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Community-based misoprostol for the prevention of post-partum haemorrhage: a narrative review of the evidence base, challenges and scale-up

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Achieving Sustainable Development Goal targets for 2030 will require persistent investment and creativity in improving access to quality health services, including skilled attendance at birth and access to emergency obstetric care. Community-based misoprostol has been extensively studied and recently endorsed by the WHO for the prevention of postpartum haemorrhage. There remains little consolidated information about experience with implementation and scale-up to date. This narrative review of the literature aimed to identify the political processes leading to WHO endorsement of misoprostol for the prevention of postpartum haemorrhage, and describe ongoing challenges to the uptake and scale-up at both policy and community levels. We review the peer-reviewed and grey literature on expansion and scale-up and present the issues central to moving forward.

Keywords: misoprostol, post-partum haemorrhage, community-based, scale-up, advance distribution

Background

Maternal mortality remains the most inequitable health indicator globally (World Health Organization, 2015b). Safe motherhood initiatives, including investments in improving access to skilled birth attendants (SBAs), emergency obstetric care, safe therapeutic abortion and contraception have resulted in significant reductions in maternal mortality globally over the last 20 years. Maternal deaths have decreased over the last quarter century from 376 034 (95% CI: 343 483 – 407 574) in 1990 to 292 982 (95% CI: 261 017–327 792) in 2013 (Kassebaum et al., 2014). The rate of decline, however, was less than half that was needed to achieve the Millennium Development Goal (MDG) target of a three quarter reduction in the maternal mortality ratio between 1990 and 2015.

Post-partum haemorrhage (PPH) is the leading cause of maternal death worldwide (Say et al., 2014). Defined as bleeding in excess of 500 mL in the first 24 hours following birth (World Health Organization, 2012a), the most common causes of PPH include uterine atony, vaginal or cervical lacerations, retained placenta tissue, and clotting disorders (Arulkumaran, Regan, Papageorghiou, Monga, & Farquharson, 2011; World Health Organization, 2012a). After years of risk stratification studies, we have no effective way of predicting who will experience haemorrhage, especially in the absence of an SBA caring for women during labour and the post-partum period (Devine, 2009; Edhi, Aslam, Naqvi, & Hashmi, 2013; El-Refaey & Rodeck, 2003; Potts & Hemmerling, 2006). This evidence forms the rationale for the primary prevention of PPH for every woman, immediately post-partum. Thirty years of global efforts have focused on training SBAs and standardizing the active management of the third stage of labour (AMTSL), said to be the single most effective method to prevent PPH at birth (Devine, 2009). Active Management of Third Stage of Labour (AMTSL) is by definition delivered by an SBA, and when administered correctly, halves the risk of PPH (Prevention of Postpartum Hemorrhage Initiative, 2009).

Uterotonics are arguably the most essential component of AMTSL (Gülmezoglu et al., 2012). Oxytocin remains the gold standard uterotonic of choice (World Health Organization, 2012a). Every major international oversight body recommends intravenous or intramuscular oxytocin for the prevention of PPH, and a tablet-form uterotonic, misoprostol (600 mcg oral), if and when oxytocin is not available (World Health Organization, 2012a). Oxytocin is heat labile and administered via injection, and thus often inaccessible to women giving birth outside health facilities (Raghavan, Abbas, & Winikoff, 2012; World Health Organization, 2012a). In practice, even when SBAs are equipped with oxytocin for home and facility births, it is often stored incorrectly and thus less efficacious (Torloni, Freitas, Kartoglu, Gulmezoglu, & Widmer, 2016; Wilson et al., 2012).

Recent efforts have focused on the use of misoprostol to reach women who deliver at home without a SBA. Misoprostol is a synthetic prostaglandin E1 originally developed for the prevention and treatment of gastric ulcers in 1985 (Garris & Kirkwood, 1989). Compared to oxytocin, misoprostol does not require refrigeration, and can be administered orally, sublingually, rectally and vaginally (Wise & Clark, 2008). Giving birth with an SBA is still recommended as the most essential step to decrease maternal mortality, and full coverage of facility births remains the ultimate goal (Murthy & Smith, 2009). Until every woman has access to an SBA, however, experts argue that the community distribution of misoprostol is a scalable and relatively safe intervention to reduce PPH (Oladapo, 2012; Prata, N. et al., 2011b; Smith, J. M., Gubin, Holston, Fullerton, & Prata, 2013). The WHO includes misoprostol for the prevention of PPH on the Essential Medicine List and community-based distribution (CBD), but has yet to recommend the advance distribution of misoprostol for self-administration (ADMSA) (World Health Organization, 2012a).

This narrative review aims to explore the context for on-going tensions between policy and practice surrounding the community-based distribution of misoprostol for PPH in low-income settings. We present a broad literature review and update the existing pilot studies on community-based distribution of misoprostol. We then outline the existing literature on expansion and scale-up to help understand why efforts to increase the availability of misoprostol in community settings countries have been protracted.

Methodology

Review methodology

A narrative review of both the qualitative and quantitative data was chosen over a systematic review to include both experimental and non-experimental descriptive studies (Whittemore & Knafel, 2005) as well as grey literature with narrative descriptions of programme challenges (Slavin, 1995). An initial set of papers were identified using the literature review strategy below, including “scale” and “scale-up” to broaden the scope of previous reviews. We conducted forward snowballing from the references of papers that met inclusion criteria. Grey literature searches from

UN agencies, governmental and non-government organisations websites and reports were included. Ethical clearance was obtained from the Human Research Ethics Committee at Charles Darwin University, Australia (HREC 2015-2445).

Literature review strategy

This review was conducted using four databases: Medline, Cochrane Review Library, CINAHL and ProQuest Dissertation & Theses Database. The search strategy included a combination of terms, including ‘misoprostol’; ‘post-partum haemorrhage’ (and variations i.e. ‘postpartum haemorrhage’, ‘post-partum hemorrhage’) ‘community-based maternal’; ‘maternal’; ‘maternal health interventions’; ‘maternal mortality’; ‘low-income setting’; ‘developing country’; ‘resource-poor setting’; ‘traditional birth attendant’; ‘scale’ and ‘scale-up’.

Inclusion and exclusion criteria

Dates were not restricted up until March 1st, 2016. Only English articles or those with an English translation were included. KH screened the literature for relevance to programmes using all modes of administration and doses of misoprostol for the prevention of PPH. Articles were excluded if the research took place in high-income countries, defined by a GNI per capita higher than 12 476 USD (World Bank, 2016). Articles were also excluded if conducted exclusively in clinical settings without a community component and if not specific to misoprostol; for example, TBA programmes that did not use misoprostol, or misoprostol for an indication other than the prevention of PPH, including abortion or induction of labour.

Results

A total of 249 articles were retrieved and screened from our search strategy. Of these, 135 full text articles were assessed for eligibility. See Figure 1. In total, 84 articles were eligible. Findings were organized into four major categories: evidence for the use of misoprostol in community settings; political momentum for the CBD of misoprostol, challenges to uptake in community settings; and the expansion and scale-up of CBD misoprostol. .

A total of 24 articles were included in the synthesis of CBD pilot studies. Many of these trials published before 2013 were detailed in the Smith et al. (2013) review of global implementation of misoprostol. The seven studies published after the 2013 review are outlined in Table 1. We identified nine studies of “scale”, defined for the purposes of this review as deliberate post-pilot efforts to expand CBD programs or include CBD of misoprostol in a national policy or operational plan. These are outlined in Table 2.

FIGURE 1 HERE

Evidence for Community-based Distribution of Misoprostol for the prevention of PPH

As early as 2002, a number of countries introduced pilot studies to assess the feasibility of distribution of misoprostol through CHWs or antenatal care (ANC) visits, with promising results (Derman et al., 2006; Mobeen et al., 2011; Prata, N, Mbaruku, Campbell, Potts, & Vahidnia, 2005; Rajbhandari et al., 2010; Sanghvi et al., 2010; Sanghvi, Wiknjastro, Chanpong, Fishel, & Ahmed, 2004). Findings from the seven pilot studies published after the Smith et al. review (2013), outlined in Table 1, drew similar conclusions to previous studies. Most trials concluded that women who used misoprostol self-reported significantly less heavy bleeding than those who did not receive uterotonics; where bleeding was objectively measured, the rate of PPH was significantly lower compared to placebo or no uterotonic. Most studies also measured significantly fewer bleeding-related referrals. The vast majority of women enrolled were able to correctly administer the medicine themselves or with the assistance of a community-based worker. Studies were often hosted in areas with very poor access to assisted deliveries, and misoprostol invariably increased uterotonic coverage - from 11.6% to 74.2% in 1 district of Nepal, for example (Rajbhandari et al., 2010). Community-based distribution of misoprostol nearly doubled the coverage rate versus distribution through health workers or ANC visits; in South Sudan, a 2014 study showed an even more dramatic difference in coverage when the drug is distributed via ANC versus home visits (17.2% versus 82.8%) (Smith, J.M., Baawo, S.D., et al., 2014) . Low coverage achieved in the Liberian study (24% of home births) was attributed to reliance on skilled health providers to counsel and distribute misoprostol. Several studies also documented that TBA and self-administered misoprostol programmes can work to bolster access to SBAs (Haver, Ansari, Zainullah, Kim, & Tappis, 2016; Prata, N. et al., 2011b). Acceptability was universally high: 87 - 99% of women would recommend misoprostol, and 54.6% - 95% were willing to pay. Several reviews have now examined the evidence for CBD of misoprostol for prevention of PPH, with similar conclusions (Flandermeyer, Stanton, & Armbruster, 2010; Smith, H. J. et al., 2015; Smith, J. M. et al., 2013). Two systematic reviews limited to randomized controlled trials (RCTs) of misoprostol in community settings were inconclusive, and called for large RCTs to confirm the safety and effectiveness of both CBD and ADMSA (Hundley et al., 2013; Oladapo, 2012).

