the intervention group (4, 1.8%) compared with the controls (15, 6.8%; RR = 3.76; 95% CI: 1.27 to 11.15; p = 0.01). The authors concluded that tranexamic acid with standard AMTSL reduced postpartum blood loss with no serious side effects associated with the tranexamic acid.

Peitsidis and Kadir carried out a systematic review of PubMed, Embase, CINAHL, Scopus, Cochrane, and DARE for available evidence on the use, efficacy and safety of tranexamic acid in the management of haemorrhage during pregnancy and for prevention and treatment of PPH. The authors found 34 articles (five RCTs, seven observational studies, and twenty-two case reports) published from 1976 to 2010. The combined effect of tranexamic acid compared with placebo was estimated to be a difference of 32.5 ml reduction in blood loss (95% CI: -4.1 to 69.13; p = 0.08). Though pulmonary embolism was reported in two cases the involvement of tranexamic acid in could neither be confirmed nor excluded. In conclusion, the authors suggested tranexamic acid is safe and effective in the prevention and management of bleeding during pregnancy and called for more investigation and larger clinical trials to confirm these findings.

A review of the February 2011 Cochrane Pregnancy and Childbirth Group’s Trials Register by Novikova and Hofmeyr searched for evidence on the effectiveness of tranexamic acid in PPH from completed and ongoing RCTs and yielded two RCTs. From a meta-analysis of these two RCTs, which involved a total of 453 women, the reviewers found that blood loss greater than 400 ml was less frequent in women who received 1g or 0.5gm IV tranexamic acid after vaginal birth or caesarean section (RR 0.51; 95% CI: 0.36 to 0.72).

5.6 Recombinant factor VIIa

According to the WHO the evidence to recommend the use of recombinant factor VIIa (rVIIa) for the treatment of PPH is weak. Additionally rVIIa is very expensive, cumbersome to administer and is associated with life threatening side effects. The WHO recommends the
use of rVIIa to be for the treatment of PPH to be limited to women with specific haematological indications.\textsuperscript{1,9}

6. **Non-pharmacological management of PPH**

The 2012 WHO recommendations for the management of PPH recommends the following non pharmacological interventions for managing PPH.\textsuperscript{9}

*Uterine massage:* A safe and inexpensive intervention to be initiated once PPH has been diagnosed.

*Bimanual uterine compression:* Could be offered as a temporary measure in the treatment of PPH due to uterine atony after vaginal delivery.

*Intrauterine balloon or condom tamponade:* May be used in the treatment of PPH due to uterine atony when other uterotonics fail or if uterotonics are not available. Possible infection is the risk associated with this intervention. The WHO identifies the use of uterine balloon or condom tamponade in the treatment of PPH as a research priority.\textsuperscript{1}

*External aortic compression:* May be provided as a temporary measure to slow down blood loss in treatment of PPH due to uterine atony after vaginal delivery, until appropriate care is available.

*Uterine artery embolization:* May be offered as a treatment for PPH due to uterine atony if other measures have failed and resources are available.

*Non-pneumatic anti-shock garments:* Recommended as a temporary measure until appropriate care is available.

The WHO recommends more research into the effects of uterine massage and intrauterine balloon or condom tamponade in the prevention and treatment of PPH respectively.\textsuperscript{9}

6.1 **Surgical interventions**

For patients who do not respond to treatment with uterotonics and other non-pharmacological interventions such as uterine massage or who have existing lacerations, large haematomas or a ruptured uterus surgical interventions are required.\textsuperscript{1,9,61} If radiological intervention is available arterial embolization may be done on haemodynamically stable patients as an alternative to surgery.\textsuperscript{65,62}
7. **Comparative Trials**

7.1 **Comparative studies from before 2004**

Four Cochrane reviews were published in 2004, and one RCT comparing intra-rectal misoprostol 600 μg with conventional oxytocics. The findings from these trials are summarized.

