KEY DATA AND FINDINGS

Medicines for Maternal Health

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Contributors

Authors

PATH: Rachel Wilson, Kristy Kade, Abiah Weaver, Arianna De Lorenzi
Systems for Improved Access to Pharmaceuticals and Services Program/Management Sciences for Health (SIAPS/MSH): Beth Yeager, Sheena Patel
United Nations Population Fund (UNFPA): Kabir Ahmed
US Agency for International Development (USAID): Deborah Armbruster, Jennifer Bergeson-Lockwood

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Executive Summary

Where a woman gives birth should not decide her fate. Excessive bleeding after childbirth and high blood pressure during pregnancy, two of the leading causes of maternal deaths, can be prevented and significantly reduced with expanded availability of maternal health medicines and supportive policies and practices to achieve scale—a critical action for meeting the Millennium Development Goal (MDG) 5 target: reducing maternal mortality by 75 percent by 2015. The three medicines—oxytocin, misoprostol, and magnesium sulphate—featured in this report have the potential to save lives and protect the well-being of mothers and their infants worldwide.

Globally, more than eight million of the 136 million women giving birth each year suffer from excessive bleeding after childbirth. [1] This condition—medically referred to as postpartum hemorrhage (PPH)—causes one out of every four maternal deaths that occur annually and accounts for more maternal deaths than any other individual cause.[a] Deaths due to postpartum hemorrhage disproportionately affect women in low-resource settings (often referred to as developing countries).[2]

The second leading cause of maternal death is pre-eclampsia and eclampsia—most often detected through the elevation of blood pressure during pregnancy—which can lead to seizures, kidney and liver damage, and death, if untreated. These conditions claim the lives of an estimated 63,000 women each year, as well as the lives of many of their babies.[3] The risk that a woman in a developing country will die of pre-eclampsia and eclampsia is approximately 300 times higher than that for a woman in a developed country.

Among the most effective medicines to prevent postpartum hemorrhage are oxytocin and misoprostol.[4] Several studies have identified magnesium sulfate as the most effective medicine for preventing and treating deadly seizures caused by pre-eclampsia and eclampsia. The need for these medicines is great and is present at every level of the health care system where deliveries occur, from urban hospitals to rural clinics (USAID, Landscape Analysis: Postpartum Hemorrhage Solutions, unpublished data, 2012).

More than 50 percent of women in low-resource settings deliver without skilled birth attendants and hours away from facilities where these medicines and emergency obstetric care should be available. Managing high blood pressure and related seizures and preventing bleeding for births that are not attended by skilled providers remain major challenges for improving maternal survival. Additional studies are needed to understand the gaps and challenges with regard to policy, regulatory, manufacturing, supply chain management, information systems, financing and demand. Once better understood, the global health organizations and countries around the world will have the information needed to most effectively address the barriers to expand access to these medicines, lower maternal death rates, and improve overall maternal health. In the meantime additional actions are possible.

In a ten-year period (2006–2016), for example, if oxytocin and misoprostol were available to all women giving birth, it is projected to prevent 41 million postpartum hemorrhage cases and save 1.4 million lives (where oxytocin is the first-line

[a] Postpartum hemorrhage (PPH) is defined as excessive vaginal bleeding (blood loss greater than 500 ml) within 24 hours of delivery.

intervention for facility-based deliveries and misoprostol is used for home deliveries) (USAID, Landscape Analysis: Postpartum Hemorrhage Solutions, unpublished data, 2012).

This report provides a review of current conditions and available evidence on maternal health medicines as well as potential actions and areas for continued study for the United Nations Commission on Commodities for Women and Children's Health to explore. Attention to the areas listed in Box 1 can contribute to improved women's health worldwide:

Box 1: Issues for action

- Quantify the unmet need for maternal health medicines so manufacturers can adequately scale up to meet that need and cost estimates to achieve universal coverage can be calculated.
- Identify global and national level expenditures for maternal health medicines so any gaps between necessary and actual funding levels can be determined and filled.
- Explore bulk purchasing mechanisms so that prices remain low while at the same time creating more attractive markets for manufacturers.
- Decrease the prevalence of substandard medicines.
- Improve national regulatory capacity to ensure that only quality medicines are available and that new medicines can effectively enter the market.
- Promote the national registration of essential maternal health medicines as identified by WHO.
- Support new product development and delivery innovations.
- Strengthen management information systems to ensure medicine availability and avoid stock outs but not too far in advance to risk expiration.
- Monitor policy implementation so gaps may be addressed.
- Improve knowledge and skills of health care providers and supply chain managers.
- Build the evidence base and human resource capacity for administration of maternal health medicines by lower-level workers so that women may receive appropriate care when delivering in their community.

The global burden of maternal mortality

The United Nations Millennium Declaration, signed by 189 heads of state in 2000, committed world leaders to achieving Millennium Development Goal (MDG) 5, improving maternal health (with targets of reducing the maternal mortality ratio—the number of maternal deaths per 100,000 live births—by three-quarters before 2015, and achieving universal access to reproductive health). Although more than half of countries are reducing maternal mortality at an accelerated pace, few are on track to achieve the goal by 2015.[b]

An estimated 273,500 maternal deaths occurred worldwide in 2011, almost all in developing countries, down from 409,100 maternal deaths in 1990.[5] Across all developing regions, the maternal mortality ratio dropped 34 percent between 1990 and 2008. Some regions, such as North Africa and the Middle East, as well as South and East Asia, have made substantial progress in reducing maternal mortality, with the pace accelerating in 125 countries since 2000. Yet the target remains far off for most countries. Twenty countries have seen no progress or have experienced increases in maternal deaths.

Nearly 90 percent of maternal deaths are concentrated in sub-Saharan Africa and South Asia. While South Asia has made steady progress, with a 53 percent drop in maternal mortality between 1990 and 2008, maternal deaths fell by 26 percent in sub-Saharan Africa during that time. About half of maternal deaths occur in six countries: Afghanistan, the Democratic Republic of the Congo (DRC), Ethiopia, India, Nigeria, and Pakistan. Targeted interventions in these countries could have a major impact on global maternal mortality. For example, Afghanistan accounts for less than one percent of global births but nearly six percent of global maternal deaths. Figure 1 shows maternal mortality by region, highlighting postpartum hemorrhage and pre-eclampsia/eclampsia as the leading causes of maternal mortality, regardless of region.[6]

[b] Maternal mortality is defined as the death of a woman while pregnant or within 42 days after the pregnancy ends, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. [World Health Organization: Maternal mortality ratio http://www.who.int/healthinfo/statistics/indmaternalmortality/en/index.html Accessed 2/13/12.]

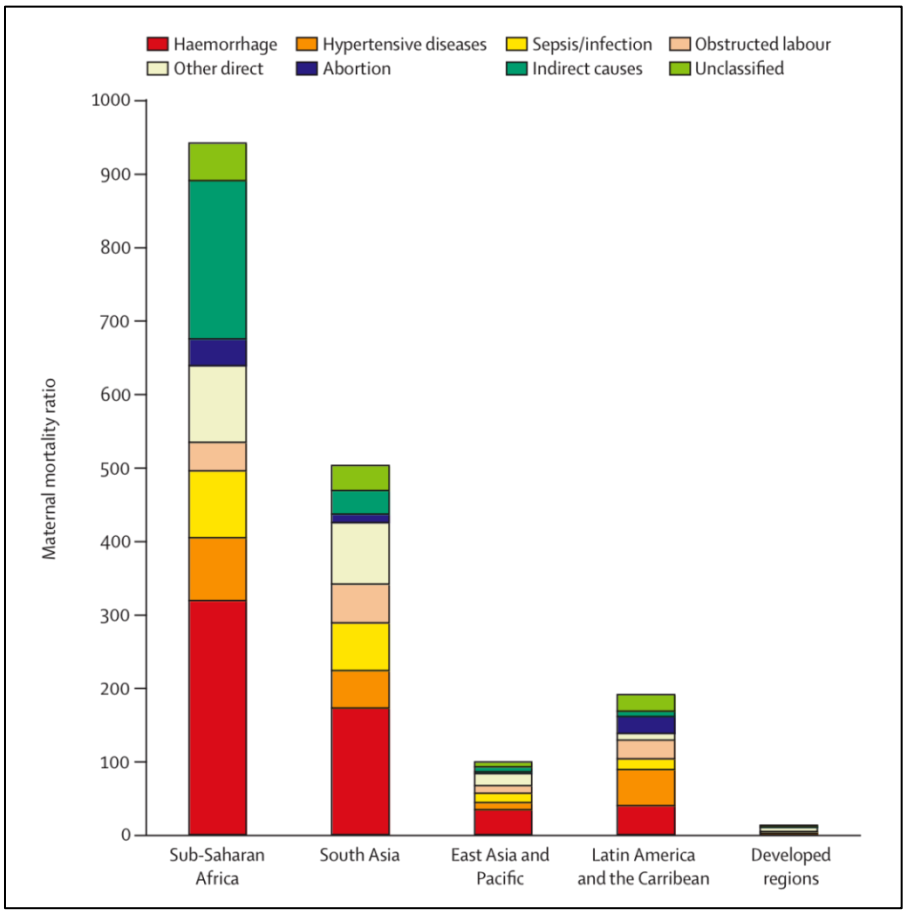


Figure 1: Postpartum hemorrhage and pre-elcampsia/eclampsia as leading causes of maternal mortality worldwide.

