Programmes for advance distribution of misoprostol to prevent post-partum haemorrhage: a rapid literature review of factors affecting implementation

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Accepted on 11 January 2015

Abstract

Recent efforts to prevent post-partum haemorrhage (PPH) in low-income countries have focused on providing women with access to oral misoprostol during home birth. The WHO recommends using lay health workers (LHWs) to administer misoprostol in settings where skilled birth attendants are not available. This review synthesizes current knowledge about the barriers and facilitators affecting implementation of advance community distribution of misoprostol to prevent PPH, where misoprostol may be self-administered or administered by an LHW.

We searched for and summarized available empirical evidence, and collected primary data from programme stakeholders about their experiences of programme implementation.

We present key outcomes and features of advanced distribution programmes that are in operation or have been piloted globally. We categorized factors influencing implementation into those that operate at the health system level, factors related to the community and policy context and those factors more closely connected to the end user.

Debates around advance distribution have centred on the potential risks and benefits of making misoprostol available to pregnant women and community members during pregnancy for administration in the home. However, the risks of advance distribution appear manageable and the benefits of self-administration, especially for women who have little chance of expert care for PPH, are considerable.

Key words: Advance distribution, community distribution, direct distribution, misoprostol, prevention, programme implementation, post-partum haemorrhage
Introduction

There have been significant improvements in maternal mortality globally over the last 20 years (World Health Organization 2012a), largely through improved access to health care services through the safe motherhood initiative that includes access to skilled birth attendants, emergency obstetric services and access to contraception. However, post-partum haemorrhage (PPH) remains the major cause of death. PPH can be routinely managed by trained health care providers in facilities with adequate supplies through active management of the third stage of labour, involving administration of an uterotonic drug (usually oxytocin), controlled cord traction and uterine massage after delivery of the placenta. For women who cannot, or choose not to access formal health services during delivery, however, PPH remains the largest cause of maternal mortality.

Recent efforts to prevent PPH among women not accessing health services have focused on increasing their access during home births to misoprostol, a synthetic prostaglandin E1 analogue with strong uterotonic properties (Alfirevic et al. 2007). While oxytocin must be kept at a controlled temperature and administered by injection, misoprostol does not require cold storage, is administered in pill form, and is available in many developing countries, making it an attractive alternative for use outside health facilities. Oxytocin remains an uterotonic drug of choice for prevention of PPH in clinical settings, but for women with limited access to clinical care, the use of oral misoprostol is recommended as an alternative to prevent PPH (Gulmezoglu et al. 2007).

There are two main ways that misoprostol can be provided in advance for use in home births. Provision by lay health workers (LHWs) for administration to women under their care has been reviewed for safety and effectiveness and the WHO has issued guidelines recommending the scale up of programmes using LHWs to distribute misoprostol in settings where skilled birth attendants are not available or accessible (World Health Organization 2012b). Advance distribution of misoprostol to women during pregnancy, where its administration can be managed by delivering women themselves, family members or traditional birth attendants (TBAs), is the other route. While potentially increasing access to this life-saving intervention, there is insufficient evidence available on the safety, effectiveness and sustainability of advance distribution of misoprostol. There have been three randomized controlled trials of community distribution and administration of misoprostol by LHWs showing safety and effectiveness (Walraven et al. 2005; Derman et al. 2006; Mobeen et al. 2011) but no large-scale evaluation or multisite implementation research on advance distribution. The WHO has identified this as a key research priority (World Health Organization 2012b).

Several programmes globally have implemented advance distribution of misoprostol and emerging evidence from operational research in these programmes suggests that making misoprostol available to women in pregnancy for use at home birth can be safe and effective. A recent review synthesizing outcomes from these programmes described different models for distribution and administration of misoprostol and assessed existing evidence on coverage, safety and effectiveness (Smith et al. 2013). The review determined that distribution of misoprostol for use at home births significantly increased access to and use of the drug, particularly when distributed and administered by a LHW, and there were few reports of alternative or incorrect use of the drug by women and/or birth attendants.

While there is increasing evidence of the coverage, safety and effectiveness of advance distribution of misoprostol to prevent PPH in a community setting (Oladapo 2012), a related and equally important question involves implementation factors that shape the outcomes of these programmes in various settings. The act of taking misoprostol just after delivery is not in itself technically complex, though correct dosage and timing are very important. However, running effective advance distribution programmes requires a combination of community awareness-raising and acceptance, effective training of LHWs and/or women in use of the drug, stable drug distribution systems and systems for ongoing monitoring and evaluation. When considering scale-up of programmes like these, understanding implementation factors will be of critical concern for policymakers and programme managers. This review aimed to assess what is currently known about the barriers and facilitators affecting implementation of programmes for advance distribution of misoprostol to prevent PPH.

Methods

Study scope and design

This study assessed evidence on the implementation of advance distribution of misoprostol to prevent PPH. It combined a rapid review of the existing literature with primary research conducted with programme stakeholders. The approach was ‘rapid’ in that it was commissioned and conducted in a short timeframe and therefore required us to compromise on some ‘systematic’ aspects of the review methodology. For example, our literature search was as comprehensive as possible in the timeframe, but we screened and assessed eligibility rapidly using simple inclusion criteria. We did not formally appraise the quality of included studies, but used simple credibility criteria to exclude studies. Findings from the rapid literature review and primary data collection were extracted and analysed separately and then integrated. Differences between the review and primary research findings were noted when relevant.

Literature review

We searched for existing literature in two phases. First, we conducted a systematic search of PubMed/Medline, EBSCO Global
Health and Web of Science using a simple search strategy to identify studies addressing provision of misoprostol in communities for LHW administration and advance distribution for self-administration of misoprostol (Supplementary Material S1). Second, we scanned reference lists of included studies, conducted open web searches and contacted experts in order to produce a more complete list of all organizations that have implemented these programmes (Supplementary Material S2). We then searched organization websites for programme evaluation reports and also contacted them directly to solicit further documentation.