TABLE 1 HERE

Political momentum for the Community-based Distribution of Misoprostol

The grey literature revealed a number of key political events that enabled misoprostol to be used in community settings for PPH. We present a chronological timeline in Figure 2.

The Derman et al. (2006) study was published amid growing evidence that misoprostol could be self-administered where SBAs and oxytocin are unavailable (World Health Organization, 2007a). In response, the WHO convened a technical consultation on the prevention of PPH in October of 2006. They concluded that oxytocin should remain the uterotonic of choice for the prevention of PPH and that there was insufficient evidence to recommend misoprostol given safety concerns and fear of misuse (Mathai, Gulmezoglu, & Hill, 2007; World Health Organization, 2007b). In 2007, WHO recommendations evolved somewhat to include misoprostol for PPH prevention in the absence of oxytocin: 'In the absence of active management of the third stage of labour, an uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH' (World Health Organization, 2007b, p. 14). The report did not address use in home births.

In 2009, the WHO released a formal statement on the use of misoprostol for prevention and treatment of PPH that explained why misoprostol was not on the WHO Essential Medicines List. They cited inconsistency of the studies comparing misoprostol to placebo; the significant risk of side effects; and concerns about the risk of maternal death given the potential for misuse (World Health Organization, 2009).

In spite of the lack of WHO support and approval, several countries had already taken steps to initiate the use of misoprostol for the prevention of PPH. In January 2006, Nigeria became the first country in the world to register misoprostol for prevention and treatment of PPH (Jadesimi & Okonofua, 2006). Ethiopia and Tanzania followed later that year, including misoprostol for PPH prevention on their respective National Essential Medicines List (Campbell & Holden, 2006).

With growing evidence and advocacy by maternal health experts, misoprostol was added to the WHO's Essential Medicines List in 2011 'for prevention of post-partum hemorrhage where oxytocin is not available or cannot be safely used' (World Health Organization, 2011, p. 29). In 2012, the WHO formally endorsed the administration of misoprostol for PPH prevention: 'In settings where SBAs are not present and oxytocin is unavailable, the administration of misoprostol (600 µg PO) by community health care workers and lay health workers is recommended for the prevention of PPH' (World Health Organization, 2012a, p. 5). In the same year, the WHO explicitly recognised that CHWs could contribute significantly to reduce PPH through the administration of misoprostol after home births

(World Health Organization, 2012b). This 2012 endorsement is considered a major turning point in garnering international support to use misoprostol for prevention of PPH (Karanja, Muganyizi, Rwamushaija, Hodoglulil, & Holm, 2013). The WHO upheld the recommendation for use of misoprostol for prevention of PPH in 2015 (World Health Organization, 2015a).

The WHO has yet to recommend the ADMSA. They cite the need for further research on safety, efficacy and coverage (World Health Organization, 2012a). Advance distribution achieves significantly higher uterotonic coverage at birth, and advocates see the lack of WHO endorsement of ADMSA as a major barrier to uptake (Smith, J.M., Baawo, S.D., et al., 2014; Smith, J. M. et al., 2013; Wells, E. et al., 2014).

FIGURE 2 HERE

Challenges to implementing misoprostol programmes in community settings

The literature is dotted with potential challenges to using misoprostol as an effective, alternative uterotonic in the absence of oxytocin, despite WHO endorsement (Chu, Brhlikova, & Pollock, 2012; Hundley et al., 2013; Oladapo, 2012; Starrs & Winikoff, 2012). The reasons for this are multifold: lack of direct evidence for reducing maternal mortality; safety and side effects; fear of misuse; reluctance to invest in CHWs; and detraction from facility-based births. One review specifically examined the barriers to implementation of community-based misoprostol programmes for prevention of PPH, and identified similar results (Smith, H. J. et al., 2015).

Lack of evidence for impact on maternal mortality

Misoprostol for prevention of PPH lacks direct evidence in reducing maternal deaths (Chu et al., 2012; Hofmeyr, Gulmezoglu, Novikova, & Lawrie, 2013; Hundley et al., 2013). RCTs comparing misoprostol to placebo in community distributions noted significant reductions in the incidence of PPH (Derman et al., 2006; Mobeen et al., 2011). However, some argue this is insufficient evidence for real reductions in maternal mortality (Chu et al., 2012; Oladapo, 2012).

Direct evidence on maternal mortality reduction is exceedingly difficult to measure given maternal mortality is a relatively rare event (Hofmeyr et al., 2009). A 2012 Cochrane systematic review assessed the effectiveness and safety of advance misoprostol distribution for PPH prevention and treatment in non-facility births (Oladapo, Fawole, Blum, & Abalos, 2012). Due to design flaws, no studies met the inclusion criteria. The lack of evidence regarding the direct impact on the reduction of maternal mortality remains a key concern for some policy and health experts.

Safety and side effects

The safety and side effect profile of misoprostol continues to be cited as a concern. Shivering, fever, nausea and

diarrhea are commonly reported side effects (Gülmezoglu et al., 2001; Oladapo, 2012). In several studies, the incidence of side effects has been significantly higher in misoprostol groups (Mobeen et al., 2011; Patted et al., 2009; Weeks et al., 2015). In a pilot study in Afghanistan, however, reported side effects were lower in the intervention group (Sanghvi et al., 2010). Many argue that the side effects are well understood, and can be easily managed (Grossman, Graves, Rwamushaija, & Park, 2010; Oladapo, 2012).

Uterine rupture is the most serious risk associated with misoprostol if taken before birth, which is true for any uterotonic (Hofmeyr, Say, & Gülmezoglu, 2005). A Cochrane review found no significant difference in maternal deaths or severe morbidity with misoprostol versus other uterotonics for the prevention or treatment of PPH (Hofmeyr et al., 2013).

Fear of misuse

Another challenge to wide-scale acceptance of misoprostol for PPH prevention is potential misuse. However, available evidence suggests that both misuse and diversion is uncommon. For example, mistimed administration of misoprostol in CBD programmes were reported as minimal (0.6%) in a global mapping study (Grenier, 2013). In a Ugandan study of 700 women, only two women had taken either misoprostol or placebo tablets early while the fetus was still in utero (Weeks et al., 2015). Similarly, in Liberia, only three of 265 women took misoprostol prior to giving birth (Smith, J.M., Baawo, S.D., et al., 2014). No adverse outcomes were reported in either study. A doctoral thesis on misuse of uterotonics in Southern Nepal found that over 90% of oral uterotonics were administered correctly according to FIGO guidelines (Connor, 2013).

Concern that misoprostol will be used for elective abortion is an ongoing concern. (Bazzano, Jones, & Ngo, 2014; Coeytaux et al., 2014; Geressu, Tibebu, Coeytaux, & Wells, 2014). When misoprostol is used alone, it is 85% effective in termination of pregnancy under 12 weeks (International Women's Health Coalition & Gynuity Health Projects, 2010). Several governments in countries where elective abortion is illegal have restricted access to misoprostol for fear it will be used for termination of pregnancies (Coeytaux & Wells, 2011; Kulczycki, 2011; Kumar, 2012). Another fear is that CHWs will use misoprostol inappropriately to induce labour (Grenier, 2013; Smith, H. J. et al., 2015). There is, however, no evidence to suggest that misoprostol distributed for the purpose of the prevention of PPH is being diverted for labour induction or pregnancy termination (Grenier, 2013; Starrs & Winikoff, 2012). The Hundley et al. (2013) systematic review concluded that while most women take the drug at the appropriate time, more research is needed to inform safety protocols and communication strategies.

Reluctance to invest in CHWs

After major investment in TBA training programmes in the 1970s and 80s, a meta-analysis revealed minimal impact on maternal mortality (Sibley & Ann Sipe, 2004). This led to the current-day reluctance from policy-makers to invest in the training of less qualified CHWs and TBAs (Prata, N. et al., 2011a). Many believe resources should be focused on training and retaining SBAs, as emphasized in the MDGs (Ronsmans, Campbell, Mcdermott, & Koblinsky, 2002). Others argue that TBAs were never armed with appropriate training and technology or reliable referral mechanisms, and misoprostol may now provide a useful tool (Karoshi & Keith, 2009; Prata, N. et al., 2011b). In combination with evidence for other low-cost interventions such as birth kits and chlorohexidine, there may now be a real opportunity for TBAs to reduce maternal and newborn mortality (Prata, N. et al., 2011b; Prata, Ndola et al., 2012). Importantly, CBD resulted in nearly double the coverage of misoprostol compared to distribution through health workers or ANC visits (Smith, J. M. et al., 2013).