Medicines overview

Expanding access to essential maternal health medicines would lower maternal death rates and improve maternal health.[7] The three maternal health medicines explored in this report—oxytocin, misoprostol, and magnesium sulfate—are medicines that prevent and treat the two leading causes of maternal death worldwide: excessive bleeding after childbirth and high blood pressure during pregnancy.

Preventing and treating postpartum hemorrhage

After a baby is born, muscles in the woman's uterus contract, clamping down on the blood vessels to help limit bleeding after the placenta has detached. If the muscles do not contract strongly enough, excessive bleeding—otherwise known as postpartum hemorrhage—can occur and threaten the woman's life.[8] It is a serious condition that requires efficient and effective treatments to prevent severe anemia, shock, the need for blood transfusion or emergency surgery, and death.[9] Postpartum hemorrhage is the leading cause of maternal death worldwide, and its management is a challenge, particularly

in home deliveries. Prevention and treatment options for excessive bleeding after childbirth include the use of uterotonic medicines to increase muscle contractions that compress the blood vessels. Uterotonic medicines increase the tone, rate, and strength of rhythmic contractions in the uterus. Oxytocin is the uterotonic medicine recommended by the World Health Organization (WHO) as the first line medicine and the most commonly used for active management of the third stage of labor (AMTSL) and to manage excessive bleeding after childbirth. For AMTSL, a skilled birth attendant will complete three basic procedures: administer an uterotonic drug to the woman within one minute following the birth, deliver the placenta with controlled cord traction, and massage the uterus after the placenta delivers.[c, 8] Globally, more than half of women give birth at home without a skilled birth attendant, and the WHO recommends that all women giving birth should have access to an uterotonic.

Oxytocin

Oxytocin is secreted naturally by the posterior pituitary—the back portion of a small gland at the brain's base that produces hormones—during later pregnancy, labor, and when the baby breastfeeds. Synthetic forms of oxytocin are found in brand-name products as well as in generic form. In moderate doses, oxytocin produces slow, generalized contractions of the muscles in the uterus with full relaxation in between. When used for postpartum hemorrhage, oxytocin takes effect sooner than most other uterotonic drugs, including misoprostol.[9] One of the major drawbacks of oxytocin, however, is that it is temperature sensitive, and loses effectiveness after three months of being stored at temperatures higher than 30 degrees Celsius (86 degrees Fahrenheit).[9] While some manufacturers' studies indicate that oxytocin can be stored at room temperature[d], the ambient temperature in tropical countries is often higher for extended periods of time. Oxytocin is most often available in 1ml glass vials, containing either 5 (international units) IU or 10 IU, and is administered by injection into the woman's vein or muscle.[9] Doses range between 10 IU for prevention of postpartum hemorrhage and up to 40 IU for treatment. The medicine costs roughly US$0.18 for 10 IU (supplier median price) and is produced by more than 100 manufacturers globally.[11, 12]

Misoprostol

Misoprostol is a prostaglandin—a synthetic hormone-like substance—found in brand-name products and other generic forms. In low-resource settings where oxytocin and a skilled birth attendant may not be available, misoprostol may be used to prevent and treat excessive bleeding after childbirth.[9] Misoprostol may also be used to treat gastric ulcers, miscarriages, or to induce abortion. The latter use explains some of the controversy surrounding the medicine and some countries' reluctance to recommend its use. Misoprostol is available in an oral tablet form, and the WHO recommends 600 micrograms orally for the prevention of postpartum hemorrhage, and permits 800 micrograms sublingually as the third line treatment for post partum hemorrhage. Tablets contain 25 (for induction), 100, or 200 micrograms, and can be stored at room temperature if appropriately packaged in double-aluminum blister packs. The cost per tablet from manufacturers is approximately US$0.15.[13] It is available from more than 50 manufacturers globally (with at least 35 in developing countries).

[c] Controlled cord traction (CCT) is defined as the method used to deliver the placenta by gently pulling on the umbilical cord while holding the uterus stable with the other hand on the abdomen.

[d] Room temperature is about 20 to 25 degrees Celsius with an average of 23 degrees Celsius (about 73 degrees Fahrenheit).

Treating pre-eclampsia and eclampsia

The second leading cause of maternal death is pre-eclampsia and eclampsia—most often detected through the elevation of blood pressure during pregnancy—which can lead to seizures, kidney and liver damage, and death, if untreated. These conditions claim the lives of an estimated 63,000 women each year, as well as the lives of many of their babies. The risk that a woman in a developing country will die of pre-eclampsia and eclampsia—often referenced as PE/E—is approximately 300 times higher than that for a woman in a developed country.[13] Several studies have identified magnesium sulfate as the most effective medicine for preventing the onset of deadly seizures caused by pre-eclampsia and eclampsia.

Magnesium sulfate

Magnesium sulfate—referenced as $MgSO_4$—is recognized by the WHO as the safest, most effective, and lowest-cost medication for treating pre-eclampsia and eclampsia. Magnesium sulfate is the standard treatment for these conditions in the majority of developed countries, but less-effective and riskier medications, such as diazepam and phenytoin, still are widely used in developing countries. Magnesium sulfate costs approximately US$0.10 per ml (supplier median price), and is produced by one global manufacturer and many local manufacturers worldwide.[14] A treatment may require up to nine vials. Magnesium sulfate is administered by injection into the woman's vein or muscle. Calcium gluconate—a mineral supplement—is an antidote available in the rare event of magnesium toxicity.[15]

Key findings

Addressing the barriers and gaps to expanding access to these medicines could help lower maternal death rates and improve overall maternal health. This report explores the current landscape and available evidence guided by a WHO framework to address eight key areas where there are potential barriers and gaps to access to quality medicines for maternal health. Those areas are: policy, regulatory, manufacturing, supply chain management, information systems, financing and demand (by both providers and consumers).

Methodology

The findings include evidence from more than 60 documents collected and provided by key stakeholders, including numerous development agencies, foundations, and implementing organizations, between Monday, December 19, 2011 and Thursday, February 9, 2012. The vast majority of global data sources reviewed describe existing or prospective conditions for misoprostol and magnesium sulfate while country-specific studies tended to focus on oxytocin and magnesium sulfate with cursory insights related to misoprostol. The clinical trials reviewed include peer-review articles published in the past two years via internationally recognized journals. The case studies reviewed include assessments of the availability and use of maternal health medicines and supplies in several countries conducted by international agencies, such as the WHO and United Nations Population Fund (UNFPA) and US Agency for International Development

(USAID)-funded projects, such Maternal and Child Health Integrated Program (MCHIP), Strengthening Health Outcomes through the Private Sector (SHOPS), Strengthening Pharmaceutical Systems (SPS) and the USAID DELIVER PROJECT; and international nongovernmental organizations, such as Population Action International (PAI).

The methodologies used to collect the data for these assessments ranged from document review and interviews with key stakeholders at the national level, to surveys at the facility and provider level. The countries for which national reports were available include five high burden countries: Bangladesh, DRC, Ethiopia, Kenya, and Tanzania. Standard treatment guidelines were reviewed for Tanzania, Uganda, and Zambia. Although this country-level data may not be representative of all countries, it provides a solid representation of the current global landscape and challenges related to the maternal health medicines. In terms of global clinical guidance, guidebooks and technical briefs for providers on the use of misoprostol for various purposes were reviewed. Documents that provide global perspectives on the three medicines under review were also examined; these documents included some journal articles but mostly reports, briefs, and presentations provided by organizations working in this field. Finally, presentations and technical briefs provided during a recent USAID symposium on misoprostol were also considered in this review.