Studies were included if they provided information about programme implementation models and factors. While we did not formally assess study quality, we only included studies with sufficient methodological detail and excluded opinion pieces or syntheses of personal experience that did not include empirical evidence. Peer-reviewed research findings were considered the most credible, but unpublished reports and other operational documentation also provided important data.

Findings from the included studies were extracted using a template informed by the SURE framework (SURE Collaboration 2011), a conceptual model of the possible factors affecting implementation of health system interventions. The framework includes: (1) knowledge, skills and attitudes among recipients of care, providers of care and other stakeholders; (2) a wide variety of health system factors; and (3) social and political factors. E.R. extracted findings into this template and H.S. and C.C. reviewed these extracted findings for coherence and consistency.

The findings were divided into first-order findings (emerging directly from data collected with participants) and second-order findings (interpretations of this data by study authors). Both sets of extracted findings were then used to identify emerging themes across the studies. The boundaries of each of these emerging themes were discussed among the authors and H.S. synthesized these themes into an overall framework for implementation facilitators and barriers. This framework was then reviewed by the other authors for accuracy and comprehensiveness.

Primary research
The primary research on stakeholder experiences involved interviews with key informants as well as brief field research with an advance distribution programme in Nepal. C.C. conducted key informant interviews face to face (n = 1) and by telephone (n = 5) with individuals identified in our literature review and by expert advisors; selection was purposive and designed to include a range of geographic areas, stakeholder perspectives and programme types and durations. H.S. conducted a 1-week field visit to Nepal (in May 2013) and interviewed government officials (n = 4), representatives of professional organizations (n = 1), international policymakers (n = 2) and international and national NGOs involved in the design and implementation of the advance distribution programme (n = 7), as well as district health staff (n = 5), female community health volunteers (FCHVs) (n = 4) and end users (n = 5) of misoprostol (pregnant and recently delivered women) in one district where advance distribution is currently being implemented. Interviews explored stakeholder experiences of advance distribution of misoprostol, and the barriers and facilitators affecting implementation of the programme in Nepal. Before each interview, we provided information about the purpose of the research and what the interviews would entail; all participants gave verbal consent to participate. We took notes during the interviews to capture the important content. All information provided was treated as confidential and used only by the review team; names were not recorded anywhere and no participant is identifiable in the review findings. The selection of the site for the field visit was done after an initial scoping of programmes and was intended to collect insights from a large and well-established programme.

H.S. extracted all interview findings into the SURE framework. Initial analysis of the field interviews was conducted separately, and a case study of the programme experiences was prepared (Supplementary Material S4). H.S. and C.C. conducted subsequent analysis to integrate findings from the field visit and key informant interviews into the literature review findings to produce an overall synthesis of programme implementation experience.

Institutional Review Board and ethical approval were obtained from the author’s institute.

Results
Overview of community-based misoprostol programmes
We identified 18 programmes (either research or implementation oriented) in 14 countries in Africa, South Asia and Southeast Asia, providing misoprostol at community level for prevention of PPH in women giving birth at home (see Table 1). Most programmes have been implemented within the last 12 years. Early programmes were randomized controlled trials conducted in single districts or provinces examining the efficacy of providing misoprostol to trained LHWs for administration at home births they attended. Several studies compared misoprostol distribution with no specific intervention for PPH and assessed PPH mortality and morbidity and safety outcomes as well as feasibility and acceptability. The majority of the available evidence is from pilot or operational research projects (n = 10) that collect data on implementation experiences including programme effectiveness (specifically, equitable coverage), feasibility, acceptability and safety (see Supplementary material Table S3).

All programmes used a dose of 600 µg misoprostol, except a quasi-experimental trial in Bangladesh (Hashima et al. 2011) which used 400 µg. Programmes use one of two main strategies to deliver misoprostol—either provision of misoprostol to LHWs for use at home births they attend (n = 7), or the more recent strategy of advance distribution to women during pregnancy (n = 11) for self-administration or administration by an untrained family or community member.

Key outcomes and features of programmes distributing misoprostol to LHWs for administration to women under their care
The principle evidence for the effectiveness and safety (side effects and adverse events) of community distribution of misoprostol comes from three, relatively large Randomised Controlled Trial conducted in the Gambia, India and Pakistan (Walraven et al. 2005; Derman et al. 2006; Mboen et al. 2011). All of the trials found that administration of misoprostol by LHWs to women in their care was associated with some reduction in bleeding or Hb post-partum compared with placebo or standard care. Misoprostol was also associated with a higher rate of transient symptoms of shivering, chills and fever. Given misoprostol’s low cost, ease of administration and relatively minor side effects, the international community is increasingly confident in its use in a community setting by trained LHWs for PPH prevention (Oladapo 2012).
Table 1. Misoprostol programme characteristics

<table>
<thead>
<tr>
<th>Programme characteristic (N= 18)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Programme location</strong></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Middle-East</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>South Asia</td>
<td>7 (39)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td><strong>Programme timeframe</strong></td>
<td></td>
</tr>
<tr>
<td>2001–04</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>2005–08</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>2009 –</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td><strong>Programme design</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Quasi-experimental or field</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>intervention</td>
<td></td>
</tr>
<tr>
<td>Operations research or pilot project</td>
<td>10 (55.5)</td>
</tr>
<tr>
<td><strong>Publication status</strong></td>
<td></td>
</tr>
<tr>
<td>Article in international peer reviewed journal</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Published report (funding agency)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Unpublished report (joint funder-partner)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td><strong>Misoprostol delivery model</strong></td>
<td></td>
</tr>
<tr>
<td>Distribution to LHWs for adminstration to women under their care</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Advance distribution to women for self-administration</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>for self- or untrained family or community member administration</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td></td>
<td>4 (22.2)</td>
</tr>
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</table>

1 We identified one conference abstract reporting a pilot randomized placebo-controlled trial in Uganda (Weeks 2013).
2 Based on definitions provided in the Cochrane Review on advance misoprostol distribution for preventing and treating PPH (Oladojo 2012).