Detraction from a facility-birth strategy

The goal of universal coverage of facility-based births lies at the core of global maternal mortality reduction efforts (Bazzano et al., 2014; United Nations, 2015). This must be accompanied by adequate numbers of SBAs, equipment and supplies, and surgical care (Murthy & Smith, 2009). Governments and policy makers cite concern that advance distribution of misoprostol will detract from facility-based birth strategies (Collins, Mmari, Mullany, Gruber, & Favero, 2016; Geressu et al., 2014; Weeks et al., 2015). This has not been borne out in Ghana (Geller et al., 2014) Indonesia (Sanghvi et al., 2004), Nepal (Khanal et al., 2012), Liberia (Smith, J.M., Baawo, S.D., et al., 2014) or Afghanistan (Sanghvi et al., 2010), where CBD misoprostol programmes found an increase in coverage of SBA and facility-based births. However, this link was not found to be directly causal and other factors such as an increase in SBA or infrastructure investment may have also influenced outcomes. In Ethiopia, place of birth (health facility or home) was not associated with women who received misoprostol during pregnancy (Sibley et al., 2014).

Scale-up of community-based distribution of misoprostol

The WHO defines scale up as the following: "...deliberate efforts to increase the impact of health service innovations successfully tested in pilot or experimental projects so as to benefit more people and to foster policy and programme development on a lasting basis" (Simmons, Fajans, & Ghiron, 2007, p. viii). Scale-up of advance distribution of misoprostol for PPH requires supportive policies and a permissive environment to back the intervention (Grenier, 2013; Karanja et al., 2013). For misoprostol, implementation is also complex, and demands support of national governments to develop national guidelines and policies, including the essential medicines list, procure and

distribute the drug, and not least, train health staff and community workers (Robinson, Kapungu, Carnahan, & Geller, 2014).

Despite explicit commitments from governments, the act of ‘going to scale’ with community-based distribution and self-administration of misoprostol has been both slow and challenging (Karanja et al., 2013; Oladapo, 2012). Delayed 2012 endorsement from the WHO for distribution by CHWs, coupled with the challenges outlined above, may limit government buy-in to scale programmes (Smith, H. J. et al., 2015).

From 2006 to 2012, there were several major developments of international programmes using misoprostol for the prevention of PPH: 15 programmes were initiated in 11 countries (Coeytaux & Wells, 2011; Smith, J. M. et al., 2013). As of 2013, more than 30 countries had registered misoprostol for PPH prevention (Grenier, 2013). In 2014, Venture Strategies Innovations developed a map of countries that have registered misoprostol by indication which depicts slightly different results (Venture Strategies Innovations, 2014). A 2012 survey found that 16 of 37 study countries had piloted ADMSA (Smith, J. M., Currie, Cannon, Armbruster, & Perri, 2014). By 2014, however, only five of these 16 countries - Afghanistan, Bangladesh, Ethiopia, Nepal and Nigeria - were actively scaling for wider distribution (Smith, J. M. et al., 2014).

Progress on Scale-up

At the time of writing, documented progress to expand advance distribution of misoprostol for PPH was available from Afghanistan, Bangladesh, Ethiopia, Ghana, Nepal, Nigeria and South Sudan. Published evaluations of scale-up efforts are limited, and only nine evaluations were retrieved (see Table 2). Bangladesh and Nepal are the only countries which have documented persistent efforts to move to scale. Three evaluations conducted by the Public Health Institute revealed varying progress on expansion of pilot studies in Ghana and Nigeria, while the project has been discontinued in Ethiopia (Wells, E. et al., 2014).

In Afghanistan, the Ministry of Public Health (MoPH) requested the support to conduct a pre and post intervention evaluation of the expansion of advance distribution of misoprostol for PPH (Haver et al., 2016). Advance distribution of misoprostol in the community significantly increased uterotonic coverage, especially in rural and remote areas (Haver et al., 2016). Community involvement, including religious leaders and CHWs, in the process of introducing the programme was seen as paramount to its success (Cristy, 2013). Based on the findings, the MoPH included expansion of misoprostol as a priority in the 2012-2016 Reproductive Health Strategy, and the authors recommended inclusion of ADSMA in the Basic Service Package (Haver et al., 2016).

In Bangladesh, the 'National Scale-up Plan' was approved in 2010 and expansion began in 2011 in 4 districts with a plan to expand nationally (Family Care International, 2012). Operations research on scale-up in 29 sub-districts in 6 provinces in Bangladesh found misoprostol distributed through clean birthing kits was effective, feasible and safe, and achieved 60% coverage of uterotonics for women who gave birth at home (Quaiyum, Holston, Hossain, Bell, & Prata, 2011). Authors recommend extending distribution beyond ANC and using other networks of trained TBAs to increase coverage and scale-up.

The Ethiopian Ministry of Health included misoprostol for the prevention of PPH within the 2011-2015 strategy to reduce maternal and newborn morbidity and mortality (Geressu et al., 2014). The strategy provided guidance for Health Extension Workers to distribute misoprostol to prevent PPH at home births. Important differences in misoprostol coverage and interpretation of national misoprostol policy were revealed between two regions of Ethiopia (95% coverage in Oromiya Region versus 25% in Amhara Region), likely due to one health authority which permitted wider distribution through skilled providers, health extension workers and community-based volunteers (Sibley et al., 2014; Spangler, Gobeze, Getachew, & Sibley, 2014). The authors recommend implementing a variety of distribution methods to assist in increasing reach (ANC, SBA, TBA and CBW) (Sibley et al., 2014). A 2014 process evaluation identified that decision makers fear induced abortion and detraction from facility-based births, which have stalled efforts to continue scale-up (Geressu et al., 2014).

In Ghana, a process evaluation of scale-up found high rates of adherence and acceptance of misoprostol within the community (Azasi, Coeytaux, & Wells, 2014). Misoprostol is integrated into the national health system's continuum of care model and distributed in advance at ANC to women who are in the third trimester. Women are provided with information about how to use the medication appropriately; emphasis is on birthing at a health facility where possible. A community outreach component has CHWs and TBAs conducting home visits to provide further information to women about safe delivery and encourage ANC attendance to receive misoprostol. In 2014, the National PPH Strategy designated scale-up of misoprostol to 30% of the country in regions with the highest burden of home births. Ghana was in a good position to scale-up, yet expansion was proceeding slowly due to limited financial resources for training and procurement as well as the underlying concern that misoprostol may be used for abortion (Azasi et al., 2014). The authors note that because the project was within a Millennium Development Village with adequate infrastructure, human resources and available services, it may be challenging to integrate the model into the Ghana Health Service.

The Government of Nepal approved a staged national scale-up of misoprostol at home births in 2010 (Government of Nepal Ministry of Health and Population, New Era, & Gynuity Health Projects, 2014). By 2012,

misoprostol reached 22 districts with assistance from international donors, and by 2013, the programme had rapidly expanded to cover 31 of 75 districts (Government of Nepal Ministry of Health and Population et al., 2014). Evaluation revealed a number of challenges, including poor coverage at 15%, stock-outs at least once in the previous 12 months of the survey were found in a third of health facilities and difficulties with retrieval of distributed but unused tablets. Low uptake of misoprostol for women who received but did not consume was attributed to higher rates of institutional births. The authors recommend a strategic focus on remote areas with frequent home births and re-emphasis on universal distribution by CHWs void of perceptions of where they believe the birth will take place (Government of Nepal Ministry of Health and Population et al., 2014).

In Nigeria, the programme model relies on TBAs and CHWs to distribute misoprostol within clean birth kits (Otiye-Igbuzor, Danmusa, Potts, Coeytaux, & Wells, 2014). One project has expanded to two districts; further expansion may be limited by the need to create new community health positions given the lack of existing structures (Otiye-Igbuzor et al., 2014). The Ministry of Health has also been reluctant to allow CHWs and TBAs to distribute the drug as they are not considered 'trained community agents' (Wells, E. et al., 2014, p.14).

South Sudan has been implementing advance distribution of misoprostol for PPH prevention since 2012 as a component of the national PPH programme (Smith, J.M., Alexander, D., et al., 2014). Advance distribution by home health promoters was found to be safe, feasible and effective with high uterotonic coverage (Smith, J.M., Alexander, D., et al., 2014). Almost 10, 000 women received uterotonics immediately after birth across the two states from 2013 - 2015, a vast improvement from almost no uterotonic coverage prior to launch (Jhpiego, 2015). While the programme had plans to expand to three additional counties (Jhpiego, 2015) it has now ceased due to funding cuts in 2016.

TABLE 2 HERE

A number of countries are in the early phases of scale-up, with no published reports at the time of writing. In Mozambique, for example, the 2013-2015 Strategy for the Prevention of PPH in the Community includes distribution of misoprostol in the community in 35 districts (Libombo et al., 2013). Similarly, India, Madagascar and Pakistan have adopted policies or guidance surrounding use of misoprostol for PPH (Larson, Raney, & Ricca, 2014; Sarwar, Cutherell, Noor, Naureen, & Norman, 2015). Obstacles to implementation persist. In Madagascar, the drug has not yet been registered for prevention of PPH due to concerns about uterine rupture and diversion for abortion (Collins et al., 2016).