Policy

The review of policies includes those at both international and national levels since international standards often inform those at the national level. The most fundamental and revealing sources of policy documentation relative to oxytocin, misoprostol, and magnesium sulfate are the essential medicines lists (EMLs) and standard treatment guidelines.[e] Clinical guidance outlined in the standard treatment guidelines, however, has much wider variability country-by-country and some subjective components including limitations on permissions for health care workers to administer the medicines. This review identifies existing evidence regarding global trends for the inclusion of these medicines on the global and national EMLs and for their recommended uses. Specific examples from countries are provided to show relevancy of these global trends.

Essential Medicines List

Every two years, the WHO convenes an Expert Committee on Selection and Use of Essential Medicines to review state-of-the-art evidence on the efficacy, safety, and cost effectiveness of medicines in order to update the WHO Model Lists of Essential Medicines (WHO EML) for adults and children. Countries are encouraged to use this model list to inform the development of their own national EMLs. In the 17th edition of the WHO EML, oxytocin, misoprostol, and magnesium sulfate are included.[16] Oxytocin is included for prevention and treatment of postpartum hemorrhage. Misoprostol is included for several obstetric and gynecological uses including "for prevention of postpartum hemorrhage where oxytocin is not available or cannot be safely used," induction of labor, and management of incomplete abortion and miscarriage. Treatment for postpartum hemorrhage with misoprostol is not included in the WHO EML. Similarly, the UNFPA guidance recommends oxytocin, and designates misoprostol where oxytocin is not available or may be unsafe to use as essential maternal health medicines (USAID, DELIVER PROJECT, USAID Procurement Strategy: Oxytocin Market

[e] Standard treatment guidelines are defined as systematically developed statements designed to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances**.** *(MSH, Drug and Therapeutics Committee Training Course, Session 10: Standard Treatment Guidelines. 2001).*

Assessment, unpublished data, 2011). Magnesium sulfate is included on the WHO EML "for use in eclampsia and severe pre-eclampsia and not for other [seizure] disorders."

Clinical guidance

The *WHO Recommendations for the Prevention of Postpartum Hemorrhage* outlines recommended protocols for the use of oxytocin and misoprostol. The document serves as the international model for standard national treatment protocols and guidelines. It states:

> In the absence of active management of the third stage of labor, an uterotonic drug (oxytocin or misoprostol) [still] should be offered by a health worker trained in its use for prevention of [postpartum hemorrhage]. For misoprostol, this recommendation places a high value on the potential benefits of avoiding [postpartum hemorrhage] and ease of administration of an oral drug in settings where other care is not available…the only trial relevant to this recommendation used 600 [micrograms] of misoprostol.[17]

The guidance assumes the presence of a trained health worker to administer the uterotonic, the medicine is used after childbirth for postpartum hemorrhage, and that 600 micrograms of misoprostol is administered. In low-resource settings, these conditions are not often met, which poses a disadvantage to the selection and use of misoprostol. A recent WHO publication—intended to clarify WHO protocols for the prevention of postpartum hemorrhage—outlines critical challenges with misoprostol administration and indicates that giving pregnant women misoprostol (for self-administration after childbirth) is not recommended.[18] This publication clarifies that distribution of misoprostol to women either through prenatal care or by community health workers is not supported by the WHO. However some countries are piloting misoprostol distribution to women at the community level and a few countries are expanding its use to the national level.

Global standards relative to the use of oxytocin versus misoprostol continue to be debated in international forums. In January 2012, USAID held a "Symposium on Misoprostol for Postpartum Hemorrhage Prevention: Getting Practical" with the goal "to explore key technical issues, increase understanding of effective programming, and inform USAID's work with misoprostol as an important component of a postpartum hemorrhage prevention strategy." Participating technical experts ultimately recommended that further study of distribution, use, and scale-up be conducted to better inform future international recommendations for national policymakers.

According to the 2010 *Status Report on Prevention and Management of Postpartum Hemorrhage and Pre-Eclampsia/Eclampsia*, misoprostol reportedly is on national EMLs in 61 percent of the 31 countries surveyed by USAID/MCHIP, although approved uses do not consistently include postpartum hemorrhage prevention or treatment. Sixty-seven percent of countries piloting distribution of misoprostol for postpartum hemorrhage prevention during home births (12) and 75 percent of countries scaling up misoprostol for home birth use (6) report having a national policy in place approving it for prevention of postpartum hemorrhage.[19] Information on misoprostol for off-label use, which is the practice of prescribing a medicine for conditions that were not originally included in the product's registration, for postpartum hemorrhage was not collected as part of the survey. It is possible that off-label use of misoprostol for obstetric purposes is occurring in countries.

Case studies show oxytocin and magnesium sulfate were included in national protocols for maternal health service provision as well as the EML and standard treatment guidelines in the majority of countries reviewed (where national data was collected and reported), including Ghana, Mali, Malawi, Mongolia, and India. Furthermore, the USAID/MCHIP survey states that most countries—except Rwanda and Ethiopia—reported that they have magnesium sulfate on their EMLs. Ethiopia reports that magnesium sulfate is under review, and it has plans to add it to the list soon.[19]

Policy implementation

While national policies to support the use of these essential medicines may exist, these policies are often not implemented. The availability of policy guidance documents at the facility level and subsequent provider recall or understanding of treatment protocols varied widely between countries. A minority of practitioners have any knowledge of guidance documents or their contents.[20, 21]

According to the Essential Competencies for Basic Midwifery Practice 2010, from the International Confederation of Midwives, midwives should have the skills to "conduct active management of the [third] stage of labor." Furthermore, midwives should also have the skill to prescribe, dispense, furnish, or administer selected, life-saving drugs (e.g., antibiotics, anticonvulsants, antimalarials, antihypertensives, and antiretrovirals) to women in need.

Multiple source documents also show that some national standard treatment guidelines limit which health providers are authorized to administer these medicines. For example, Bolivia, DRC, Ethiopia, Guatemala, and Zimbabwe do not yet authorize midwives to diagnose severe pre-eclampsia and eclampsia or give the first dose of magnesium sulfate to prevent seizures. In DRC, a prescription is required for magnesium sulfate, but midwives are not authorized to write them (see Box 2). Furthermore, in Ethiopia, it is noteworthy that health workers with a "nurse diploma" and health assistants are administering medicines that prevent or reduce seizures (caused by pre-eclampsia and eclampsia) without national policy authorization.[22] Ethiopia plans to include midwife authorization in the scale-up training of magnesium sulfate. In Guatemala, magnesium sulfate only can be given by a midwife if no doctor is available. While in Zimbabwe, magnesium sulfate only can be used in hospitals.[19] In Uganda, reviewers found confusion and conflicting reports among providers and professional associations about the national guidelines for the health worker cadres allowed to provide the first dose. [23]

Box 2: Lack of knowledge of treatment guidelines in DRC, Ghana, and Mali for magnesium sulfate use

In 2009, the USAID-funded Strengthening Pharmaceutical Systems (SPS) Program implemented by Management Sciences for Health (MSH) assessed the availability and management of emergency obstetric medicines in DRC, Ghana, and Mali. The studies found that while providers were familiar with the prevention and treatment guidelines for postpartum hemorrhage, many were not familiar with the treatment options and guidelines for pre-eclampsia and eclampsia using magnesium sulfate. These examples demonstrate a consistent gap between policy and practice.