Many low-resource countries have started to translate this confidence into practice by training LHWs in administration of misoprostol. These programmes utilize low-skilled health workers including TBAs, Community Health Workers (CHWs), FCHVs and others, cadres collectively referred to here as LHWs, health workers who receive on-the-job training and perform health care delivery functions, but have no formal professional qualifications (Lewin et al. 2010).

In the programmes we reviewed, misoprostol was distributed to either CHWs (Hashima et al. 2011), TBAs (Prata et al. 2009a) or via clean delivery kits (CDKs) (Quaiyum et al. 2011; Mir et al. 2012; Prata et al. 2012c). CHWs and TBAs administered the drug at home births immediately after delivery. In settings using CDKs, the drug was administered by TBAs at delivery, or self-administered. All programmes included some health worker training and in most cases, LHWs were already trained by and working for existing programmes (Prata et al. 2009a; Hashima et al. 2011; Prata et al. 2012c). Most programmes provided additional training on misoprostol, although training duration and content were not clear. In the quasi-experimental trials, CHWs and TBAs also received additional training on study purpose and data collection methods.

Although the emphasis in training LHWs was on administration of the drug, the trial in Bangladesh reported sensitizing pregnant women, their husbands and other family members about misoprostol and PPH (Hashima et al. 2011), and in Pakistan the programme included community awareness-raising activities (Mir et al. 2012). The ready acceptance and uptake of misoprostol in these programmes was in part attributed to this awareness-raising and involvement of influential family and community members.

Key outcomes and features of programmes distributing misoprostol to women in advance, for self-administration

With increasing confidence in the effectiveness and safety of the drug, and feasibility of community distribution, many countries have started to explore advance distribution of misoprostol to women during pregnancy, to increase uterotonic coverage among women who face multiple barriers to accessing skilled delivery care, and who may or may not be accompanied by an LHW or other birth attendant. However, there are concerns about the risks of making misoprostol available to women in advance of delivery, including use of misoprostol as an abortifacient or to induce labour, and incorrect use of the drug too soon before or too late after delivery.

Evidence about the implementation experiences of advance distribution programmes comes mainly from pilot or operational studies (n = 9); and two programmes were evaluated in quasi-experimental trials [Afghanistan (Sanghvi et al. 2010) and Indonesia (Sanghvi et al. 2004)]. In some instances, pilot projects involved just one district or state [Bangladesh (The Respond Project/EngenderHealth 2010), Nepal (Rajbhandari et al. 2010) and Nigeria (Prata et al. 2012a)] but in most cases implementation was on a larger scale involving 2–5 districts and involving large numbers of women, ranging from 2000–19 000 women. Evaluations of pilot and operational studies reported on programme effectiveness, feasibility, acceptability and in some cases safety (alternative or incorrect use of the drug) (Supplementary Material S3).

We found 11 programmes implementing advance distribution of misoprostol (Sanghvi et al. 2004; Federal Ministry of Health Ethiopia et al. 2008; Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; Rajbhandari et al. 2010; Sanghvi et al. 2010; The Respond Project/EngenderHealth 2010; Karanja et al. 2011; Bique et al. 2011; Ifakara Health Institute et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012). In these programmes, women received misoprostol from LHWs, from facility or outreach-based antenatal care programmes, or from a combination of these mechanisms (Table 2). Timing of misoprostol provision varied according to distribution method. In five programmes, women received the drug at home visits late in pregnancy, mainly from CHWs (Sanghvi et al. 2004; Ministry of Health Zambia et al. 2010; Rajbhandari et al. 2010; The Respond Project/EngenderHealth 2010; Ifakara Health Institute et al. 2011). In programmes where Antenatal Care (ANC) providers distributed the drug, it was given late in pregnancy at ANC visits, except in Ghana where women received it any time after 12 weeks of pregnancy (Ghana Health Services and Venture Strategies Innovations 2012).

In advance distribution programmes, various modes of drug administration are possible. Inevitably some women receiving misoprostol in advance will end up delivering at health facilities, others will deliver at home with semi-skilled birth attendants, or untrained family or friends, and some deliver at home alone. Women could thus be assisted or supervised in taking the drug or may self-administer the drug. These individuals could also discourage use of misoprostol.

Programmes included training for CHWs and ANC providers on distribution of misoprostol for PPH prevention and, in some cases, on how to deliver information on its use to women. Little detail is provided on the extent, content and duration of training. Where additional community volunteers helped with community
sensitization and awareness raising campaigns (Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; Ifakara Health Institute et al. 2011; Karanja et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012), they received programme information and training on how to support and inform women who received misoprostol but were not permitted to distribute or administer the drug.

All programmes reported providing counselling to pregnant women, usually on the purpose, correct dose and timing, risks, common side effects of misoprostol, and the importance of institutional delivery. Counselling almost always involved family members or other support persons, and women usually received a pamphlet or leaflet with pictorial and/or written information on how to take the tablets. Only two programmes, Afghanistan (Sanghvi et al. 2010) and Indonesia (Sanghvi et al. 2004), required women to first demonstrate their understanding of the information provided. Most of the pilot programmes engaged in activities to inform and educate communities where misoprostol was being distributed to women in advance of birth; participants included influential community members, women’s groups and community leaders.

Most of the pilot programmes appeared to be implemented in partnership with ministries of health and/or national professional organizations, and supervision of health workers distributing misoprostol was done through existing health service delivery structures. However, supervision and monitoring of implementation was usually done in close collaboration with external programme funders, technical support partners and in-country research or professional organizations.

Many programmes mentioned methods to document the number of misoprostol tablets distributed, including a special misoprostol ‘addendum’ to the ANC card, numbered packets, or project-specific forms. Some programmes also mentioned methods to monitor local drug supply by having regular supervisory meetings with CHWs (Rajbhandari et al. 2010; Sanghvi et al. 2010; The Respond Project/EngenderHealth 2010), replacing lost or damaged packets (Sanghvi et al. 2004; Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010), monitoring and restocking districts as needed, or recovering and accounting for all unused misoprostol at postnatal home visits (Rajbhandari et al. 2010; The Respond Project/EngenderHealth 2010).