Discussion

This review highlights the evidence and historical timeline for community-based misoprostol for the prevention of PPH, the challenges surrounding its use, and minimal progress on scale-up to date. The scientific literature and operations research remains incomplete, but the available literature suggests that in practice, misoprostol approaches the safety and efficacy of other uterotonics. CBD programmes have consistently demonstrated that CHWs can distribute misoprostol, and women can take the medication appropriately. WHO recommends misoprostol as a safe, affordable and feasible strategy for women who give birth at home and included it on the Essential Medicines List; however, the WHO fell short of endorsing advance community-based distribution. Policy makers in several countries have been reluctant to make it a national priority, in part because of hesitant WHO support and lack of RCTs. Ongoing concerns about safety, efficacy, and aptitude of CHWs plague the history of misoprostol; notably, concerns about diversion and misuse for both induction of labour and induced abortion underpin much of the stagnation in expanding national programmes, including in Ethiopia (Geressu et al., 2014; Spangler et al., 2014).

Strategies to overcome fear of misuse have been trialed, including branding the tablets as ‘safer after-birth’ (Vallely et al., 2016 p.2) and establishing strict controls that monitor distribution and retrieval of unused pills (Azasi et al., 2014; Geller et al., 2014; Grenier, 2013; Vallely et al., 2016; Wells, E. et al., 2014). Strict controls applied in a pilot, however, may not be feasible or sustainable for scale-up due to the heavy administrative burden; health staff and CHWs can encourage women to return unused doses of misoprostol to the health facility without tracking each pill (Azasi et al., 2014). The politics of who can distribute medicines also threatens the expansion of advance distribution of misoprostol in Nigeria and Ethiopia despite a successful pilot phase. Disquietude about relinquishing power to community-based workers is a recurrent theme through the history of CHW engagement (Perry & Zulliger, 2012). The advance distribution of misoprostol through antenatal care visits bypasses CHWs altogether, especially where networks are weak; the corollary to that is clear evidence that community based distribution can double coverage (Smith, J. M. et al., 2013).

We describe several efforts to expand community distribution of misoprostol in Afghanistan, Bangladesh, Ethiopia, Ghana, Nepal, Nigeria and South Sudan. They share a combination of successful pilot studies, central leadership, integration into national reproductive and maternal health strategies, and existing cadres of CHWs or TBAs. Several country examples highlight the need for strategic investments including infrastructure, supplies, equipment and training, combined with careful results-based monitoring are needed to sustain misoprostol programmes and reach those most in need (Freedman et al., 2007). Documentation of programme expansion is weak, and is not always congruent with what is happening in practice; for example, colleagues have reported that programmes are expanding in Pakistan and Tanzania, but no formal documentation was found in this review. Even among countries like Ethiopia and South Sudan with successful pilots, explicit government commitment and integration within national

policy and strategies, few have been able to operationalize national programmes. Many of the challenges moving from the pilot stage to policy and widespread implementation are expected in scaling interventions (Smith, J.M., De Graft-Johnson, Zyaee, Ricca, & Fullerton, 2015; Wells, E. et al., 2014). Governments may benefit from assistance to develop national guidelines, drug monitoring and distribution, coverage and monitoring plans, inclusion on the national essential medicines list and training staff and CHWs (Robinson et al., 2014).

It remains unclear to what extent the challenges highlighted in the literature have deterred scale-up of community-based or advance distribution of misoprostol for PPH. USAID's Maternal and Child Health Program is currently undertaking the study of scale-up of advance distribution of misoprostol for self-administration (ADMSA) to better understand the factors that facilitate and restrict successful scale-up. Implementation science could assist other countries and organizations who are planning the scale-up of ADMSA and inform key strategies to avoid delays (Grenier, 2015).

Decision makers are likely sensitive to the wording used by WHO in the PPH guidelines, highlighted by the controversy in Nigeria and Ethiopia of what constituted a "community health care worker or a lay health care worker" (World Health Organization, 2012a, p. 5). In 2010, the WHO clarified its position stating "While WHO does not condemn the community distribution of misoprostol during pregnancy, WHO does not recommend such practice because its potential benefits and harms are currently unknown and recommends proper research to evaluate its role in reducing maternal deaths" (World Health Organization, 2010, p.1). The brief concludes by stating that WHO has a cautious position regarding the advance distribution of misoprostol during pregnancy and recommends further rigorous research which will be reviewed critically and used to update recommendations to Member States as appropriate (World Health Organization, 2010).

Lack of clear endorsement of the advance distribution is related to trust in both the CHW and women themselves – not to sell, not to misuse, abort or induce or accelerate labour and ultimately to take misoprostol at the right time (Wells, Elisa et al., 2016). The WHO argues for further research on safety, efficacy and coverage before they will support CBD (World Health Organization, 2012a). This review and that of Smith et al (2013) negates many of these concerns. The behavioural outcomes of interest have been successfully studied in operations research studies and are difficult to elucidate in an RCT (Geller et al., 2014; Potts & Hemmerling, 2006). Further research is required to better understand the factors that drive national scale-up and institutionalization, and to inform WHO policy recommendations on advance distribution of misoprostol for prevention of PPH.

Conclusion

This review supports the rationale for providing alternative uterotonics to women with little choice but to deliver at home. We conclude that it is a relatively safe, affordable and simple method to prevent PPH for women unable to access health facilities or an SBA. Experience to date suggests that we can simultaneously bolster the coverage and quality of skilled attendance at birth and strengthen health systems to bring advance distribution of misoprostol to scale.

A number of challenges to advancing the use of misoprostol for PPH prevention were highlighted; their influence on decision makers remains poorly understood. Expansion and scale-up of community distribution of misoprostol is ongoing in several countries; however coverage remains incongruent with the large number of pilot studies and evidence in favour of its use. Operations research at the country-level is urgently needed to inform evidence-based decision-making and programme planning, and to understand the critical pathways that allowed decision makers to progress past the pilot phase to scale an evidence-based maternal health intervention.