- In **DRC**, 100 percent of providers surveyed use oxytocin as the first choice of medicine for postpartum hemorrhage but only 58 percent use it within the recommended time. No treatment guidelines exist for the use of magnesium sulfate for pre-eclampsia and eclampsia and only eight percent of providers used magnesium sulfate.[24]
- In **Ghana**, only 33 percent of facilities visited had guidelines that mentioned the use of 10 IU oxytocin, but more than 60 percent of respondents had fairly good knowledge on the use of uterotonic medicines for the prevention and treatment of postpartum hemorrhage.[25]
- In **Mali**, more than 90 percent of delivery room managers surveyed knew that oxytocin is a recommended medicine to prevent and treat postpartum hemorrhage, however only 45 percent were aware that magnesium sulfate is the recommended medicine to prevent and treat pre-eclampsia and eclampsia. The majority of managers at the government-operated central medicine store were not aware of treatment guidelines for both oxytocin (35 percent) and magnesium sulfate (8 percent).[26]

A WHO survey related to the Global Reproductive Health Strategy (World Health Assembly Resolution 55.12) assessed the implementation of magnesium sulfate as well. In about 85 percent of the surveyed 58 countries, magnesium sulfate was available for use. However, the institutional, infrastructural, or policy-based issues that hinder women from accessing this medicine in case of need include: providers continuing to rely on diazepam due to relative ease of use in some rural facilities; hesitancy of providers to administer magnesium sulfate due to perceived side effects; and delays in getting the second dose when health centers transfer the patient to upper level of care after giving the first dose. In some cases, magnesium sulfate use was limited to specialized care facilities. National guidelines detailing obstetric roles for intermediate facilities and training health providers in administering magnesium sulfate could improve the actual use of this medicine appropriately.

Although several countries restrict medicine administration authorization to a particular health care worker skill level, task-shifting occurs nonetheless. In Malawi, according to national policy, registered nurses are not authorized to administer injections of oxytocin. However, in 16 percent of the hospitals included in the survey, and 50 percent of the health centers, they are doing so. Likewise, enrolled nurses and nurse technicians are not authorized to administer injections of oxytocin, but in 26 percent of the hospitals and 64 percent of the health centers surveyed, they are reported as doing so.

Figures 2-4 demonstrate policy and practice for the three medicines of interest.[19]

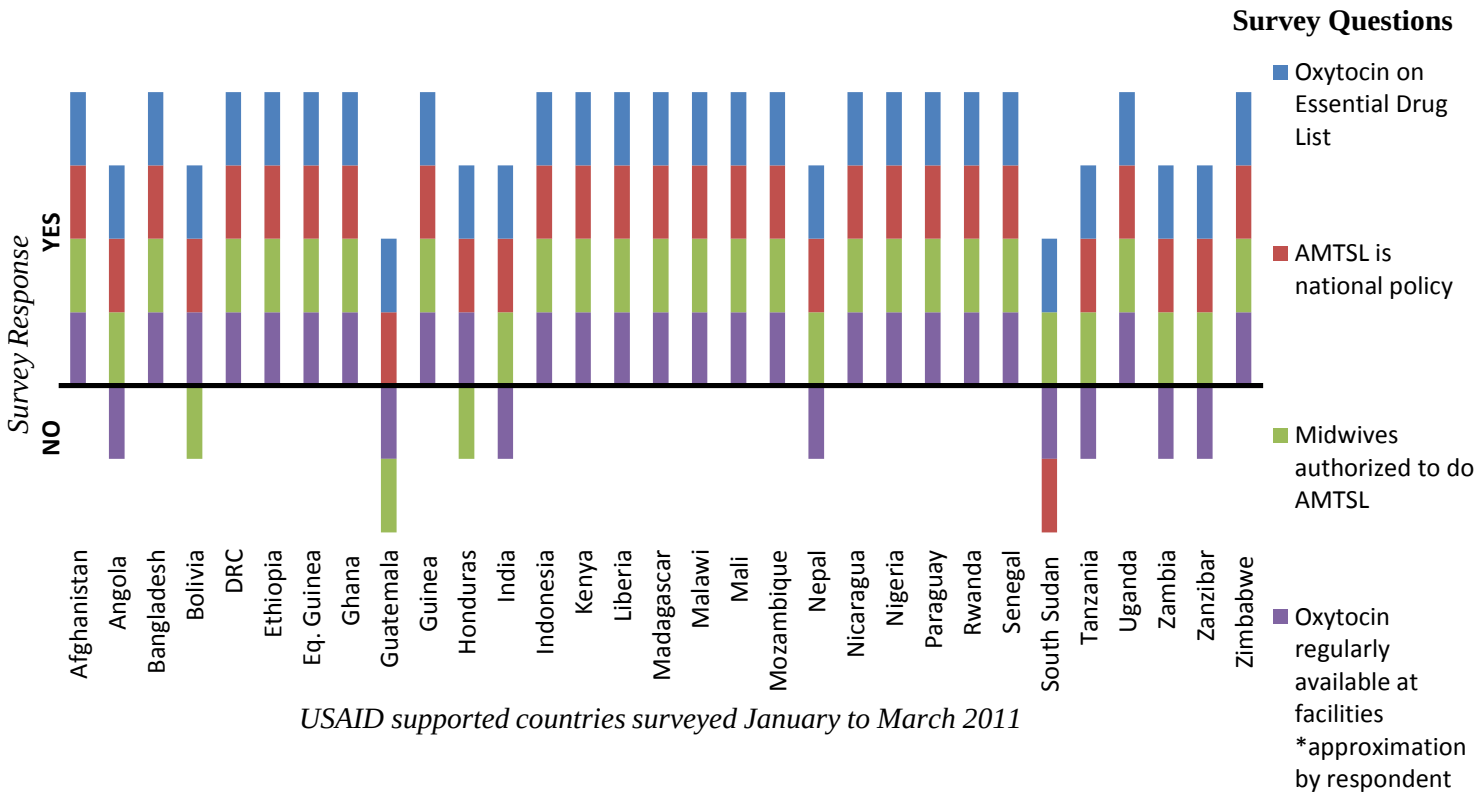
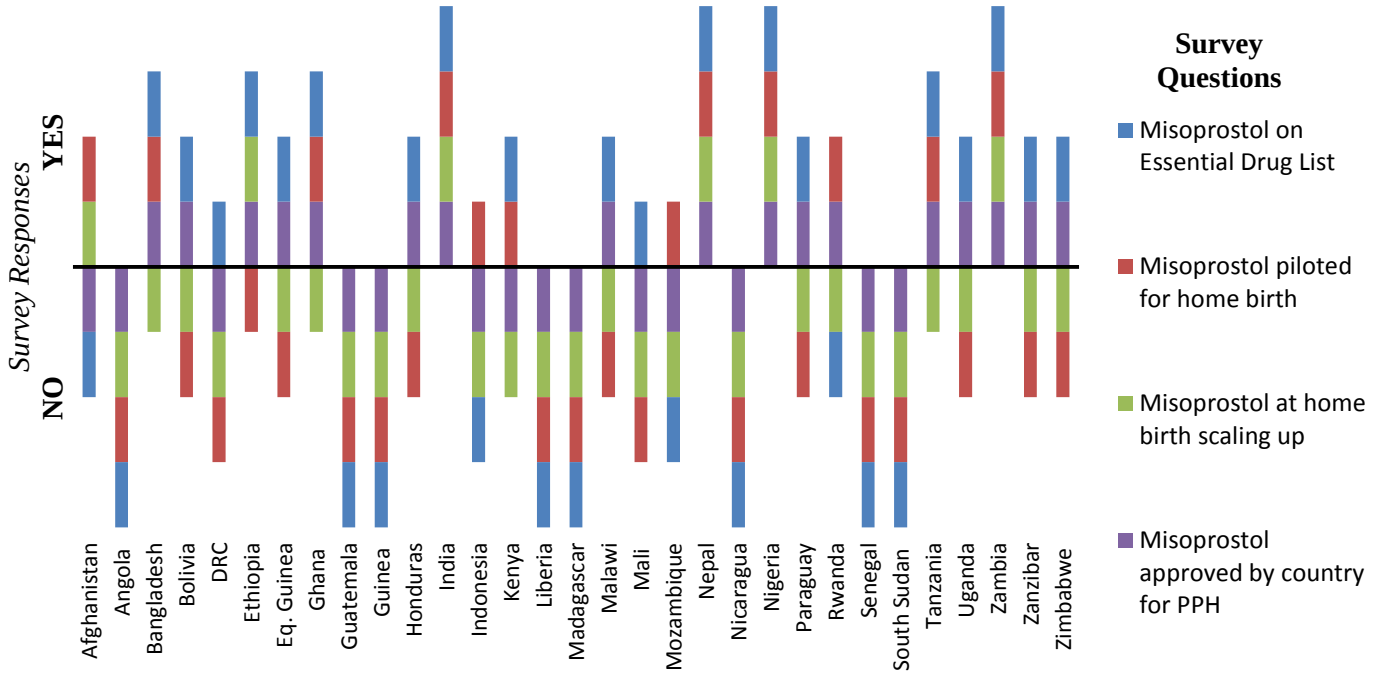


Figure 2: National expansion of active management of the third stage labor (AMTSL).