i). The use of ergometrine-oxytocin in active management of PPH shows a small, but statistically significant reduction in the risk of PPH compared to oxytocin alone for a blood loss of 500 ml. No difference was observed between the two interventions for blood loss more than 1000 ml. The side effects observed for ergometrine-oxytocin were statistically significant compared to oxytocin alone. These included elevated blood pressure, vomiting, and nausea (Cochrane Review 2004).63

ii). Rectal misoprostol, when compared to ergometrine-oxytocin injection, was found to have a statistically significant reduction in the number of women who continued to bleed and those who required medical co-interventions to control the bleeding. No significant differences were observed regarding surgical interventions to control intractable haemorrhage including hysterectomy, internal iliac artery ligation and/or uterine packing. The reviewers concluded that 800 μg rectal misoprostol may be a useful as a first line drug for the treatment of PPH (Cochrane Review 2004).64

iii). Oral misoprostol 600 μg is less effective than conventional injectable uterotonics in reducing blood loss greater than 1000 ml (Cochrane Review 2004).

iv). Compared to conventional injectable uterotonics, prostaglandins reduced blood loss in the third stage of labor but are associated with more side effects (Cochrane review 2004).65

v). Active management, when compared with expectant management was associated with reduced risks of maternal blood loss, postpartum haemorrhage of more than 500 ml and prolonged third stage of labor. Active management is, however, associated with an increased risk of side effects such as nausea, vomiting, and hypertension, where ergometrine is used.66

vi). An RCT conducted in 2002 in Turkey, compared intra-rectal misoprostol 600 μg and oxytocin-methylergometrine. The incidence of PPH was 9.8% in the misoprostol group compared to 3.5% in the oxytocin-methylergometrine group in the management of third stage labour. Rectal misoprostol was comparable to IV oxytocin alone, but less effective than oxytocin plus methylergometrine.67

7.2 **Recent comparative trials on managing PPH**

*Annex 1* shows the details of recent clinical trials comparing the various interventions for managing PPH. Evidence from these studies are summarized below:

i) For women with risk factors for uterine atony, rectal misoprostol (600 μg) is as effective as oxytocin infusion (20IU) as an adjunct to AMTSL for prevention of postpartum haemorrhage.68
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ii) Sublingual powdered formulation of misoprostol (400 μg) may be superior to IV oxytocin (10IU) in preventing postpartum blood loss.69 Chaudhuri et al. also showed that 400 μg sublingual misoprostol was equivalent to 10 units of oxytocin IV in the prevention of PPH after vaginal birth in women with low-risk of PPH.70

iii) Sublingual misoprostol (800 μg) may be non-inferior to oxytocin IV (40IU) in the treatment of women with primary PPH who had or had not been exposed to prophylactic oxytocin.52,53 The authors of these studies concluded that misoprostol may be used as first line treatment for PPH in settings where the use of oxytocin is not feasible.

iv) Compared to rectal misoprostol 400 μg, intramuscular injection of oxytocin 10IU, and intramuscular injection (0.5 mg ergometrine + 5IU oxytocin), intravenous injection of methylergometrine 0.2 mg was found to be the most effective in reducing the duration of third stage of labor, the amount of blood loss and the incidence of PPH (p = 0.000096, 0.000017 and 0.03 respectively).71 No significant differences were found in pre-delivery and post-delivery hemoglobin concentration amongst the four groups (p = 0.061). The authors of this study suggested misoprostol should be reserved for use in low resource settings and where other uterotonic drugs were not available.

v) Carbetocin was as effective as oxytocin in the prevention of postpartum haemorrhage in women with severe preeclampsia.20 The safety profiles of the two drugs were found to be similar. However, carbetocin does not have a major haemodynamic effect in women with severe preeclampsia and the volume per dose for its administration is lower than that of oxytocin.20 This may be a good option for the management of third stage labor in women with hypertensive disorders during pregnancy.

vi) Carbetocin and a combination of oxytocin and ergometrine have similar efficacy in preventing PPH in women who deliver vaginally.72 However the former has a better safety profile. The combination of oxytocin and ergometrine was more commonly associated with nausea and vomiting tremor, sweating, retching and uterine pain.