Case study: community PPH prevention in Nepal

We collected empirical evidence of implementation experiences from a wide range of stakeholders in a short field visit to Nepal, where a large-scale and mainly successful advance distribution programme is in operation (detailed case study provided in Supplementary Material S4). We conducted key informant interviews in Kathmandu and further interviews took place with district health staff, FCHVs and end users of misoprostol (pregnant and recently delivered women) in two village development committees in a district in the Western region of Nepal where advance distribution has been implemented since 2006. Interviews documented stakeholder views on advance distribution of misoprostol, and the barriers and enablers to implementing both the pilot programme and the scaled-up programme. These programme experiences were incorporated into the overall framework presented in the next section on the factors influencing implementation of programmes for advanced distribution of misoprostol. Table 3, however, extracts some of the key findings on barriers and enablers in the Nepal case in order to highlight the interrelationships of health system, community/policy and end user factors in this case study.

Factors influencing implementation of advance distribution of misoprostol

Using data from the literature as well as primary research in Nepal and key informant interviews, we developed a comprehensive inventory of factors influencing the implementation of community-based misoprostol programmes. We categorized factors into those that operate at the health system level, factors related to the community and policy context and those factors more closely connected to the end user.

Health system factors influencing implementation

We identified several sets of health system factors influencing implementation of advance distribution programmes, including training and supervision, service delivery challenges, supply and procurement, monitoring and reporting, use of LHW platforms and financial factors. The narrative below highlights some key aspects of these six sets of health system factors and Table 4 provides further detail for each set.

Training is critical to ensure LHWs involved in distributing misoprostol have adequate knowledge of the rationale for misoprostol use, appropriate dosage and timing, as well as the necessary skills to deal with side effects and refer women with continued bleeding or other complications. There is evidence that TBAs (Federal Ministry of Health Ethiopia et al. 2008; Prata et al. 2009a; Prata et al. 2009b), auxiliary nurse midwives (ANMs) (Diadhiou et al. 2011) and other community volunteers (Sanghvi et al. 2004; Hashima 2009b) are well placed to provide this training.
Table 3. Factors influencing scale-up of advance distribution in Nepal

<table>
<thead>
<tr>
<th>Health system factors</th>
<th>Community and policy context</th>
<th>End user factors</th>
</tr>
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<tbody>
<tr>
<td>District programme staff and government officials are concerned about delivery of drugs to districts and severe procurement delays through the government system</td>
<td>Technical partners are concerned about FCHV performance post-pilot, especially enthusiasm for the role and motivation to reach women in remote areas as well as continued provision of adequate counselling</td>
<td>Women accept misoprostol, report understanding its use, and do not report any severe side effects</td>
</tr>
<tr>
<td>Technical partners concerned about gaps in reporting mechanisms at community level and infrequent monitoring through the district health system</td>
<td>Sub-health post-staff identified errors and incomplete reporting in FCHVs registers</td>
<td>The popularity of misoprostol has increased, it is valued by women, and there is evidence of demand generation</td>
</tr>
<tr>
<td>Professional organizations and technical partners are uncertain about whether there are no reports of drug misuse, or whether there is no system set up to collect this data</td>
<td>District health staff defend the district health system for misoprostol monitoring and reporting but acknowledge capacity weaknesses</td>
<td>Misoprostol availability does not influence women’s perception, or actual uptake, of facility deliveries</td>
</tr>
<tr>
<td>Technical partners highlighted the requirement for more intense training of illiterate LHWs</td>
<td>Sub-health post-staff and women suggest that misoprostol distribution reduces harmful post-partum practices in the community</td>
<td></td>
</tr>
</tbody>
</table>

et al. 2011; Prata et al. 2012a) trained in misoprostol use can safely and effectively administer misoprostol at the right time. Most LHW distribution programmes seem to provide specific training on misoprostol to already trained LHWs, but the content varied and it is hard to know the extent of training given and the topics covered.

Advance distribution programmes often use existing government health service delivery structures and health workers involved in misoprostol distribution are supervised via existing arrangements. While this is important for programme sustainability beyond pilot projects, the reality in many programmes is that district health teams also rely on implementing partners to oversee record keeping and ensure monitoring and reporting tools for misoprostol are understood and used. For example, in Nepal, implementing partners had concerns about supervision of FCHVs and sub-health post staff by overburdened district supervisors. Other technical partners to the Nepal programme described low commitment to supervision of FCHVs among district health staff, particularly in remote areas, yet in these areas, FCHVs are more likely to require more intensive supervision. Key informants raised similar concerns about the broader quality of training and supervision for ANMs in India, e.g. who were tasked with facilitating home use of misoprostol.

While many programmes report effective distribution of misoprostol to women via ANC visits and resultant increases in uterine coverage at home and facility births (Federal Ministry of Health Ethiopia et al. 2008; Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; The Respond Project/EngenderHealth 2010; Bique et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012; Ifakara Health Institute et al. 2011; Karanja et al. 2011), there are important drawbacks to delivering misoprostol through facilities. Provision of the drug at ANC visits might work in settings where ANC attendance is high, but in many countries in Africa and Asia few women return to ANC after 32 weeks, precluding distribution to women late in pregnancy [see e.g. Tanzania (Ifakara Health Institute et al. 2011)]. Some programmes have either started to distribute misoprostol earlier in pregnancy, or incorporated complementary distribution mechanisms using other cadres of health worker closer to communities. However, there are also concerns with this model since CHWs may not be sufficiently motivated to reach the poorest or most remote women in their communities. In Nepal, some technical partners reported that FCHVs in more remote districts are less enthusiastic about their role, more likely to be illiterate, and because of this require more intensive training and closer monitoring to ensure they actively seek out pregnant women in their communities. Other stakeholders provided examples of how FCHV visits to women sometimes lapse, especially during periods where the drug is unavailable due to procurement and supply problems.