USAID supported countries surveyed January to March 2011

Figure 3: Expansion and scale-up of postpartum hemorrhage reduction (PPH) programs using misoprostol.

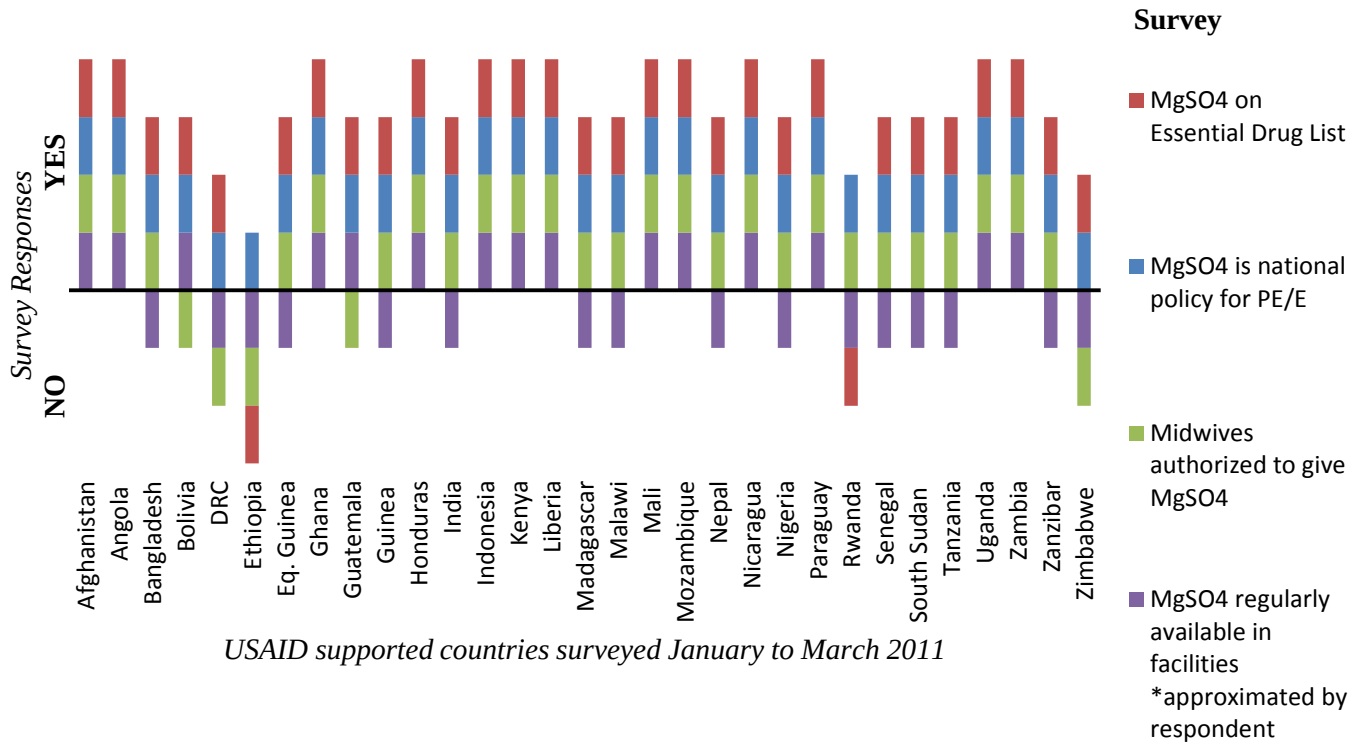


Figure 4: Expansion and scale-up of magnesium sulfate use.

Regulatory

Regulation of medicines at the national level includes registration, quality control and quality assurance measures within the public and private sectors, such as quality testing and post-marketing surveillance, which is the practice of monitoring the safety of a medicine after its release into the market. Regulation is the market gateway for manufacturers and, as seen in some national examples, if too restrictive or permissive, it can have clinical and economic impacts.

Registration

Registration or market approval of a drug by a country's drug regulatory agency grants permission for a product from a specific manufacturer to be marketed in that country for the medical indications for which the application is made. The drug is then added to the country's list of registered medicines. Since oxytocin and magnesium sulfate are included in national policies for maternal health in most countries, it is expected that these medicines would be registered in most countries. Evidence of this can be found in the USAID/MCHIP report, which identified that magnesium sulfate is registered in all countries (31) surveyed across all regions.[19] Oxytocin also has registration approval in most countries studied. However, product registration is not a static state since the validity of a manufacturer's registration is for a fixed time period. This means that manufacturers have to reapply for registration according to a schedule set by the national regulatory authority (NRA). When stringently applied, registration of medicines is provided for specific products produced at specific manufacturing facilities only after the facility has been inspected by the NRA.

This costly process is out of reach for many countries with limited resources, and as a result, many accept less stringent standards for registration. This reality also means that the number of registered products in a given country can vary widely since products are continuously being added and dropped from the list of registered medicines. In the Philippines, for example, more than 32 registered oxytocin products are available from 16 manufacturers. This may contribute to capacity constraints in both inspection and analysis by the NRAs but also the increased likelihood of price reduction by virtue of competition. It is possible that a single manufacturer might register a medicine under multiple brands as a means of preserving price stability.[28]

Confusion may also result when multiple formulations of the same medicine are available within a given health care facility and are not necessarily the same as what is recommended in the country's standard treatment guidelines. This requires providers to calculate the difference and adjust administration accordingly.

Additionally, any combination device, such as a pre-loaded injection device, requires dual registration (both the device and medicine) and therefore faces a more complex regulatory pathway.[18] Oxytocin in a pre-loaded, and auto-disabled injection device is a product-plus-delivery system available for prevention of postpartum hemorrhage in pilot countries, including Mali, Argentina and Guatemala.[f] However, despite clear benefits including ease of administration and appropriate dosing, use of the pre-loaded injection device presents additional regulatory obstacles.

Misoprostol has been registered to treat gastric ulcers in more than 80 countries, but it also has been used off-label in the care of women during and after pregnancy.[28] This makes it difficult to identify whether the medicine is being appropriately dosed and administered in low-resource settings and what impacts on maternal mortality its use may have. The first registration of misoprostol for prevention and treatment of postpartum hemorrhage was in Nigeria in 2006. Subsequent regulatory approvals of the medicine for obstetric and gynecologic use in countries, including Bangladesh, India, Nigeria, Ethiopia, Kenya, Malawi, Mozambique, Nepal, Pakistan, Somaliland, South Africa, Sudan, Tanzania, Uganda, and Zambia, indicates there may be a trend to increase registration in the future.[13] Little information is available at the time of this review on the registration of magnesium sulfate for maternal use.

Quality assurance

The weak capacity of NRAs to regulate the quality and use of medicines, including the three that are the subject of this report, has been widely documented. For example, a 2010 report from the George Institute for International Health states "medicine regulatory agencies in Africa face particularly significant challenges in meeting their mandate."[29] Also, a 2004 WHO study reported that 90 percent of African NRAs lacked sufficient capacity to guarantee the quality, efficacy, and safety of medicines in their country. Likewise, a study conducted by the WHO in 2006 concluded that the NRAs of Algeria, Morocco, Nigeria, Senegal, Tunisia, and Zimbabwe were functional but needed "strengthening in regulation of clinical trials" amongst other things; and that the NRAs of Egypt, Ethiopia , Ghana, and Uganda had "potential" although they were not yet fully functional.[30] Furthermore, in a 2010 assessment of NRAs, the WHO found that while the majority of countries had a regulatory quality control laboratory, few had an effective quality monitoring system in place, and "quality control testing was not used optimally to complement other regulatory functions." Similarly, most countries had

[f] Field evaluations were planned in 2011 in Nicaragua, Honduras and Ghana. The product is registered in Argentina, Guatemala, Honduras, Nicaragua, Bolivia, Paraguay, Ecuador and Uruguay.

policies and structures in place to monitor the safety, efficacy and quality of medicines in the market, but implementation of post-marketing surveillance was weak.