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References

- Arulkumaran, S., Regan, L., Papageorghiou, A. T., Monga, A., & Farquharson, D. (2011). *Oxford Desk Reference: Obstetrics and Gynaecology*. New York: Oxford University Press
- Azasi, E., Coeytaux, F., & Wells, E. (2014). *Community-based distribution of misoprostol for prevention of postpartum hemorrhage: a continuum of care model in Ghana*. Oakland, CA: Public Health Institute.
- Bazzano, A., Jones, L., & Ngo, T. (2014). Stakeholder's perception of misoprostol: a qualitative investigation. *International Journal Womens Health*(6), 389-393. doi: <http://dx.doi.org/10.2147/IJWH.S58638>
- Campbell, M., & Holden, M. (2006). Global availability of misoprostol. *International Journal of Gynecology & Obstetrics*, 94, Supplement 2, S151-S152. doi: [http://dx.doi.org/10.1016/S0020-7292\(06\)60020-9](http://dx.doi.org/10.1016/S0020-7292(06)60020-9)
- Chu, C. S., Brhlikova, P., & Pollock, A. M. (2012). Rethinking WHO guidance: Review of evidence for misoprostol use in the prevention of postpartum haemorrhage. *Journal of the Royal Society of Medicine*, 105(8), 336-347. doi: 10.1258/jrsm.2012.120044
- Coeytaux, F., Hessini, L., Ejano, N., Obbuyi, A., Oguttu, M., Osur, J., & Shuken, K. (2014). Facilitating women's access to misoprostol through community-based advocacy in Kenya and Tanzania. *International Journal of Gynaecology & Obstetrics*. doi: <http://dx.doi.org/10.1016/j.ijgo.2013.10.004>
- Coeytaux, F., & Wells, E. (2011). *Mapping misoprostol for postpartum hemorrhage: Organizational activities, challenges, and opportunities*. New York, U.S.A: Family Care International.
- Collins, L., Mmari, K., Mullany, L. C., Gruber, C. W., & Favero, R. (2016). An exploration of village-level uterotonic practices in Fenerive-Est, Madagascar. *BMC Pregnancy and Childbirth*, 16(1), 1-10. doi: 10.1186/s12884-016-0858-3
- Connor, A. L. (2013). *The use and misuse of uterotonics and related adverse material and perinatal health outcomes in rural Southern Nepal*. (3578781 Ph.D.), The Johns Hopkins University, Ann Arbor.
- Cristy, C. (2013). *Community-based development-scaling up the correct use of misoprostol at home births in Afghanistan*. (1545273 M.S.), Arizona State University, Ann Arbor.
- Dao B, Ngabo F, Zoungrana J, Rawlins B, Mukarugwiro B, & P, M. (2015). Increasing access to prevention of postpartum hemorrhage interventions for births in health facilities and at home in four districts of Rwanda. *African Journal of Reproductive Health*, 15(4), 58-67
- Derman, R. J., Kodkany, B. S., Goudar, S. S., Geller, S. E., Naik, V. A., Bellad, M. B., . . . Moss, N. (2006). Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *The Lancet*, 368(9543), 1248-1253
- Devine, P. C. (2009). Obstetric hemorrhage. *Seminars in Perinatology*, 33(2), 76-81. doi: 10.1053/j.semperi.2008.12.004
- Edhi, M. M., Aslam, H. M., Naqvi, Z., & Hashmi, H. (2013). "Post partum hemorrhage: causes and management". *BMC Research Notes*, 6, 236. doi: 10.1186/1756-0500-6-236
- Ejembi, C. L., & Prata, N. (2010). *Prevention of postpartum hemorrhage at home births in five communities around Zaria, Kaduna State, Nigeria: technical report*. V. S. Innovations.
- El-Refaey, H., & Rodeck, C. (2003). Post-partum haemorrhage: definitions, medical and surgical management. A time for change. *British Medical Bulletin*, 67(1), 205-217. doi: 10.1093/bmb/ldg016
- Family Care International. (2012). *Misoprostol for postpartum hemorrhage: reaching women wherever they give birth stories of success in Bangladesh, Nepal, and Zambia*. New York, NY: Family Care International.
- Flandermeyer, D., Stanton, C., & Armbruster, D. (2010). Uterotonic use at home births in low-income countries: a literature review. *International Journal of Gynecology & Obstetrics*, 108(3), 269-275. doi: <http://dx.doi.org/10.1016/j.ijgo.2009.12.001>
- Freedman, L. P., Graham, W. J., Brazier, E., Smith, J. M., Ensor, T., Fauveau, V., . . . Agarwal, K. (2007). Practical lessons from global safe motherhood initiatives: time for a new focus on implementation. *The Lancet*, 370(9595), 1383-1391. doi: [http://dx.doi.org/10.1016/S0140-6736\(07\)61581-5](http://dx.doi.org/10.1016/S0140-6736(07)61581-5)
- Garris, R., & Kirkwood, C. (1989). Misoprostol: a prostaglandin E1 analogue. *Clinical pharmacy*, 8(9), 627
- Geller, S., Carnahan, L., Akosah, E., Asare, G., Agyemang, R., Dickson, R., . . . Mensah-Homiah, J. (2014). Community-based distribution of misoprostol to prevent postpartum haemorrhage at home births: results from operations research in rural Ghana. *BJOG*, 121(3), 319-325. doi: 10.1111/1471-0528.12447
- Geressu, T., Tibebu, S., Coeytaux, F., & Wells, E. (2014). *Community-based distribution of misoprostol for prevention of postpartum hemorrhage: an innovative approach in Ethiopia*. Oakland, CA: Public Health Institute.
- Government of Nepal Ministry of Health and Population, New Era, & Gynuity Health Projects. (2014). *Evaluation of postpartum hemorrhage prevention program in Nepal*. Kathmandu, Nepal: Government of Nepal Department of Health.
- Grenier, L. (2013). *Advance distribution of misoprostol for self-administration: Expanding coverage for the prevention of postpartum hemorrhage*. Baltimore, MD: Jhpiego.
- Grenier, L. (2015). personal communication.
- Grossman, A., Graves, A., Rwamushaija, E., & Park, C. (2010). Misoprostol for safe motherhood: one tablet, two life-saving indications. *African Journal of Midwifery and Women's Health*, 4(3), 121-125
- Gülmezoglu, A. M., Lumbiganon, P., Landoulsi, S., Widmer, M., Abdel-Aleem, H., Festin, M., . . . Elbourne, D. (2012). Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. *The Lancet*, 379(9827), 1721-1727. doi: [http://dx.doi.org/10.1016/S0140-6736\(12\)60206-2](http://dx.doi.org/10.1016/S0140-6736(12)60206-2)

- Gülmezoglu, A. M., Villar, J., Ngoc, N. T., Piaggio, G., Carroli, G., Adetoro, L., . . . Schulz, K. (2001). WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet (London, England)*, 358(9283), 689-695
- Haver, J., Ansari, N., Zainullah, P., Kim, Y.-M., & Tappis, H. (2016). Misoprostol for prevention of postpartum hemorrhage at home birth in Afghanistan: program expansion experience. *Journal of Midwifery & Women's Health*. doi: 10.1111/jmwh.12413
- Hofmeyr, G. J., Gülmezoglu, A. M., Novikova, N., & Lawrie, T. A. (2013). Postpartum misoprostol for preventing maternal mortality and morbidity. *The Cochrane database of systematic reviews*, 7, 1-146. doi: 10.1002/14651858.CD008982.pub2.
- Hofmeyr, G. J., Gülmezoglu, A. M., Novikova, N., Linder, V., Ferreira, S., & Piaggio, G. (2009). Misoprostol to prevent and treat postpartum haemorrhage: A systematic review and meta-analysis of maternal deaths and dose-related effects. *Bull World Health Organ*, 87(9), 666-677. doi: 10.2471/BLT.08.055715
- Hofmeyr, G. J., Say, L., & Gülmezoglu, M. A. (2005). Systematic review: WHO systematic review of maternal mortality and morbidity: the prevalence of uterine rupture. *BJOG*, 112(9), 1221-1228. doi: 10.1111/j.1471-0528.2005.00725.x
- Hundley, V. A., Avan, B. I., Sullivan, C. J., & Graham, W. J. (2013). Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence. *BJOG*, 120(3), 277-285
- International Women's Health Coalition, & Gynuity Health Projects. (2010). *Abortion with self-administered misoprostol: A guide for women*. Retrieved from <https://iwhc.org/resource/abortion-self-administered-misoprostol-guide-women/>
- Jadesimi, A., & Okonofua, F. E. (2006). Tackling the unacceptable: Nigeria approves misoprostol for postpartum haemorrhage. *J Fam Plann Reprod Health Care*, 32(4), 213-214
- Jhpiego. (2015). *Jhpiego in South Sudan*. Baltimore, Maryland: Jhpiego.
- Karanja, J., Muganyizi, P., Rwamushaija, E., Hodoglulig, N., & Holm, E. N. (2013). Confronting maternal mortality due to postpartum hemorrhage and unsafe abortion: a call for commitment. *African Journal of Reproductive Health*, 17(2), 18-22
- Karoshi, M., & Keith, L. (2009). Challenges in managing postpartum hemorrhage in resource-poor countries. *Clinical Obstetrics & Gynecology*, 52(2), 285-298 214p. doi: 10.1097/GRF.0b013e3181a4f737
- Kassebaum, N. J., Bertozzi-Villa, A., Coggeshall, M. S., Shackelford, K. A., Steiner, C., Heuton, K. R., . . . Lozano, R. (2014). Global, regional, and national levels and causes of maternal mortality during 1990-2013: A systematic analysis for the global burden of disease study 2013. *The Lancet*, 384(9947), 980-1004. doi: [http://dx.doi.org/10.1016/S0140-6736\(14\)60696-6](http://dx.doi.org/10.1016/S0140-6736(14)60696-6)
- Khanal, L., Dawson, P., Silwal, R. C., Sharma, J., Kc, N. P., & Upreti, S. R. (2012). Exploration and innovation in addressing maternal, infant and neonatal mortality. *Journal of Nepal Health Research Council*, 10(21), 88-94
- Kulczycki, A. (2011). Abortion in Latin America: changes in practice, growing conflict, and recent policy developments. *Studies in Family Planning*, 42(3), 199-220
- Kumar, R. (2012). Misoprostol and the politics of abortion in Sri Lanka. *Reproductive Health Matters*, 20(40), 166-174 169p. doi: 10.1016/S0968-8080(12)40652-8
- Lane, C., & Andriamiadana, J. (2012). *Assessment of USAID/Madagascar youth programming and recommendations for future action to improve reproductive health outcomes among Malagasy youth*.
- Larson, A., Raney, L., & Ricca, J. (2014). *Lessons learned from a preliminary analysis of the scale-up experience of six high-impact reproductive, maternal, newborn, and child health (RMNCH) interventions* Baltimore, MA: Jhpiego.
- Libombo, A., Bique, C., da Luz Vaz, M., Jamisse, L., Reis, V., David, E., . . . Amade, N. (2013). *Strategy for the prevention of postpartum hemorrhage at the community level*. Maputo, Mozambique: Ministry of Health
- Mathai, M., Gülmezoglu, A. M., & Hill, S. (2007). Saving women's lives: evidence-based recommendations for the prevention of postpartum haemorrhage. *Bull World Health Organ*, 85(4), 322-323. doi: 10.2471/blt.07.041962
- Mobeen, N., Durocher, J., Zuberi, N., Jahan, N., Blum, J., Wasim, S., . . . Hatcher, J. (2011). Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: A randomised placebo-controlled trial. *BJOG*, 118(3), 353-361. doi: 10.1111/j.1471-0528.2010.02807.
- Murthy, P., & Smith, C. L. (2009). *Women's Global Health and Human Rights*. Mississauga, Canada: Jones and Bartlett Publishers Canada.
- Oladapo, O. T. (2012). Misoprostol for preventing and treating postpartum hemorrhage in the community: A closer look at the evidence. *International Journal of Gynecology & Obstetrics*, 119(2), 105-110. doi: <http://dx.doi.org/10.1016/j.ijgo.2012.08.004>
- Oladapo, O. T., Fawole, B., Blum, J., & Abalos, E. (2012). Advance misoprostol distribution for preventing and treating postpartum haemorrhage. *The Cochrane database of systematic reviews*, 2, 1-14. doi: 10.1002/14651858.CD009336.pub2
- Otive-Igbuzor, E., Danmusa, S., Potts, J., Coeytaux, F., & Wells, E. (2014). *Community-based distribution of misoprostol for prevention of postpartum hemorrhage: public and private sector approaches in Nigeria*. Oakland, CA: Public Health Institute.
- Patted, S. S., Goudar, S. S., Naik, V. A., Bellad, M. B., Edlavitch, S. A., Kodkany, B. S., . . . Geller, S. E. (2009). Side effects of oral misoprostol for the prevention of postpartum hemorrhage: results of a community-based