A Cochrane Review by Su et al. compared the effectiveness of carbetocin with conventional uterotonic agents in preventing PPH.40 This review focused on RCTs which compared carbetocin with other uterotonic agents, carbetocin with a placebo or carbetocin with no prophylactic treatment against PPH. The authors identified 11 studies involving 2635 women from the Cochrane Pregnancy and Childbirth Group’s Trials Register (1 March 2011), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2011, Issue 1 of 4), MEDLINE (1966 to 1 March 2011) and EMBASE (1974 to 1 March 2011).

From the review findings, six trials compared 100 μg carbetocin with oxytocin. Carbetocin was administered as intravenous dosage across the trials, while oxytocin was administered intravenously at varied dosages. Four trials compared intramuscular carbetocin and an intramuscular combination of oxytocin and ergometrine for women undergoing vaginal deliveries. Three of the trials were on women with no risk factor for PPH, while one trial was on women with risk factors for PPH. One trial compared the use of intravenous carbetocin with placebo. Use of carbetocin was associated with a significant reduction in the need for therapeutic uterotonics (RR = 0.62; 95% CI: 0.44 to 0.88; four trials with a total of 1 173 women who underwent caesarean session) compared to oxytocin. Carbetocin was associated with a reduced need for uterine massage following both caesarean delivery (RR = 0.54; 95% CI: 0.37
to 0.79; two trials, 739 women) and vaginal delivery (RR = 0.70; 95% CI: 0.51 to 0.94; one trial, 160 women) compared to oxytocin.

There was a lower mean blood loss in women who received carbetocin compared to a (mean difference -48.84 ml; 95% CI -94.82 to -2.85; four trials, 1030 women). The need for additional uterotonic agents was not statistically significant between the two groups. However, the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group: nausea (RR = 0.24; 95% CI 0.15 to 0.40; four trials, 1030 women); vomiting (RR = 0.21; 95% CI 0.11 to 0.39; four trials, 1030 women). The incidence of postpartum hypertension was significantly higher in women who received a combination of oxytocin and ergometrine compared to those who received carbetocin. There was no difference in the risk of heavy bleeding between patients given IV oxytocin and IV carbetocin. However, women who received oxytocin were more likely to require additional uterotonics following caesarean sections.

8. Summary of changes since 2004

Notable changes have taken place in the research and management of PPH since 2004.

1. TI Pharma Hot Medicines Consortium has made substantial breakthroughs in developing a heat stable oxytocin, the number one recommended intervention for preventing and treating PPH.\textsuperscript{15,14} Though this progress is promising and worth noting, further research studies are needed to make a heat stable oxytocin available for therapeutic use.

2. There is now more evidence supporting the acceptability, effectiveness, feasibility of use, and safety of the oxytocin-Unject at the hospital and community level.\textsuperscript{39,38,34} The challenges of expertise in dose measurement and injection skills required to administer oxytocin in ampoules have been technically resolved by the oxytocin-Unject device.

3. A major concern regarding the use of oxytocin-Unject identified in the 2004 report was that in the case of an interrupted cold chain delivery and storage system, the quality of the oxytocin in the Unject device could not be assured. This challenge has also been overcome by the development of the Unject with time-temperature exposure indicator. This technology has been successfully piloted in Mali and is currently undergoing an community randomized trial in Ghana.\textsuperscript{15,39,34}

4. In 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL.\textsuperscript{43,44,45,46,47} However, over the past decade the efficacy of misoprostol for PPH prevention has been well documented at both the hospital and community level.\textsuperscript{16,18,19,48} The evidence-based misoprostol regimen for PPH prevention is a single 600μg dose administered orally to women immediately after vaginal delivery of the last baby.\textsuperscript{16,19}

5. The effectiveness of sublingual misoprostol in treating PPH has now been established.\textsuperscript{16,52,53} However, there is still lack of clarity on the most appropriate dose that will be safe and effective to minimize adverse effects.\textsuperscript{16} The 2012 WHO recommendations for managing PPH identified as a research priority the determination of the minimum effective dose of misoprostol for treating PPH.\textsuperscript{9}

6. In 2004 oxytocin and ergometrine were the only medicines for PPH on the WHO EML. In 2011 ergometrine was removed and oral misoprostol was added to the EML.
7. Tranexamic acid and carbetocin have recently been suggested as alternative interventions.\textsuperscript{60,59,38,40,177} According to the WHO, tranexamic acid may be offered as a treatment for PPH if first, second, and third line treatments have failed to stop the bleeding or the bleeding is partly due to trauma.\textsuperscript{1} The usefulness of tranexamic acid in PPH treatment is worth exploring through further research. On the other hand, carbetocin does not have a strong advantage over its analogue oxytocin, except perhaps in women with (pre) eclampsia.