Misoprostol is widely available in low-income regions, increasingly from manufacturers in developing countries, and it is on national Essential Drug Lists in 19 of 31 countries recently surveyed by UNFPA (United Nations Population Fund 2012). Despite this, in many countries where misoprostol programmes exist, there are problems with procurement and regular supply and distribution to districts. There were also minor concerns expressed by key informants about the quality of the drug preparation in some countries. A report from Venture Strategies Innovations highlights procurement and supply problems stemming from the way manufacturers package misoprostol tablets; few provide a three-pill blister pack required for PPH prevention which means districts often have to repackage tablets leading to delays in supply (United Nations Population Fund 2012).

Since scale up of the Nepal misoprostol programme, the drug is supposed to be procured through the government system but key informants at all levels described severe delays. Some attributed this to the fact that misoprostol is a new drug and not yet integrated into the district supply mechanism. Because they have struggled to procure their own steady supplies of misoprostol, implementing partners in Nepal have been instrumental in monitoring supply at district level and moving supplies between facilities to ensure availability where there are stock outs. Some technical partners were of the view that this close monitoring of district supplies is unlikely to continue when the government takes ownership of the programme in all districts.

Other health system factors deemed important in the literature and in our primary research relate to adequate monitoring and reporting of misoprostol use and safety. Most pilot programmes used specific registers or reporting cards to record distribution of misoprostol to women and to document actual use during postnatal visits. In most cases, these forms were separate from forms for other maternal health indicators in the existing health management information system (HMIS) (Federal Ministry of Health Ethiopia et al. 2008; Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; Bique et al. 2011; Ifakara Health Institute et al. 2011;
Table 4. Health system factors affecting advance distribution of misoprostol

1. Training & supervision of LHWs and health facility staff to deliver misoprostol
   In LHW distribution programmes training is critical for safe and appropriate administration of misoprostol
   In advance distribution programmes, good quality training of misoprostol distributors is key for confidence that women receive correct info on misoprostol
   In some pilot programmes implementation partners provide a lot of training support; this could influence the quality of training provided in programmes run by governments alone
   Availability of refresher training will determine ability to maintain LHW skills and knowledge in scaled up programmes
   Commitment of government staff to supervision will influence quality of programme outputs at scale

2. Service delivery challenges
   Distribution of misoprostol via CHWs achieves high coverage rates, but to what extent do LHWs reach women in the most rural and remote areas?
   Distribution via ANC depends on women making repeat or return visits and fails to reach women in remote areas
   Some providers suggest it is contradictory to provide misoprostol to women through facilities where oxytocin is available
   Some pilot reports indicate high levels of knowledge recall among health workers trained to administer misoprostol
   Reports suggest trained LHWs can safely and correctly administer misoprostol to women at home births
   Overall health workers report positive attitudes towards misoprostol for prevention of PPH
   Unlike already overburdened ANC providers, LHWs seem willing to take on the distribution of misoprostol and regard it as straightforward to administer compared with other interventions
   LHWs are motivated to provide misoprostol, and feeling confident and capable of counselling women
   In advanced distribution programmes, there are some concerns about the extent to which health workers maintain adequate counselling and information to pregnant women over time

3. Supply and procurement of the drug
   Many pilots used LHWs and government workers to collect data on misoprostol use and safety on bespoke forms
   Concerns about ensuring misoprostol reporting gets integrated into HMIS; aligning misoprostol reporting with existing government system
   Concerns about government staff motivation for reporting in absence of partners
   Problems with accurate reporting retrieving data from lowest level LHWs as some illiterate LHWs struggle to complete reporting
   Scale-up programmes need to collect reliable data on impact of advanced distribution on PPH incidence and mortality
   Implementing partners are good at routinely collecting data on programme challenges; ability of government system to do this at scale up
   Availability and capacity of government staff to conduct timely monitoring and reporting
   Effectiveness of data reporting channels between community, district, central levels can affect availability of data on misoprostol
   Methods of accounting for misoprostol tablets distributed by LHWs or ANC providers are generally inadequate

4. Monitoring & reporting on misoprostol
   Pilots have used LHWs and government workers to collect data on misoprostol use and safety on bespoke forms
   Concerns about ensuring misoprostol reporting gets integrated into HMIS; aligning misoprostol reporting with existing government system
   Concerns about government staff motivation for reporting in absence of partners
   Problems with accurate reporting retrieving data from lowest level LHWs as some illiterate LHWs struggle to complete reporting
   Scale-up programmes need to collect reliable data on impact of advanced distribution on PPH incidence and mortality
   Implementing partners are good at routinely collecting data on programme challenges; ability of government system to do this at scale up
   Availability and capacity of government staff to conduct timely monitoring and reporting
   Effectiveness of data reporting channels between community, district, central levels can affect availability of data on misoprostol
   Methods of accounting for misoprostol tablets distributed by LHWs or ANC providers are generally inadequate

5. LHW platforms for distribution
   It can be relatively straightforward to add misoprostol to well-established LHW programmes since LHWs are already responsible for implementing MCH interventions
   Programmes need to consider the extent to which incentives for LHWs and other cadres are needed to facilitate implementation of misoprostol; in some cases LHW status is of more value than incentives
   Relationship and trust between women and LHWs could influence acceptance of misoprostol

6. Financial resources for misoprostol distribution
   Government ability to allocate funds to misoprostol intervention could influence extent of scale-up
   Not much is known about the cost of implementing misoprostol and which model is more cost-effective
   Opportunities for private sector collaboration could influence the extent to which programmes are scaled up

Karanja et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012; Smith et al. 2013). In Nepal and in other programmes, implementing partners and district-level health staff identified problems with accurate and timely reporting from the lowest cadre involved in distribution. Few programmes had formal systems in place to account for used and unused tablets; at best this involved CHWs recovering unused tablets and empty packets at postnatal follow-up visits. Some FCHVs are illiterate and find it difficult to complete the simple misoprostol reports, often needing help from immediate supervisors and district health staff report difficulty in interpreting FHCV reports. Further challenges relate to the effectiveness of data-reporting mechanisms between community and district levels and weaknesses in the management use of health information at district level. All of our key informants spoke about the challenges of maintaining adequate monitoring and evaluation systems for these programmes over time and at scale.