Similarly, medicine quality assurance mechanisms vary widely between countries studied during this review. Most countries agree that manufacturers need to become certified in "good manufacturing practices" (GMP) as defined by the WHO, and some countries tested medicines imported from suppliers upon receipt to ensure alignment with WHO standards. However, unregistered and unapproved medicines are often widely available, especially in the private sector, and many regulatory authorities are unable to restrict their availability. Mongolia has unregistered medicines or brands of oxytocin or magnesium sulfate with an unknown origin and quality at the user level.[20] In the Philippines, while misoprostol is banned in the country due to sensitivities related to its potential use for termination of pregnancy, it was still found to be available in field areas.[32] In Lao People's Democratic Republic (Lao PDR), provincial authorities indicated registration was a requirement for procurement, however, none of the formulations observed during field visits were registered with the NRA.

Although the number of formulations of oxytocin and magnesium sulfate procured in the public sector were limited in most countries, some countries have a large variety of formulations available.[33] In Lao PDR, none of the formulations on the market were consistent with the treatment guidelines. Magnesium sulfate, for example, is available in 20 percent and 15 percent formulations while the WHO recommendation is 50 percent.[33]

Based on the data available, it is challenging to assess which countries are using the medicines for off-label uses.

Manufacturing

The supply side of oxytocin, misoprostol, and magnesium sulfate consists of numerous manufacturers. While some manufacturers compete in global markets, others limit themselves or are limited to local markets. As a complete examination of manufacturers is beyond the scope of this review, manufacturer's product packaging and presentations as well as pre-market quality assurance mechanisms are reviewed, noting any critical impacts of their products at the user level.

Labeling and packaging

Venture Strategies Innovation (VSI) reported 200 microgram misoprostol tablets are manufactured in either blister packs or bottles, and come in blister packs of 3, 4, 10, 20, or 30 pills or bottles of 60 or 120 pills. As misoprostol is used for other indications, including post-abortion care, package size is not a concern for the professional health provider. However, since the current dosing regimen for prevention of postpartum hemorrhage is 600 micrograms, a three-pill pack would be preferable for countries allowing or planning to allow at home use of the medicine. Few manufacturers produce the three-pill blister pack, creating procurement challenges for developing countries. Additionally, manufacturing minimums from 100,000 to 200,000 tablets are often too great for one country to meet and splitting batches between countries can be complicated as countries often require specific secondary packaging, which increases the costs of production and acts as a deterrent to the supplier.[33]

A Concept Foundation quality study on misoprostol content and purity collected 76 samples from Argentina, Bangladesh, Cambodia, Egypt, Kenya, India, Mexico, Nigeria, Pakistan, Peru and Vietnam. Thirty-four had less than 90 percent of labeled content (8 had less than 20 percent), and after one year of degradation, 19 of 31 samples tested had less than 90 percent of labeled content (7 had less than 20 percent). Furthermore, the medicine appeared to degrade within three months to one year with 31 of 58 samples having impurities greater than industry standards (18 had more than twice the limit). The study concluded that not only were there significant problems with the content and purity of many misoprostol products but that the degradation of some of the medicines would not have been detected by pre-shipment quality control measures.[34]

National case studies also identified issues with variants in medicine storage requirements. Manufacturer instructions for oxytocin in Ghana made no mention of cold storage requirements but instead indicated only a need for a cool, dry place out of direct light (see Box 3).[24] Similarly, some manufacturers package misoprostol in aluminum-PVC (plastic) blister packs (preformed packaging), as opposed to the recommended double aluminum, which can make the medicine susceptible to damaging humidity.[35]

Box 3: Variants in manufacturer storage instructions for oxytocin

- In **Nepal**, despite procuring from only GMP-certified manufacturers, an UNFPA/WHO assessment found a general absence of product information leaflets or correct storage specification (for oxytocin) in the medicine boxes.[35]
- In **Ghana**, wide variations in manufacturer recommendations and actual storage of oxytocin exist. None of the manufacturers in Ghana instructed oxytocin to be stored at 2-8 degrees Celsius and only 50 percent instructed it to be stored in a cool, dry place. Twenty-nine percent of manufacturers instructed that misoprostol be kept away from light.[24]

None of the reports reviewed indicated the presence or absence of medicine instructions—including warnings and adverse reactions information—either from the manufacturer or the distributing provider.

Manufacturers

According to a Population Council brief, "magnesium sulfate is rarely globally manufactured because its low cost leaves little profit-based incentive for pharmaceutical companies to produce it." National examples for acquiring the medicine are documented as follows:

> More commonly, such as in Mexico (where eclampsia is the number one cause of maternal death), magnesium sulfate must be acquired at a country-level from domestic pharmaceutical companies or through federal governments. In South Africa, where more than 50 percent of maternal deaths are caused by eclampsia, the government has approved the manufacture of magnesium sulfate by the domestic producer Adcock Ingram Critical Care. In Nigeria, where eclampsia is responsible for as many as 40 percent of maternal deaths in the northern region, there are no domestic manufacturers of the drug (but the MacArthur Foundation helped to engage

a pharmaceutical company to manufacture magnesium sulfate, leading to a steady supply) (Lowe R., Brief: Magnesium Sulfate, VSI, PATH, unpublished data, 2011 and MacArthur Foundation-correspondence).

A Concept Foundation study showed that misoprostol is available widely and cheaply in generic formulations in most countries with approximately 50 manufacturers worldwide and some 35 in developing countries. At least 27 brands of misoprostol exist in India and 19 brands exist in lower-middle income countries, excluding China and South Korea. Manufacturing methods, process, and the type of packaging used influence quality for the life of the medicine.[34] Some manufacturers of misoprostol have made medicines to be exported for obstetric use in low-income countries, most notably in South Asia, Sub-Saharan Africa, and South East Asia.

It should be noted that oxytocin, misoprostol and magnesium sulfate are eligible for the WHO Prequalification of Medicines Program which allows manufacturers to submit comprehensive information on their products so qualified assessment teams can prequalify them for bulk purchase by procurement agencies based on production and quality. To date no manufacturers' medicine has qualified under this program.[39]

Supply chain management

Data reviews attempted to discover national and local management processes for medicines including the quantification, procurement, distribution, storage and inventory management of oxytocin, misoprostol and magnesium sulfate. Quantification includes estimating the quantity and cost of the products required for a specific health program (or service), and to ensure an uninterrupted supply for the program, determining when the product should be procured and distributed.[37] Open and transparent procurement includes the processes of tendering (obtaining formal offers), placing an order with the selected manufacturer or supplier, and procedures for ensuring the quality of the medicines procured. Maternal health care, like many primary health care services, can be severely hampered by supply-chain constraints.

Procurement

Medicines in the public sector may be procured centrally or via decentralized mechanisms. In centralized procurement models, national health programs forecast needs for a future period and reconcile available funds with the quantities required before putting out a tender (formal offer) and placing an order. Centralized forecasting of maternal health medicines is challenging due to the limited availability of data about their use. Estimates are subsequently based on demographic and morbidity data, which may or may not represent the actual need.

In a decentralized procurement model, medicines are procured directly by regional, district, and/or community facilities. The benefits include potentially shorter lead times[g], a more robust system especially in instances of disaster, and potentially better forecasting. The drawbacks include lack of standardization in quality and identifying characteristics of the medicine[h]; disadvantages with regard to economies of scale; differences in monitoring and evaluation (M&E) standards and gaps in pharmaceutical management and forecasting methods. The advantages and disadvantages

[g] Lead time is defined as the lead time is the time between the placement of the order and receipt of medicines.

[h] Identifying characteristics are defined as the consistency of color, size, shape and markings and are key to the patients' ability to purchase the correct medicine and quantity.

mentioned often also apply to private sector procurements, which in developing countries most often follow the decentralized model.

Whether following a centralized or decentralized procurement model, across health sectors, countries often face challenges with accurately quantifying their need for the medicines. In Mongolia, reviewers found inadequate methods as well as staff knowledge and skills for forecasting essential medicines. Standard forms and procedure guidelines for conducting a forecast were not available. Additionally, drug therapeutic committees—a group essential to determining which medicines will be available, at what cost, and how they will be used—were weak or not functioning well enough to provide direction.[i, 21] In Ghana, pharmacists in 90 percent of public health facilities and 96 percent of private health facilities use historical consumption methods to quantify oxytocin and/or misoprostol need.[25] A review in Vanuatu discovered that procurement is generally based on a past annual procurement plan with evidence-based selection and a consumption-only calculation method that are not part of the government procurement system.[37]

In addition to quantifying the need for medicines, procurement officers in both the public and private sectors lack training to control and ensure the quality of the medicines. Medicines from manufacturers that have not been approved by the WHO or stringent regulatory authorities require rigorous testing after they are received to prevent damaged or substandard medicines from entering the market and being used. Concerns for quality are particularly acute where medicines are procured at local levels. For example, large proportions (75 percent or greater) of hospitals and health centers in Malawi stock misoprostol although the government-operated central medical store has not maintained stock of misoprostol for two years. Health centers report that government sources are supplying an average of two-thirds of medicines—which is not possible according to the store's stock levels—and that private sector and nongovernmental organizations are providing the remainder.[38] The assumption is that public health centers are procuring more misoprostol outside public health system channels than reported. Broader recurring supply chain issues, like this, result from lack of policy enforcement via monitoring and supervision; poorly designed or implemented logistics management information systems; weak infrastructure with low staffing at the district and facility level creating gaps in supply management and provider coverage; and a limited pool of skilled human resources at all levels of the health system.