8. The WHO no longer recommends early cord clamping as part of AMTSL, unless the baby suffers asphyxia and needs to be moved quickly to resuscitation.

9. **Need for further research**

**Medicine development**

1. The TI Hot Pharma Consortium’s initiative to develop a heat stable oxytocin is promising and should be further pursued. The development of a therapeutically effective heat stable oxytocin will solve the current challenges of cold storage for oxytocin. The thermostable oxytocin should be packaged in Unijets to provide it with an additional advantage of ease of use in low resource settings.

2. There is the need for studies to determine a standard, safe, and effective dose of oral and sublingual misoprostol for preventing and treating PPH.\textsuperscript{36,19}

3. Research is needed to discover new and easy to use treatments for PPH in cases where prophylactic measures fail.

**Clinical studies**

4. Further research is needed to explore the potential of tranexamic acid in treating PPH. Trials comparing the safety and efficacy of tranexamic acid and tranexamic acid in addition to existing uterotonics would be helpful.

5. The usefulness of carbetocin instead of oxytocin in treating PPH in women with pre-eclampsia should also be explored. Carbetocin does not have a major hemodynamic effect in women with severe preeclampsia and the volume per dose for its administration is lower than that of oxytocin.\textsuperscript{20}

**Health systems research**

6. The use of oxytocin-Uniject with the TTI should be scaled up especially in low resource settings in tandem with adequate post marketing pharmacovigilance studies.

7. A system of collecting or estimating routine data on the incidence of PPH and severe PPH should be established.

8. There is evidence that sublingual misoprostol is beneficial in the treatment of PPH, especially where there is no access to oxytocin. However evidence is currently limited on the effectiveness of its use by less skilled or lay caregivers at the community level.\textsuperscript{19} Operational research is needed to determine if the benefits of advanced community distribution of misoprostol to pregnant women and to lower cadre health workers at the community level outweigh the potential disadvantages. The WHO identifies a study on the effectiveness of antenatal distribution of misoprostol to pregnant women for self-
administration during the third stage of labour in settings where the use of injectable uterotonic is not possible as a key research priority.

9. Regulatory barriers that prevent lower cadre health workers from administering oxytocin or misoprostol should be removed especially in low resource settings.

Finally, research is needed to discover new, patient-friendly and easy-to-use medicines for preventing and treating PPH. According to a 2012 commissioners report of the United Nation Commission on Life-saving Commodities for Women and Children, if current interventions for the management of PPH are improved (development of a thermo-stable oxytocin formulation, the promotion of the oxytocin-Uniject with a TTI technology and the development of a non-parenteral inhalation or intranasal spray oxytocin, etc.) and equitable access is achieved, about 15 000 maternal deaths would be avoided in the next five years.74

**10. Why the burden of PPH still persists**

Much progress has been made in terms of research into finding solutions to the burden of PPH. However this progress has not completely stemmed the tide against women dying due to haemorrhage during childbirth. One reason for this is the fact that there is no “silver bullet” for the prevention or treatment of PPH. Between 3 to 16.5% of women will go on to experience PPH even after AMTSL with existing interventions.16 Oxytocin, the current gold standard for the prevention and treatment of PPH has serious limitations because of its instability in tropical climates and the need for trained personnel for administration. Until the use of the oxytocin-Uniject becomes widespread, the expertise required to administer the medicine will still be a barrier to its use in low resource settings. Until a heat stable formulation of oxytocin is developed, the quality of oxytocin if available in low resource settings cannot be guaranteed because of lack of cold chain storage.

The new interventions that have been suggested, for example the use of tranexamic acid and balloon or condom tamponade in the treatment of PPH still require further research to qualify their use.