- randomised controlled trial in rural India. *Journal of Maternal-Fetal & Neonatal Medicine*, 22(1), 24-28 25p. doi: 10.1080/14767050802452309
- Perry, H., & Zulliger, R. (2012). *How effective are community health workers? An overview of current evidence with recommendations for strengthening community health worker programs to accelerate progress in achieving the health-related millennium goals 2012*. Baltimore.
- Potts, M., & Hemmerling, A. (2006). The worldwide burden of postpartum haemorrhage: Policy development where inaction is lethal. *International Journal of Gynecology & Obstetrics*, 94, Supplement 2(0), S116-S121. doi: [http://dx.doi.org/10.1016/S0020-7292\(06\)60003-9](http://dx.doi.org/10.1016/S0020-7292(06)60003-9)
- Prata, N., Ejembi, C., Fraser, A., Shittu, O., & Minkler, M. (2012). Community mobilization to reduce postpartum hemorrhage in home births in northern Nigeria. *Social Science & Medicine (1982)*, 74(8), 1288-1296. doi: 10.1016/j.socscimed.2011.11.035
- Prata, N., Gessesew, A., Abraha, A. K., Holston, M., & Potts, M. (2009). Prevention of postpartum hemorrhage: options for home births in rural Ethiopia. *Afr J Reprod Health*, 13(2), 87-95
- Prata, N., Mbaruku, G., Campbell, M., Potts, M., & Vahidnia, F. (2005). Controlling postpartum hemorrhage after home births in Tanzania. *International Journal of Gynecology & Obstetrics*, 90(1), 51-55. doi: <http://dx.doi.org/10.1016/j.ijgo.2005.03.007>
- Prata, N., Passano, P., Rowen, T., Bell, S., Walsh, J., & Potts, M. (2011a). Where there are (few) skilled birth attendants. *Journal of Health, Population & Nutrition*, 29(2), 81-91 11p
- Prata, N., Passano, P., Rowen, T., Bell, S., Walsh, J., & Potts, M. (2011b). Where there are (few) skilled birth attendants. *J Health Popul Nutr*, 29(2), 81-91
- Prata, N., Quaiyum, M. A., Passano, P., Bell, S., Bohl, D. D., Hossain, S., . . . Begum, M. (2012). Training traditional birth attendants to use misoprostol and an absorbent delivery mat in home births. *Social Science & Medicine*, 75(11), 2021-2027 2027p. doi: 10.1016/j.socscimed.2012.06.028
- Prevention of Postpartum Hemorrhage Initiative. (2009). *Tackling the biggest maternal killer: How the prevention of postpartum hemorrhage initiative strengthened efforts around the world*. Washington, DC: PATH.
- Quaiyum, M. A., Holston, M., Hossain, S. A. S., Bell, S., & Prata, N. (2011). *Scaling Up of Misoprostol for Prevention of Postpartum Hemorrhage in 29 Upazilas of Bangladesh: Final Report*. Dhaka, Bangladesh: Venture Strategies Innovations.
- Raghavan, S., Abbas, D., & Winikoff, B. (2012). Misoprostol for prevention and treatment of postpartum hemorrhage: what do we know? What is next? *International Journal of Gynaecology & Obstetrics*, 119 Suppl 1, S35-38. doi: 10.1016/j.ijgo.2012.03.013
- Rajbhandari, S., Hodgins, S., Sanghvi, H., McPherson, R., Pradhan, Y. V., & Baqui, A. H. (2010). Expanding uterotonic protection following childbirth through community-based distribution of misoprostol: operations research study in Nepal. *International Journal of Gynaecology & Obstetrics*, 108(3), 282-288. doi: 10.1016/j.ijgo.2009.11.006
- Robinson, N., Kapungu, C., Carnahan, L., & Geller, S. (2014). Recommendations for scale-up of community-based misoprostol distribution programs. *International Journal of Gynecology & Obstetrics*, 125(3), 285-288. doi: <http://dx.doi.org/10.1016/j.ijgo.2013.12.005>
- Ronsmans, C., Campbell, O. M., McDermott, J., & Koblinsky, M. (2002). Questioning the indicators of need for obstetric care. *Bull World Health Organ*, 80(4), 317-324
- Sanghvi, H., Ansari, N., Prata, N. J. V., Gibson, H., Ehsan, A. T., & Smith, J. M. (2010). Prevention of postpartum hemorrhage at home birth in Afghanistan. *International Journal of Gynecology & Obstetrics*, 108(3), 276-281. doi: <http://dx.doi.org/10.1016/j.ijgo.2009.12.003>
- Sanghvi, H., Wiknjastro, G., Chanpong, G., Fishel, J., & Ahmed, S. (2004). *Prevention of postpartum hemorrhage study West Java, Indonesia*. Baltimore, MD: JHPIEGO.
- Sarwar, Z., Cutherell, A., Noor, A., Naureen, F., & Norman, J. (2015). Analysis of misoprostol and chlorhexidine policy gains in Pakistan: the advocacy experience of Mercy Corps Pakistan. *Health Research Policy And Systems / Biomed Central*, 13 Suppl 1, 50-50. doi: 10.1186/s12961-015-0037-4
- Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, A.-B., Daniels, J., . . . Alkema, L. (2014). Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health*, 2(6), e323-e333. doi: [http://dx.doi.org/10.1016/S2214-109X\(14\)70227-X](http://dx.doi.org/10.1016/S2214-109X(14)70227-X)
- Sibley, L. M., & Ann Sipe, T. (2004). What can a meta-analysis tell us about traditional birth attendant training and pregnancy outcomes? *Midwifery*, 20(1), 51-60. doi: 10.1016/s0266-6138(03)00053-6
- Sibley, L. M., Spangler, S. A., Barry, D., Tesfaye, S., Desta, B. F., & Gobeze, A. G. (2014). A regional comparison of distribution strategies and women's awareness, receipt, and use of misoprostol to prevent postpartum hemorrhage in rural Amhara and Oromiya regions of Ethiopia. *Journal of midwifery & women's health*, 59 Suppl 1, S73-82. doi: 10.1111/jmwh.12136.
- Simmons, R., Fajans, P., & Ghiron, L. (2007). *Scaling up health service delivery: from pilot innovations to policies and programmes*. Geneva: WHO.
- Slavin, R. E. (1995). Best evidence synthesis: An intelligent alternative to meta-analysis. *Journal of Clinical Epidemiology*, 48(1), 9-18. doi: [http://dx.doi.org/10.1016/0895-4356\(94\)00097-A](http://dx.doi.org/10.1016/0895-4356(94)00097-A)
- Smith, H. J., Colvin, C. J., Richards, E., Roberson, J., Sharma, G., Thapa, K., & Metin Gülmezoglu, A. (2015). Programmes for advance distribution of misoprostol to prevent post-partum haemorrhage: a rapid literature review of factors affecting implementation. *Health Policy and Planning*. doi: 10.1093/heapol/czv012