Distribution and storage

After procurement is executed and supplies are received, medicine is distributed according to the country's established inventory control mechanism. When a government-managed central medical store receives an order, they will either send medicines as requested (pull method) by the lower levels of the health system, or quantities deemed appropriate and necessary are provided (push method) to regional facilities. While some regional facilities may function as service delivery points, others serve only as storage facilities and distribute medicines to district and community facilities (either through push or pull mechanisms). Most of the country-specific documents reviewed did not describe the distribution process for the medicines.

In general, national case studies showed that medicine storage conditions in the (central level) facilities visited had appropriate security levels, clean facilities and adequate spacing and shelving. However, while stock cards and temperature monitoring cards were available in most facilities, they were sometimes misunderstood or incorrectly and

[i] Drug therapeutic committees evaluate the clinical use of drugs, develop policies for managing drug use and administration and manage the formulary system. The committee has broad responsibilities in determining which drugs will be available, at what cost and how they will be used.

incompletely applied, resulting in medicine exposures to ambient temperatures as well as gaps in stock-level monitoring, which may contribute to stock outs.[j, 21, 39] In some countries, such as Mali, issues including lack of "first to expire, first out" compliance, regular monitoring of expiration dates, and refrigerator temperature records were barriers to adequately managing the medicine supply.[27]

As has been previously mentioned and demonstrated through examples in Mongolia and Bangladesh, oxytocin is often stored inappropriately outside of cold storage conditions.[21] In Vanuatu, oxytocin is stored in room temperature outside of its secondary packaging even when working refrigerators are available.[37] The circumstances may be due more to information provided by manufacturers on storage requirements (see Manufacturing) than neglect. For instance, in Bangladesh, stakeholders reported that oxytocin only needed to be kept in temperature-controlled storage during the hot summer months; in winter, a temperature controlled supply chain was not thought to be necessary.[39] Misoprostol has sensitivities to humidity depending on packaging, and recommended storage is typically at 25 degrees Celsius or less, in a dry place.

Information systems

The ongoing processes of monitoring performance and evaluating intervention impacts are a core program management support function. In the context of this review, research on management information systems (MIS) for logistics and associated tools as well as their impacts on availability, accessibility, and appropriate use of the medicines are reviewed. Robust internal M&E systems resulting in regular reporting and complete feedback loops—from local to national levels and back—are, however, critical components of national and international policy and decision making processes and are highly encouraged by international partners.

Inventory management

MIS implementation and use of associated tools, such as stock cards—a MIS tool designed to track designated medicine stock levels—and expiration charts, for each medicine reviewed, varied within levels of the public management sector. Although inventory records were found in some facilities, logistics information in several countries studied was either used improperly or not at all. In Ghana, for example, 86 percent of the public health facilities used a MIS to monitor consumption patterns—a key data input to medicines forecasting in some countries—as compared to 55 percent of private health facilities.[25] Where a MIS was not available, managers relied on poor substitutes to regulate stock levels, including ledger and tally cards (30 percent of public sector facilities) or visual/physical inventory (in the private sector).[39] Even countries with a widespread MIS, often did not correctly use stock cards. In Mali, for example, most of the facilities (91 percent) had stock cards available, but less than three-quarters of them were used correctly and less than a third had their cards up to date.[25] Of the lower level facilities, less than half had a stock card.

[j] Stock outs are when a pharmacy, medical store or health facility temporarily has no medicine on the shelf; it can affect one medicine or many medicines. (MSH, Rational Pharmaceutical Management Plus. Available at: http://www.msh.org/projects/rpmplus/Resources/TrainingInitiatives/Drug-Therapeutics-Committees.cfm)

Monitoring and evaluation of programs

M&E methods and frequency vary from country to country. Most countries maintain some semblance of an M&E system, if only in policy guidance documents, although typical performance and impact indicators are reported irregularly if at all. While not explicitly studied in the course of this review, M&E is often most challenging across disease portfolios and health programs at the community level. Poor human resources capacity (e.g., lack of training, high turnover, and multi-tasking staffs), lack of national-level information analysis and feedback and little funding to support M&E at local levels are all common contributors. As efforts move forward to roll out misoprostol within countries with a high maternal mortality burden, it is important to develop indicators of progress early, to monitor standards for success and to evaluate at regular intervals. Without these, no true program progress or measurable outcome can be ascertained.

Financing

The literature reviewed explores health costs, apparent and hidden fees that contribute to those costs, and financial barriers that may be prohibitive to providing or receiving treatment. This section also provides a summary of the information available on international donor versus national contributions. At the national level, the focus is primarily on budgeting given that line item allocations are the most revealing of organizational structures and prioritizations.

Budgeting

No comprehensive information about the sources of donor or national funds used for maternal health medicines was available to the reviewers. Similarly, no information was available in donor or national budgets about the proportion and level of funds earmarked for oxytocin, misoprostol, or magnesium sulfate procurements. Should such information be sought or studied in the future, researchers may also consider reviewing whether national programs that procure uterotonics choose to procure oxytocin, misoprostol or both.

What is known, however, is that maternal health medicines and supplies intended for use in national health system facilities are often funded by donors or by international or local organizations in most of the countries (for which data is available). Whereas in others, these medicines are funded solely via the Ministry of Health.[27] The variability may be due to local budgeting practices for maternal health allocations. Maternal health medicines are typically included in general essential medicine budget lines, making it difficult to determine actual allocations and spending on individual medicines.[40]

In both Bangladesh and Uganda, maternal health medicines are included in a general budget line for maternal, child and reproductive health supplies (Bangladesh) or for reproductive and maternal health supplies (Uganda)—an allocation which is often under spent in both countries. In Uganda, reviewers found that, on average, less than 10 percent of designated funds for supplies were actually spent. Similarly in Bangladesh, only 45 percent of the designated supply budget line had been spent with one year left in an extension of the program. In Bangladesh, maternal health medicines have historically been procured using a combination of internally generated funds and pooled donor funds under the health sector program managed by the World Bank. [40]

Regardless of the funding source or level, careful budgeting can greatly impact maternal health program success. Stronger links between appropriate budget reporting and analysis and maternal mortality increase the potential to expand

information, encourage debate and promote accountability by showing whether government promises are being translated into sound policies and appropriate allocations.[41] Ministries of Finance also are often important players in budgeting and finances for maternal health supplies. In many countries, it is the Ministry of Finance that releases funds for use by the Ministry of Health. For example, in Uganda, delays at the Ministry of Finance were cited as a major cause of stock outs and low expenditures for supplies.

Financing mechanisms

The documents reviewed did not include much description of financing mechanisms available for maternal health. However, the UNFPA *State of the World's Midwifery* report from 2011, surveyed countries on financing models currently available. The majority of countries were reportedly not implementing innovative strategies such as incentive schemes, conditional transfers, or insurance systems. [41] Slightly less than half of the countries surveyed provided free access to institutional births, and only a third had cost-recovery models in place.