Factors related to community and policy context
We identified several sets of community and policy context factors influencing implementation of advance distribution programmes, including fears about misuse, fears about disincentivizing facility births and the national and global policy environments. The narrative below highlights some key aspects of these three sets of community and policy factors; Table 5 provides further detail.
The risk of alternative or incorrect use of misoprostol is one of the most politically charged arguments against the provision of the drug to women in advance of birth. In several published reviews, authors express concern about women taking misoprostol at the wrong time, especially before delivery of the last baby in cases of multiple pregnancy, or to induce labour or abortion (Flandermeyer et al. 2010; Chu et al. 2012; Hadis and Woyessa 2012; Prata et al. 2012b). Although there is evidence from the published literature that trained LHWs can safely and correctly administer misoprostol under controlled experimental circumstances (Walraven et al. 2005; Prata et al. 2009a; Diadhio et al. 2011), there is less evidence on the competence of untrained birth attendants to effectively administer misoprostol at the right time and dose. Unpublished reports of pilot projects contain data on the number of women taking the appropriate dose at the correct time during home delivery, usually based on self-reporting post-partum (Federal Ministry of Health Ethiopia et al. 2008; Ejembi and Prata 2010; Rajbhandari et al. 2010; Ministry of Health Zambia et al. 2010; The Respond Project/EngenderHealth 2010; Bique et al. 2011; Ifakara Health Institute et al. 2011; Karanja et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012). None of the trials or operational research projects reports on alternative uses of the drug; collecting such data may not have been feasible in many countries.

Most of the key informants we interviewed expressed confidence in the ability of both LHWs and women themselves to understand and correctly administer misoprostol. They reported that the use of misoprostol by LHWs or women for induction or abortion were extremely low in their experience, with several adding that misuse by clinicians to speed up labour was a much greater concern. In Nepal, however, several stakeholder groups raised concerns about alternative uses of misoprostol as a result of its availability in the community. There was a perception that extensive media coverage of the multiple uses of misoprostol, and this posed a real risk for misuse of misoprostol distributed for preventing PPH (600 μg dose) for termination of pregnancy and without consulting a medical professional, which could lead to complications. There was also concern that increased availability of the drug in communities could lead to it being sold on the ‘black market’ to women wishing to terminate pregnancies.

The main expressed concern centred on the medical risks associated with unsupervised use of misoprostol for labour induction or abortion. Policymakers were also concerned that distribution of the drug via district health workers and FCHVs could open up the possibility of a black market for the drug and exploitation by these cadres of health worker. One key informant in India reported that access to misoprostol at the community level without a prescription was already common there. He argued, however, that this meant that advance distribution should proceed and be paired with education and awareness efforts to support appropriate use in the community.

Some policymakers in Nepal were suspicious of the original rationale for advance distribution of misoprostol, questioning whether the intention of technical partners was to pilot the drug for preventing PPH or for medical abortion. Technical partners, however, described how they had changed the packaging of misoprostol for PPH, included pictorial information, and changed the name to ‘mother safety pills’ to distinguish the pills and prevent association with medical abortion. Technical partners also considered the tracking of misoprostol tablets distributed in the community.

None of the FCHVs we interviewed in Nepal had encountered any misuse of the drug by women in their communities. The only data available on inappropriate use of misoprostol is from the evaluation of the pilot study, where there was only one report of a woman taking misoprostol before delivery (out of 13,069 women who took misoprostol); this was in the context of a domestic dispute, the woman was 38 weeks pregnant, received appropriate medical attention and delivered a healthy baby (Rajbhandari et al. 2010). Ironically, this case was often cited by individuals we interviewed either as evidence that there is a risk of inappropriate use or that the risk of misuse by women who have access to the drug before delivery is exceedingly small.

There is also frequent reference in the literature to concerns that availability of misoprostol for home births would divert attention away from efforts to improve access to oxytocin and skilled care at birth (Chu et al. 2012). However, this view is countered in evaluations of pilot programmes in Afghanistan (Sanghvi et al. 2010), Nepal (Rajbhandari et al. 2010) and Zambia (Ministry of Health Zambia et al. 2010) that indicate women in pilot areas were in fact more likely to seek skilled attendance or give birth at institutions and that availability of misoprostol did not negatively influence women’s plans to deliver at a facility. Key informants argued that rates of facility births have stalled in many countries for a long time and that the barriers to facility birthing, such as transport and referral challenges, are more substantial and intractable than any actual
Table 6. End-user factors affecting advanced distribution programmes

1. Acceptability of misoprostol

Pregnant women generally accept misoprostol for the prevention of PPH, would recommend it to others and in some cases would be willing to pay for the drug. For the few women who take misoprostol and experience side effects, most report they are manageable, transient and/or tolerable. Misoprostol enjoys easy popularity; women can see it saves lives and there is evidence of demand generation in rural districts in Nepal. District health workers and LHWs in report a reduction in harmful post-partum practices such as forcefully extracting the placenta.

Reports suggest a minority of women do not accept misoprostol and reasons include mistrust of the drug, lack of information about the drug, requirements to sign consent forms, fear of side effects and requiring husband’s permission.

2. Pregnant women’s ability to self-administer appropriately

Reports indicate high levels of knowledge and understanding of the rationale for misoprostol use, dosage and timing among post-partum women. Available evidence suggests women generally have the skills to take the correct dose of misoprostol at the right time.

For women who report not taking misoprostol after delivery at home, reports suggest various explanations including women forget, do not want to take the full dose, family opposition or influence, or they gave birth at the maternal home and forgot to take misoprostol tablets with them.