Maternal mortality due to haemorrhage is preventable with timely medical treatment. However, delays in allowing pregnant women the access to timely medical treatment result in high maternal mortality. Factors that contribute to delay in deciding to seek care include the actors involved in decision-making (individual, spouse, relatives, family), the status of women, illness characteristics, distance from the health facility, financial and opportunity costs, previous experience with the health care system, and perceived quality of care. Factors contributing to delay in reaching a health facility include physical accessibility, such as the distribution of facilities, travel time from home to facility, availability and cost of transportation, and condition of roads. Factors responsible for delays in receiving adequate care while patient is at the health facility include adequacy of the referral system, shortages of supplies, equipment, and the competence of available personnel. The non-availability or lack of access to appropriate technologies, such as oxytocin-Uniject, heat stable oxytocin or oxytocin packaged with the TTI technology contributes to the delay in patients receiving appropriate care at health facilities. The current technologies available are beyond the training and the skills of lower cadre health workers who most often work at the community
level. Interventions to minimize these delays may include the use of misoprostol by lower cadre health workers at the community level. The September 2012 commissioners report of the United Nation Commission on Life-saving Commodities for Women and Children identified regulatory barriers to the use of some life-saving commodities such as oxytocin by lower-level health workers.

11. Conclusion

Postpartum haemorrhage still remains the leading cause of maternal mortality. Though the burden of PPH is highest in developing countries, the incidence of PPH is on the increase in developed nations. Current preventive and treatment interventions are inadequate and inequitably distributed. While much has been done to improve on the existing interventions including the development of heat stable oxytocin and the development of the oxytocin-Uniject with a TTI technology, these improvements are either not yet therapeutically available for use or are not yet deployed on a large scale. More research is needed develop new interventions, improve on existing interventions, and to ensure that the existing technologies as well as those to be developed are equitably distributed to reduce the burden of PPH.

References


PATH. Newsflash: Oxytocin can take the heat... More storage flexibility with a TTI [Internet]. [cited 2012 Oct 10]. Available from: http://www.pphprevention.org/files/TTIWebAnnouncement_001.pdf


Update on 2004 Background Paper, BP 6.16 Postpartum Haemorrhage


Update on 2004 Background Paper, BP 6.16 Postpartum Haemorrhage


## Update on 2004 Background Paper, BP 6.16 Postpartum Haemorrhage

### Annex

#### Annex 6.16.1: Recent comparative studies on uterotoincs

<table>
<thead>
<tr>
<th>Study design / Year</th>
<th>Setting of study</th>
<th>Study population</th>
<th>Interventions compared</th>
<th>Results</th>
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</table>
| **Misoprostol (rectal) versus oxytocin (infusion) for the prevention of PPH**<sup>6</sup> | Double blind RCT/2009 | University Teaching Hospital in Nigeria | 264 pregnant women with identifiable risk factors for uterine atony in Nigeria | Rectal misoprostol (600 mg; n = 132) after routine AMTSL versus Oxytocin infusion (20 IU in 500 ml; n = 132) after routine AMTSL | 1. No significant difference in the mean intrapartum blood loss between the two groups: 387.28 +/- 203.09 versus 386.73 +/- 298.51, (p = 0.07).  
2. Postpartum hematocrit drop was significantly less in the misoprostol group. 1.0 ± 2.036 versus 2.915 ± 3.103, (p<0.001)  
3. No difference between the two arms in the requirement for additional intervention for uterine atony: 7 (5.6%) versus 6 (4.7%) 0.74 (p = 0.74). | Shivering, pyrexia and vomiting are more frequent with misoprostol, though usually self-limited. | Rectal misoprostol is as effective as oxytocin infusion as an adjunct for prevention of postpartum haemorrhage in women with risk factors for uterine atony |
| **Misoprostol (powdered sublingual) versus oxytocin (IM) for the prevention of PPH**<sup>5</sup> | Double blind RCT / 2007 to 2008 | A teaching hospital in Belgaum India | 652 women with a singleton pregnancy at >28 weeks of gestation, with cephalic presentation, anticipating vaginal delivery and with hemoglobin > 8 g/dl upon presentation | 400 μg powdered sublingual misoprostol (n=321) versus 10IU intramuscular oxytocin (n=331) | 1. Mean blood loss with sublingual misoprostol and oxytocin IM were 192 ± 124 ml and 366 ± 136 ml respectively, (p< 0.001)  
2. The incidence of PPH was 3.1% with misoprostol and 9.1% with oxytocin (p = 0.002).  
3. Proportion of women with hemoglobin decline greater than 10% in the misoprostol and oxytocin groups were 9.7% and 45.6% respectively (p< 0.001) | Nausea, vomiting, shivering and fever were significantly greater in the misoprostol group than in the oxytocin group | Sublingual misoprostol is more effective than intramuscular oxytocin in reducing PPH, with only transient side effects being greater in the misoprostol group |
### Misoprostol (sublingual) versus oxytocin (IM) for the prevention of PPH<sup>5</sup>