- Smith, J., Baawo, S., Subah, M., Sirtor-Gbassie, V., Howe, C., Ishola, G., . . . Dwivedi, V. (2014). Advance distribution of misoprostol for prevention of postpartum hemorrhage (PPH) at home births in two districts of Liberia. *BMC Pregnancy and Childbirth*, *14*(1), 1-10. doi: 10.1186/1471-2393-14-189
- Smith, J. M., Alexander, D., Ma, J., Dimiti, A., Dwivedi, V., Ochieng, I., . . . McKaig, C. (2014). Advance distribution of misoprostol for the prevention of postpartum hemorrhage in South Sudan. *International Journal of Gynecology & Obstetrics*, *127*(2), 183-188. doi: <http://dx.doi.org/10.1016/j.ijgo.2014.05.016>
- Smith, J. M., Baawo, S. D., Subah, M., Sirtor-Gbassie, V., Howe, C. J., Ishola, G., . . . Dwivedi, V. (2014). Advance distribution of misoprostol for prevention of postpartum hemorrhage (PPH) at home births in two districts of Liberia. *BMC Pregnancy Childbirth*, *14*, 189. doi: 10.1186/1471-2393-14-189
- Smith, J. M., Currie, S., Cannon, T., Armbruster, D., & Perri, J. (2014). Are national policies and programs for prevention and management of postpartum hemorrhage and preeclampsia adequate? A key informant survey in 37 countries. *Glob Health Sci Pract*, *2*(3), 275-284. doi: 10.9745/GHSP-D-14-00034
- Smith, J. M., de Graft-Johnson, J., Zyaee, P., Ricca, J., & Fullerton, J. (2015). Scaling up high-impact interventions: How is it done? *International Journal of Gynecology & Obstetrics*, *130*, Supplement 2, S4-S10. doi: <http://dx.doi.org/10.1016/j.ijgo.2015.03.010>
- Smith, J. M., Gubin, R., Holston, M. M., Fullerton, J., & Prata, N. (2013). Misoprostol for postpartum hemorrhage prevention at home birth: an integrative review of global implementation experience to date. *BMC Pregnancy Childbirth*, *13*(44). doi: 10.1186/1471-2393-13-44
- Spangler, S. A., Gobezaayehu, A. G., Getachew, T., & Sibley, L. M. (2014). Interpretation of national policy regarding community-based use of misoprostol for postpartum hemorrhage prevention in Ethiopia: a tale of two regions. *Journal Of Midwifery & Women's Health*, *59* Suppl 1, S83-S90. doi: 10.1111/jmwh.12154
- Starrs, A., & Winikoff, B. (2012). Misoprostol for postpartum hemorrhage: moving from evidence to practice. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, *116*(1), 1-3
- Torloni, M. R., Freitas, G. C., Kartoglu, U. H., Gulmezoglu, A. M., & Widmer, M. (2016). Quality of oxytocin available in low-and middle-income countries: a systematic review of the literature. *BJOG* 1-11. doi: 10.1111/1471-0528.13998
- United Nations. (2015). *Sustainable Development Goals: 17 Goals to transform our world*. Retrieved from <http://www.un.org/sustainabledevelopment/health/>
- Vallely, L., Homiehombu, P., Walep, E., Moses, M., Tom, M., Kelly-Hanku, A., . . . Homer, C. S. E. (2016). Feasibility and acceptability of clean birth kits containing misoprostol for self-administration to prevent postpartum hemorrhage in rural Papua New Guinea. *International Journal of Gynecology and Obstetrics*, 301-306. doi: <http://dx.doi.org/10.1016/j.ijgo.2015.10.018>
- Venture Strategies Innovations. (2014, September 2014). *Resources: Registration map*. Retrieved from <http://www.vsinnovations.org/resources.html>
- Webber, G. C., & Chirangi, B. (2014). Women's Health in Women's Hands: A Pilot Study Assessing the Feasibility of Providing Women With Medications to Reduce Postpartum Hemorrhage and Sepsis in Rural Tanzania. *Health Care Women Int*, *35*(7-9), 758-770. doi: 10.1080/07399332.2014.915843
- Weeks, A., Ditai, J., Ononge, S., Faragher, B., Frye, L. J., Durocher, J., . . . Alfirevic, Z. (2015). The MamaMiso study of self-administered misoprostol to prevent bleeding after childbirth in rural Uganda: a community-based, placebo-controlled randomised trial. *BMC Pregnancy And Childbirth*, *15*, 219-219. doi: 10.1186/s12884-015-0650-9
- Wells, E., Coeytaux, F., Azasi, E., Danmusa, S., Geressu, T., McNally, T., . . . Tibebu, S. (2014). *Scaling up Access to Misoprostol at the community level to improve maternal health outcomes in Ethiopia, Ghana, and Nigeria: findings from an evaluation of different models*. Chicago, U.S.A: McArthur Institute.
- Wells, E., Coeytaux, F., Azasi, E., Danmusa, S., Geressu, T., McNally, T., . . . Tibebu, S. (2016). Evaluation of different models of access to misoprostol at the community level to improve maternal health outcomes in Ethiopia, Ghana, and Nigeria. *International Journal of Gynecology & Obstetrics*, *133*(3), 261-265. doi: <http://dx.doi.org/10.1016/j.ijgo.2016.04.002>
- Whittemore, R., & Knafl, K. (2005). The integrative review: updated methodology. *Journal of Advanced Nursing*, *52*(5), 546-553. doi: 10.1111/j.1365-2648.2005.03621.x
- Wilson, R., Kade, K., Weaver, A., De Lorenzi, A., Yeager, B., Patel, S., . . . Bergeson-Lockwood, J. (2012). *Medicines for maternal health: Working paper prepared for the united nations commission on life saving commodities for women and children*. New York, U.S.A.
- Wise, A., & Clark, V. (2008). Strategies to manage major obstetric haemorrhage. *Current Opinion in Anesthesiology*, *21*(3), 281-287
- World Bank. (2016). *World Bank country and lending groups: country classification*. Retrieved from <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519>
- World Health Organization. (2007a). *WHO Recommendations for the Prevention of Postpartum Haemorrhage*. Geneva, Switzerland.
- World Health Organization. (2007b). *WHO recommendations for the prevention of postpartum haemorrhage*. Geneva, Switzerland: WHO.
- World Health Organization. (2009). *WHO statement regarding the use of Misoprostol for postpartum haemorrhage prevention and treatment*. Geneva: WHO.

- World Health Organization. (2010). Clarifying WHO position on misoprostol use in the community to reduce maternal death. In D. o. R. H. a. Research (Ed.), (pp. 1-2). Geneva, Switzerland: WHO.
- World Health Organization. (2011). *WHO model list of essential medicines 17th list*. Geneva, Switzerland: WHO.
- World Health Organization. (2012a). *WHO recommendations for the prevention and treatment of postpartum haemorrhage*. Italy: WHO.
- World Health Organization. (2012b). *WHO recommendations: optimizing health worker roles to improve access to key maternal and newborn health interventions through task shifting*. Italy: WHO.
- World Health Organization. (2015a). *Executive summary the selection and use of essential medicines (2015): Report of the 20th WHO expert committee on the selection and use of essential medicines* Geneva, Switzerland.
- World Health Organization. (2015b). *Maternal Mortality: Fact sheet N.348*. Retrieved from <http://www.who.int/mediacentre/factsheets/fs348/en/>