3. Importance of IEC

The few pilot programmes that report concerns about unsupervised use of misoprostol by women highlight the need for proper messages on the correct use of the drug. Pilot community distribution programmes highlight the importance of community awareness and education campaigns.

Reports suggest the importance of involving specific community representatives such as drug sellers, women’s advocates, elders, and pastors and church members in deciding how best to deliver messages about misoprostol to women. In programmes focused on LHW administration, providing information and education to influential family (husbands and mothers in law) and community members as well as women could be an important way to reinforce and support women’s use of misoprostol.

In some contexts social marketing of misoprostol has helped legitimize its use for PPH.

Factors related to end users

Factors related to the end user, including acceptability of misoprostol, ability to self-administer appropriately and the importance of information, education and communication (IEC) campaigns seem to be important influences on the success of community-based distribution programmes. The narrative below highlights some key aspects of these end-user factors; Table 6 provides further detail.

Acceptance of new interventions by end users, as well as knowledge of the intervention and its intended impact, is important for uptake. Use of misoprostol to prevent PPH seems to enjoy widespread acceptance among pregnant women delivering at home and their families, although there is less information available on wider community acceptability. Several pilot programme evaluations and all the key informants report that women receive misoprostol as highly acceptable, would be willing to take it again in a future pregnancy, would recommend it to other women and in some cases would be willing to pay for it (Federal Ministry of Health Ethiopia et al. 2008; Prata et al. 2009b; Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; Rajbhandari et al. 2010; Sanghvi et al. 2010; Bique et al. 2011; Diadhiou et al. 2011; Hashima et al. 2011; Ifakara Health Institute et al. 2011; Karanja et al. 2011; Ghana Health Services and Venture Strategies Innovations 2012; Mir et al. 2012).

In Nepal, technical partners, district health workers, FCHVs and women themselves reported that the drug is easily accepted by women and women’s knowledge about misoprostol for preventing PPH had increased. The reasons they gave related to seeing other women in the community take the drug, being thankful that the government is helping to prevent maternal deaths from post-partum bleeding, and the impact of women hearing ‘success stories’ of post-partum bleeding being reduced in women taking misoprostol. One FCHV reported that rather than wait for her to distribute misoprostol at 8 months, women now ask for misoprostol and demand the drug earlier in pregnancy.

The existence and experience of side effects of misoprostol and how these might influence uptake and use of the drug is frequently reported on. The most common side effects are shivering and pyrexia (or fever), sweating, chills and in fewer cases, nausea and vomiting (Walraven et al. 2005; Prata et al. 2009a; Mobeen et al. 2011; Mir et al. 2012). However, in evaluations of self-administration programmes women reported side effects were transient and knowledge of these effects did not deter them from taking misoprostol or using...
the drug in the future (Ejembi and Prata 2010; Ministry of Health Zambia et al. 2010; Rajbandari et al. 2010; Karanja et al. 2011).

Another important influence on end-user uptake of a new intervention like misoprostol is the relevance and appropriate delivery of IEC campaigns. Several programmes distributing misoprostol in advance for self-administration advocate that campaigns should involve influential family members as well as wider community representatives to help support messaging about the purpose and correct dosage and usage of the drug (Federal Ministry of Health Ethiopia et al. 2008). In programmes focused on LHW provision, evaluations suggest that providing information on misoprostol to husbands, family and community members could help to reinforce the use of misoprostol but could also encourage women to deliver at facilities (Ifakara Health Institute et al. 2011).

Discussion

Despite possibly being ‘the most studied drug in sexual and reproductive health since the early 1990s’ (Oladapo 2012) and enjoying widespread support as a safe and effective replacement for standard-of-care uterotonics where access to health care is limited (World Health Organization 2012b), advance distribution of misoprostol for administration at home births to prevent PPH has struggled to gain acceptance (Prata et al. 2009b; Chu et al. 2012; Starrs and Winikoff 2012; Prata et al. 2012b; Smith et al. 2013). Most of the debates around community-based programmes have not been about the safety or efficacy of misoprostol in preventing PPH but instead have centred on other potential risks and benefits of making this drug available to pregnant women in advance for administration at birth in the home.

Taken as a whole, the findings from our rapid literature review and primary research indicate that advance distribution of misoprostol for LHW or self-administration at home births can be both feasible and acceptable at all levels—end user, health system, community and policy—if implemented with attention to the key barriers and facilitators identified above. The implementation barriers we identified represent important threats to any community-based programme, especially when taken to scale. However, it is also crucial to note that most of these barriers reflect existing health system weaknesses in many countries, often the very same ones that already prevent access to care and in turn, the need for community-based distribution.

Among the challenges we noted were inconsistencies in training depth and content, weak supervisory structures, interrupted drug supplies and poor health information management. Not surprisingly, these barriers were less evident in the more protected pilot programmes we reviewed but were more common in the few available descriptions of scaled-up programmes. While these underlying health system weaknesses represent medium- and long-term risks to these programmes, we did not find evidence that they were critical to the success or failure of particular programmes for providing misoprostol. We also did not find evidence that community-based programmes greatly exacerbated health system barriers or constraints, or that health system barriers greatly increased the health risks associated with advance distribution of misoprostol.

The irony, of course, is that the more effective a health system, the less need there should be for community-based interventions for the prevention of PPH in the first place. Health system barriers, in particular, should therefore be a central focus for policymakers and programme managers (Chu et al. 2012) but should not too quickly be used to delay the development of community-based strategies to distribute misoprostol.

While we did find some concerns about advance distribution at the end user, community and policy levels, we did not find evidence that barriers related to acceptability would be likely to threaten the longer-term implementation of these programmes. While community and policymaker concerns around the incorrect use of misoprostol or its use for other purposes was a common theme across our data, these concerns never appeared to represent a critical barrier to developing and implementing these programmes safely and effectively (though they may have prevented or delayed development of programmes in the first place). Basic awareness-raising efforts with partners, families and communities to communicate the potential benefits and correct use of misoprostol were described as often effective in overcoming these concerns. Also important to addressing these concerns were simple health education efforts with pregnant women in the form of appropriate ANC or LHW counselling and design of health information materials and packaging.