<table>
<thead>
<tr>
<th>Study design / Year</th>
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<th>Results</th>
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<th>Conclusion</th>
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<tr>
<td>Double blind RCT / 2009 to 2010</td>
<td>Hospital in Kolkata, India, 530 women without risk of PPH</td>
<td>400 µg of misoprostol given sublingually within one minute of delivery (n=265) versus 10 units of oxytocin IM within one minute of delivery (n=265)</td>
<td>1. Incidence of PPH and postpartum blood loss in the misoprostol group were similar to those in the oxytocin group (6% versus 5.7%, p=0.85 and 153 ml versus 146 ml, p=0.36 respectively). 2. No significant differences between the two arms regarding drop in hemoglobin level in 24 hours, the need for additional uterotonic drug, and the need for blood transfusion</td>
<td>Shivering and pyrexia were more common in the misoprostol than in the oxytocin group</td>
<td>The efficacy of 400 µg of misoprostol administered sublingually was equivalent to that of 10 units of oxytocin given intramuscularly for prevention of PPH in low-risk vaginal delivery.</td>
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### Misoprostol (sublingual) versus oxytocin (IM) for the treatment of PPH<sup>6</sup>

<table>
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<tr>
<th>Study design / Year</th>
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<tr>
<td>Double blind non-inferiority trial / 2005 to 2008</td>
<td>Four hospitals in Ecuador, Egypt, and Vietnam, 978 women not exposed to prophylactic oxytocin diagnosed with primary PPH</td>
<td>800 µg misoprostol (n=488) versus 40 IU intravenous oxytocin (n=490) (Clinical equivalence of misoprostol defined as the upper bound of the 9.5% CI falling below margin of 6%).</td>
<td>1. Active bleeding was controlled within 20 minutes for 440 (90%) women given misoprostol and 468 (96%) of women given oxytocin (RR = 0.94, 95% CI 0.91–0.98; crude difference 5.3%, 95% CI 2.6–8.6). 2. Additional blood loss of 300ml or greater after treatment occurred for 147 (30%) of women receiving misoprostol and 83 (17%) receiving oxytocin (RR 1.78, 95% CI 1.40-2.26).</td>
<td>Shivering and fever were significantly more common with misoprostol than with oxytocin.</td>
<td>In women who had not received oxytocin prophylaxis, misoprostol is clinically equivalent to oxytocin in treating post-partum bleeding suspected to be due to uterine atony.</td>
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## Misoprostol (sublingual) versus oxytocin (IM) for the treatment of PPH

**Study design / Year**: Double blind non-inferiority trial / 2005 to 2008  
**Setting of study**: Five hospitals in Burkina Faso, Egypt, Turkey, and Vietnam  
**Study population**: 809 women exposed to prophylactic oxytocin diagnosed with PPH  
**Interventions compared**: 800 μg misoprostol (n = 407) versus 40IU intravenous oxytocin (n=402)  
**Results**: 1. Active bleeding was controlled within 20 minutes after initial treatment for 363 (89%) women given misoprostol and 360 (90%) given oxytocin (RR = 0.99, 95% CI 0.95–1.04; crude difference 0.4%, 95% CI –3.9 to 4.6).  
2. Additional blood loss of 300ml or greater after treatment occurred for 139 (34%) women receiving misoprostol and 123 (31%) receiving oxytocin (RR = 1.12, 95% CI 0.92–1.37).  
**Adverse effects**: Shivering and fever were significantly more common among women who used misoprostol compared to women who used oxytocin.  
**Conclusion**: In women who had received oxytocin prophylaxis, misoprostol is clinically equivalent to oxytocin in treating post-partum bleeding suspected to be due to uterine atony.