Figure 1. Screening and Inclusion Methods

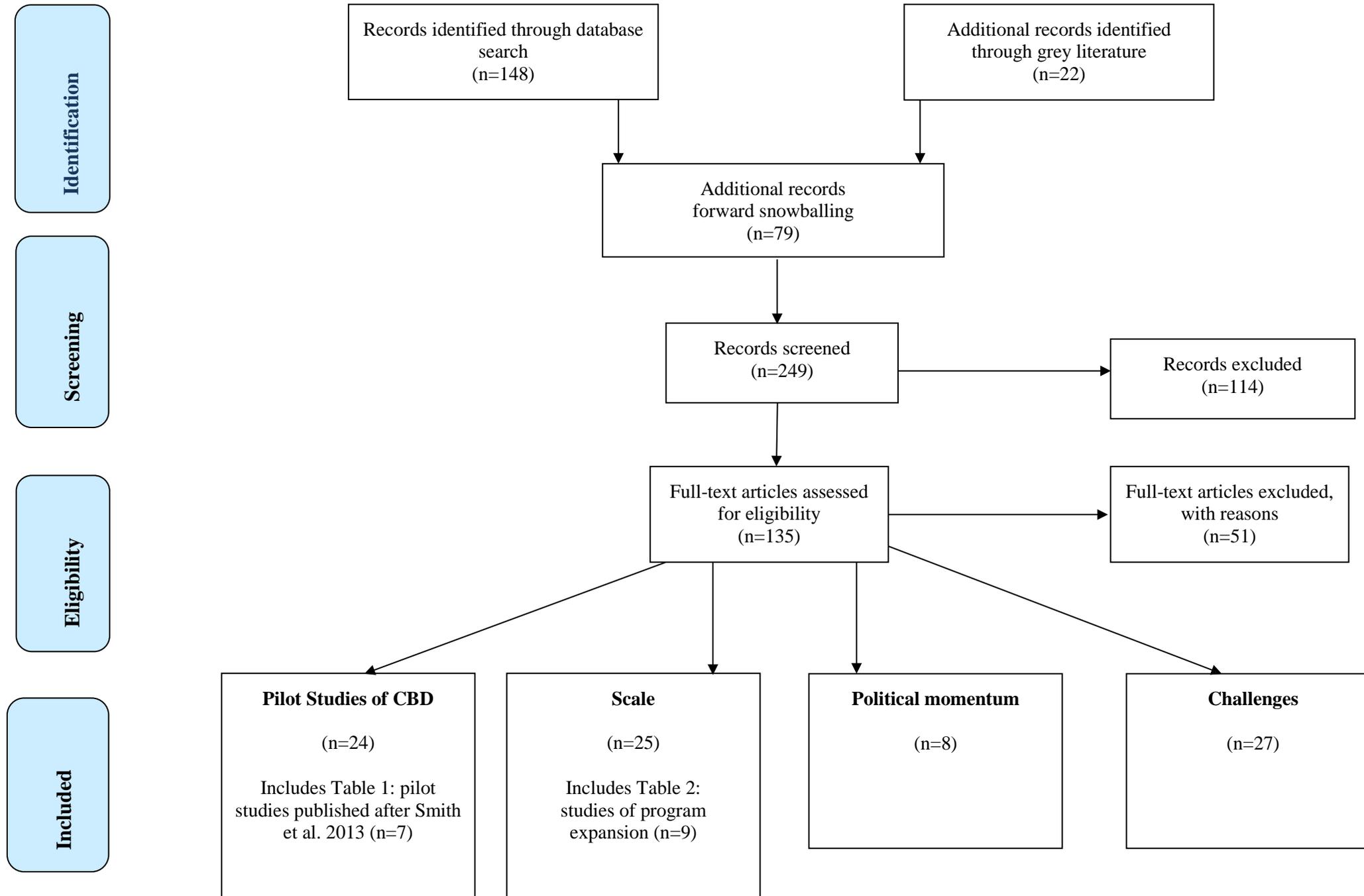


Figure 2: Timeline of progression of use of misoprostol for PPH 1

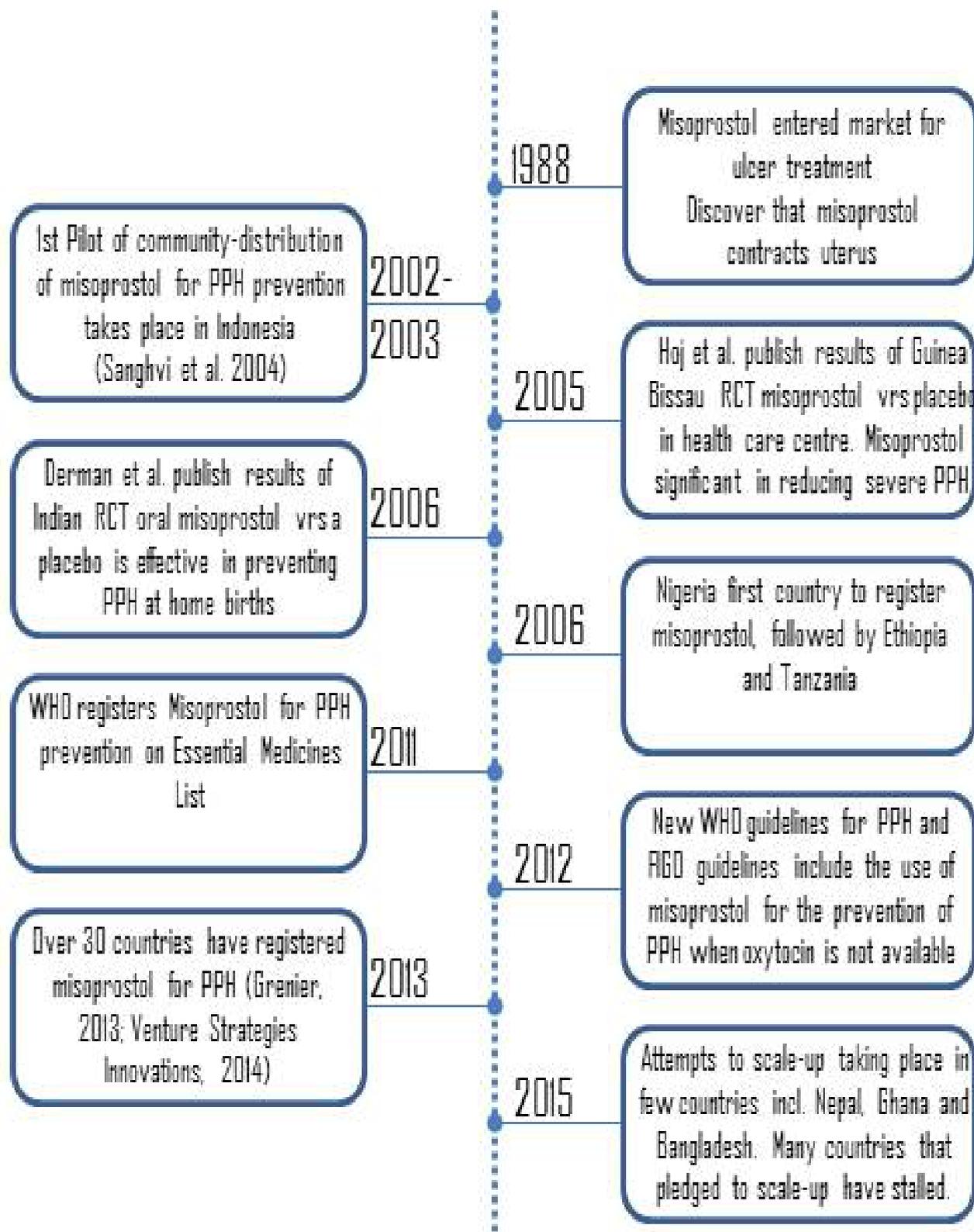


Table 1. Studies on the use of misoprostol for prevention of PPH at home births since Smith et al.'s 2013 Global Review (7)

Year (s) of distribution	Country	Distribution and administration method	Dose	Design	No women enrolled	No women who took misoprostol at home birth
January 2011 June 2012	Ghana (Geller et al., 2014)	ANC + self-administered	600 mcg PO	Pilot study, 1 district	654 18 communities intervention (Group A); 12 communities control (Group B)	96
February-July 2012	Tanzania (Webber & Chirangi, 2014)	Research assistants or at health facility + self-administered	600 mcg PO	Prospective intervention study, 1 district	642 intervention; no control	642
May 2012-July 2012	Uganda (Weeks et al., 2015)	ANC + self-administered	600 mcg PO	Randomised, double-blind, placebo-controlled trial, 1 district	374 intervention; 374 placebo controls	290
September 2012-February 2013	Rwanda (Dao B et al., 2015)	CHW distributed + administered	600 mcg PO	Longitudinal observational study, 4 districts	4074; no control group <i>*1,231 surveyed post-partum</i>	598
October 2012-March 2013	South Sudan (Smith, J.M., Alexander, D., et al., 2014)	ANC and by CHW + self-administered	600 mcg PO	Observational, 1 county	787; no control group	527
December 2012-June 2013	Liberia (Smith, J. et al., 2014)	ANC (78%) + self administered or by an SBA (21.8%)	600 mcg PO	Longitudinal observational study, 2 districts	980; no control group	265
April 2013-October 2014	Papua New Guinea (Vallely et al., 2016)	ANC as part of a clean birthing kit + self-administered	600 mcg PO	Pilot study, 1 district	200; no control group	112 self-administered

Table 2: Studies assessing scale-up of misoprostol for prevention of PPH

Country	Study Design	Coverage	Mode of Distribution	Key dates:
Afghanistan (Haver et al., 2016)	Before & after evaluation	20 Districts in 5 provinces	CHW - self-administration	<ul style="list-style-type: none"> • 2005-2007 Pilot study • January 2011 - April 2012 Intervention • November-December 2010 and March-April 2012 Pre and post data collection
Bangladesh (Quaiyum et al., 2011)	Large scale operations research; 118 500 women enrolled	29 Sub-districts in 6 districts	ANC or TBA via safe birthing kit, self-administration or TBA	<ul style="list-style-type: none"> • 2007 Misoprostol Use Policy and roll-out plan • May 2009-September 2010 pilot • May 2009-2010 ongoing monitoring
Ethiopia (Sibley et al., 2014).	Before & after evaluation	2 Regions (3 woredas in each)	SBA, TBA & Health Extension Workers, Oromiya Region SBA & Health Extension Workers, Amhara Region	<ul style="list-style-type: none"> • July 2005- July 2007 pilot • May 2012-June 2012 Evaluation
Ethiopia (Spangler et al., 2014)	Qualitative interviews with health officials	2 Regions	SBA, TBA & Health Extension Workers in Oromiya Region Amhara Region SBA & Health Extension Workers	<ul style="list-style-type: none"> • April-August 2012 Evaluation
Ethiopia (Geressu et al., 2014)	Process evaluation	1 Region (2 Administrative Zones)	CHW: Lay youth mentors and Community Health Extension Workers administered	<ul style="list-style-type: none"> • 2010 misoprostol registered for PPH • 2010 August-December distribution • 2014 June – November Evaluation
Ghana (Azasi et al., 2014)	Process evaluation	1 project area in 1 district	ANC (7 months+) -self administration	<ul style="list-style-type: none"> • 2008- 2012 pilot implementation , distribution ongoing • 2010 misoprostol on National Essential Medicines List • June-November 2014 Evaluation
Nigeria (Otiye-Igbuzor et al., 2014)	Process evaluation	2 States, 11 areas & 2 communities	CHWs: TBAs via clean birthing kits prior to or at birth & drug keepers for self-administration or to TBA	<ul style="list-style-type: none"> • 2009 pilot (Ejembi & Prata, 2010; Prata, N., Ejembi, Fraser, Shittu, & Minkler, 2012) • 2010 scale-up in 2 states commenced • June-November 2014 Evaluation
Nepal (Government of Nepal Ministry of Health and Population et al., 2014)	Outcome evaluation; 90 rural clusters	9 Districts	CHWs (8 months+) - self-administration	<ul style="list-style-type: none"> • January 2006- June 2008 pilot • 2010 national scale-up approved • 2013 Evaluation
South Sudan (Smith, J.M., Alexander, D., et al., 2014)	Observational	1 County	ANC & CHW-self-administration	<ul style="list-style-type: none"> • October 2012 -March 2013 Evaluation