Ambiguity in the global health policy arena around community-based distribution was also frequently cited as a concern. As with the concerns about incorrect or unintended use, however, we found that lack of WHO endorsement for models of advance misoprostol provision did not represent a critical barrier when other conditions were in place. These conditions included moderate but consistent advocacy from technical partners, the facilitation of a technical consensus among local and international professional organizations (like that initiated at the Bangkok Conference), engagement with community structures to develop understanding and acceptance and the growing recognition by all players of the public health urgency of maternal mortality from PPH.

In fact, the internal debates in programmes and countries about this new approach generally were reduced to a simple question—are the potential barriers to and health risks of community-based distribution of misoprostol greater than the costs of persistent, preventable maternal mortality associated with PPH in settings where skilled birth attendance is not a realistic option in the near future? Whatever the concerns stakeholders may have expressed about the risks and costs of advanced distribution of misoprostol, we did not find evidence that these concerns offset this broader risk-benefit question.

In settings where access to facilities is impeded by geographical, financial or sociocultural barriers, or where primary health services are weak, women can benefit from, in the short-term at least, community-based access to misoprostol. There was therefore little belief among those we spoke with at all levels that health system barriers should be a reason not to implement advance distribution. There were concerns that advance distribution would disincentivize skilled birth attendance, but again, none of the programme staff or end users we spoke with reported this as an outcome. Furthermore, what little empirical evidence we do have on this question points to the possibility that advance distribution may increase facility births, by increasing contact with pregnant women and one-to-one interaction offers the opportunity to promote early care seeking and referral during pregnancy. As well as these indirect means of promoting skilled birth attendance, misoprostol programmes often include specific training for health workers on the importance of encouraging facility births, community awareness and education campaigns, and counselling for women and families on danger signs in pregnancy and the importance of facility delivery. The potential effect of simultaneously increasing availability of misoprostol and actively promoting facility births may not be fully recognized in community and clinic programmes described as misoprostol ‘distribution’ programmes.
Limitations

Our description of the factors that need attention during scale up of advance distribution of misoprostol, and our assessment that none of them should present any serious obstacle to safe scale up, are based on the available evidence, which does have a range of limitations. First, current evidence on programme effectiveness and implementation experiences of programmes using models of advance distribution of misoprostol comes mainly from pilot or operational studies (see also (Oladapo et al. 2012)). When judging the quality of these evaluations, a key consideration is the type of study design and whether it is good enough to understand whether the programme works or not (Rychetnik et al. 2002). Most of the pilot or operational studies did not specify a design or consider the most appropriate time to evaluate the various outcomes. A second important consideration is the potential for bias in observational study designs, and without due consideration of the composition of comparison groups (even in before and after designs) or the influence of concurrent interventions, programmes or secular trends, many of these operational studies are highly confounded. A further consideration is transferability to other potential recipients beyond the pilot areas; and while many of the pilot studies were conducted in several districts, there is a lack of large-scale evaluations, particularly of scaled-up programmes under normal programmatic conditions. Most reports of pilot programmes were either authored and published by the funding agency, or jointly authored by funders and implementation partners but unpublished, and therefore not subject to external review.

There are also weaknesses in the way data were collected in these programme evaluations. Most pilot programmes relied on ANC providers or CHWs to administer questionnaires to postnatal women at follow up clinic visits; yet substantial numbers of women do not attend postnatal visits, so loss to follow up was a limitation in most pilot studies. Reporting on blood loss usually relied on women’s own estimates, which is obviously less reliable than direct collection of post-partum blood, but accurate assessment of post-partum blood loss is extremely difficult in any setting. Several programmes trained women and TBAs to use calibrated kanga (pre-cut pieces of rectangular fabric) to measure blood loss and while not perfect, this approach appears to be culturally acceptable and more accurate than visual estimation (Prata and Gerds 2010). Other weaknesses included lack of clarity on methods for recording maternal deaths in women taking misoprostol.

With respect to the limitations of the design of this rapid literature review (Grant and Booth 2009), we did not set out to systematically appraise the methods or findings of the studies we included, and we did not draw conclusions based on the quality of evidence, though we have summarized the limitations of the evidence base above (and in Supplementary Material S5). We recognize that the evidence in the review is weighted towards implementing partner reports and interviews with implementing partners and researchers; we have less information on policy makers’ opinions, and end users’ experiences, of community-based misoprostol distribution. The case study that provided most of the in-depth primary data in this review is based on a largely successful misoprostol programme; we do not have information on less successful cases. We focused our literature search on community-based distribution of misoprostol, and scoped organizations involved in implementation; based on this search, we did not identify examples of programmes that failed outright. It would be important to locate any such reports and determine whether factors other than those reported above are responsible for lack of success or prevented governments from even considering implementation.

Like any community health programme, achieving the outcomes observed in some of the initial pilot programmes of advance distribution of misoprostol will be a challenge at scale and over the long term. However, the risk of harms and other threats to the programmes appear manageable and the potential benefits of both self- and LHW administration of misoprostol, especially for women who have no realistic chance of receiving expert care for PPH, are considerable.

Acknowledgements

We thank Dr João Paulo Souza and the Department of Reproductive Health and Research, World Health Organization, Geneva for commissioning the work. We acknowledge staff at the Jhpiego office in Kathmandu, Nepal who helped to organize logistics for the field visit, and arranged interviews with key stakeholders in the misoprostol programme.

Funding

We thank UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP) and the United States Agency for International Development (USAID) for funding this work.

Ethical Approval

The protocol for this study was reviewed and approved by the Faculty of Health Science’s Human Research Ethics Committee at the University of Cape Town (Ref: 561/2012).

Supplementary Data

Supplementary data are available at HEAPOL online.

Conflict of interest statement. None declared.

References


Ghana Health Services, Venture Strategies Innovations. 2012. Distribution of Misoprostol at Antenatal Care Visits for Prevention of Postpartum