## Carbetocin versus oxytocin in the prevention of PPH

**Study design / Year**: Double blind RCT / 2010  
**Setting of study**: Hospital  
**Study population**: 60 women with singleton pregnancies of more than 28 weeks’ gestation who were admitted to hospital with severe preeclampsia  
**Interventions compared**: Carbetocin 100 μg + Ringer’s lactate solution 10ml injected directly into the vein over two minutes versus Oxytocin 20 U diluted in 1000 ml of Ringer’s lactate solution, administered intravenously at a rate of 125 ml/hour  
**Results**: 1. No significant differences in mean arterial pressure and heart rate between the groups (both before and after drug was given)  
2. No differences between the carbetocin and oxytocin groups in hemoglobin concentration, rates of oliguria after delivery  
3. No difference between the two groups in the need for additional uterotonics  
**Adverse effects**: Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension  
**Conclusion**: Carbetocin is as effective as oxytocin in preventing postpartum bleeding in women with severe preeclampsia, with no alterations in hemodynamic status and with few side effects.
## Carbetocin versus combination of oxytocin and ergometrine (combinatio of oxytocin and ergometrine )

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<tr>
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<tr>
<td>Double blind RCT / 2005 to 2008</td>
<td>Referral hospital in Singapore</td>
<td>370 pregnant women who had no contraindication for vaginal delivery</td>
<td>One ampoule of combination of oxytocin and ergometrine (5 iu of oxytocin and 500 microgram of ergometrine) intramuscularly (n=185) versus 100 microgram carbetocin intramuscularly (n=185)</td>
<td>1. 14% and 17% of women in the carbetocin group and combination of oxytocin and ergometrine group respectively had postpartum haemorrhage requiring additional uterotonics (p = 0.384). 2. The proportion of women in each group who had postpartum haemorrhage were the same (1.6%) and the estimated blood loss was similar between the two groups</td>
<td>Compared to the carbetocin group, women who had combination of oxytocin and ergometrine were four times more likely to experience nausea and vomiting. Tremor, sweating, retching and uterine pain were also more common with combination of oxytocin and ergometrine. Carbetocin and combination of oxytocin and ergometrine thus seems to have the same efficacy. However the former has a better safety profile</td>
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## Misoprostol (rectal) versus oxytocin (IM) versus methylergometrine (IV) versus ergometrine + oxytocin (IM)

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<tr>
<td>Prospective non RCT / 2007 to 2008</td>
<td>Hospital in Baroda, India</td>
<td>200 women with singleton pregnancy, between 37 and 42 week of gestation, anticipated vaginal delivery, vertical lie, no high risk factors for PPH</td>
<td>AMTSL with tablet misoprostol 400μg rectal versus AMTSL with IM oxytocin 10 IU versus AMTSL with IV methyl ergometrine 0.2 mg versus AMTSL with injection combination of oxytocin and ergometrine (methyl ergometrine 0.5 mg + oxytocin 5 IU)</td>
<td>1. Methylergometrine to be the most effective in reducing the duration of third stage of labor, the amount of blood loss and the incidence of PPH (p = 0.000096, 0.000017 and 0.03 respectively). 2. Compared to the other medicines, women given misoprostol had the highest need for additional oxytocics and blood transfusion (p = 0.037 and 0.009 respectively). 3. No significant differences were found in pre-delivery and post-delivery hemoglobin concentration amongst the four groups (p = 0.061)</td>
<td>Shivering and pyrexia in significantly higher in the misoprostol group, while nausea, vomiting and headache were more associated with methylergometrine and ergometrine–oxytocin. Compared to the other four medicines, methylergometrine has the best uterotonic property. Authors suggested misoprostol be reserved for use in only low resource settings and where other uterotonic drugs were not available</td>
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