Private sector financing

A USAID-funded SHOPS rapid assessment report revealed pertinent insights into the role of the private sector and associated financial impacts to each level of the health system:

> According to the International Finance Corporation (IFC)'s report on "Business of Health in Africa," about 60 percent of the US$16.7 billion spent on health in 2005 in Africa was financed primarily by individuals through out-of-pocket expenditures. (These private sources refer to commercial banks, investors, and other non-state sources of funds. IFC also estimates that the market for health care will increase to US$35 billion by 2016.) Fifty percent of that spending was captured by private providers. This percentage was confirmed in a separate analysis by UNICEF and the African Development Bank, which found that more than half (or more) of health expenditures in Africa is spent on non-state providers. Private providers comprise both the formal and non-formal sectors. Overall, for expenditures that are captured by the private sector, for-profit providers garner about 65 percent, social enterprises 15 percent, nonprofits 10 percent, and traditional healers 10 percent.[42]

In some countries, misoprostol and even oxytocin are available for purchase in the private market at pharmacies and medicine shops. In Uganda, for instance, the private sector supplements the supplies available at public sector facilities, and women or their families are provided with a list of necessary medications to purchase from local pharmacies. [23] At private-sector facilities, financing of supplies, including these maternal health commodities, is usually supported by user fees, creating a budget and an incentive to keep essential medicines available. In Bangladesh, reviewers found a corporate social responsibility program, in which a large local corporation pays for the delivery fees, including supply costs, for poor women in several areas.[40]

Demand by Providers

Product availability refers to the existence of the medicines in the market for patient consumption when sought. Similarly, the availability of related services includes provider prescribing and dispensing practices. Education and training strongly influence the quality and level of provider care as well as acceptable standards of practice. Although documents supporting this review stem from the public sector; the private sector is a key component of a comprehensive review of availability.

Availability

A recent USAID/MCHIP survey outlined not only global unavailability of oxytocin, misoprostol and magnesium sulfate but also underscored potential reasons for the current landscape, stating that "across the 31 countries[k] surveyed, programs for the prevention and management of pre-eclampsia and eclampsia are not as well developed as postpartum hemorrhage programs. Figures 5 and 6 illustrate the availability of oxytocin and magnesium sulfate at facilities.[19] Program effectiveness is in question; when a minority of facilities has consistent availability of the medicine, and even fewer respondents report consistent use of the medicine. Findings from this survey indicate a disparity between nationally approved policies and education guidelines to reduce postpartum hemorrhage and pre-eclampsia and eclampsia and actual services delivered." The survey concluded that oxytocin potency, temperature-controlled supply chain, supplies for injection, adequate staffing at facilities, supervision, and training needs may all be contributing to inconsistent availability and may require further investigation.[19]

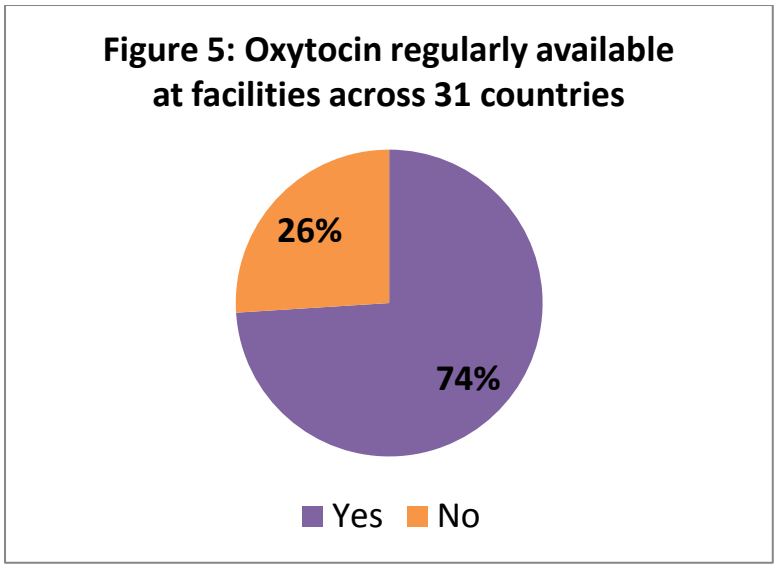


Figure 5: Oxytocin regularly available at facilities across 31 countries.

[k] Countries surveyed by region include: Angola, DRC, Ethiopia, Equatorial Guinea, Guinea, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Sudan, Tanzania, Uganda, Zambia, Zanzibar, Zimbabwe (Africa), Afghanistan, Bangladesh, India, Indonesia, Nepal (Asia), Bolivia, Guatemala, Honduras, Nicaragua, Paraguay (Latin America)

A separate study assessing the global availability of misoprostol showed there was an improvement in availability in some low-income regions. Misoprostol saw the greatest increases in sales between 2002 and 2007 in Asia with dramatic increases in Bangladesh (128 percent) and India (646 percent).[13] The high number of 100 local misoprostol producers in India either only sell products locally or are solely contract manufacturers, a fact which may contribute to the dramatic sales increases in the country.

National reports of oxytocin and magnesium sulfate also indicated general availability with some stock outs. In Malawi, stock outs in the previous year for oxytocin and magnesium sulfate were experienced in about one-third of hospitals and health centers. Small proportions of health centers (eight percent) had never stocked oxytocin whereas 46 percent had never stocked magnesium sulfate. In Bangladesh, a 2009 study found that only 55 percent of district hospitals and 38 percent of health centers reported oxytocin availability.[40] The same study found that only two percent of facilities were prepared for "obstetric first aid" with magnesium sulfate, oxytocin and antibiotics.

There was little information available to the reviewers on provider knowledge, attitudes, and practices with respect to oxytocin or misoprostol.[23] In Uganda, providers were reported to be slow to transition from using ergometrine (another uterotonic) to oxytocin for postpartum hemorrhage. Providers also reported high acceptability of misoprostol to prevent postpartum hemorrhage, in part because the tablets are easier to administer and more acceptable to patients than an injection. Preferences for one medicine over another may explain patterns of availability, particularly at the community level as well.[23]

Although magnesium sulfate is endorsed by national policy in all countries surveyed, only 48 percent of countries reported magnesium sulfate as consistently available in facilities with obstetric services, irrespective of region (see Figure 6).[19]

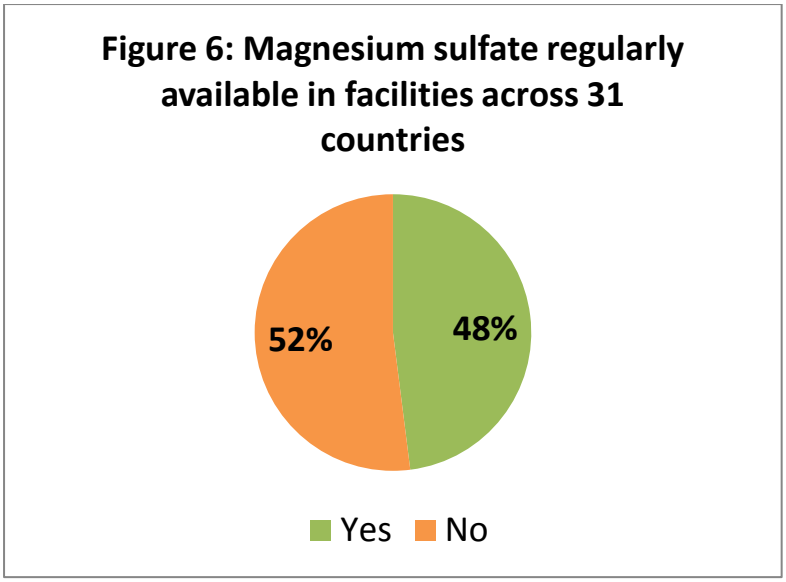


Figure 6: Magnesium sulfate regularly available in facilities across 31 countries.

Using data from recent Emergency Obstetric and Newborn Care Needs Assessments conducted by Ministries of Health from 13 countries, UNFPA, UNICEF, WHO and AMDD calculated an estimate of the population coverage of life-saving maternal medicines. The proportion of births in facilities was multiplied by the percent of facilities included in the assessment sample where oxytocin, misoprostol and magnesium sulfate were available to calculate the estimated population coverage. The average coverage for oxytocin was 36%, with a high of 83% in Guyana and a low of 13% in Niger. The average coverage for magnesium sulfate was only 16%, with a high of 44% in Burkina Faso, and no coverage in Ethiopia. While these are just rough estimates, they do provide some indication of the current low levels of coverage of these essential maternal health medicines (UNFPA, data from recent National Emergency Obstetric and Newborn Care Needs Assessments compiled by UNFPA, Technical Division, unpublished data, February 12, 2012). Misoprostol was not available in 8 of the 13 countries. Afghanistan and Cambodia were the only countries where misoprostol was found in a substantial number of facilities (95% and 23% respectively).

Demand generation and provider knowledge

In a study of the private sector in Kenya, SHOPS reported that oxytocin, misoprostol, and magnesium sulfate are all "marketed through the private sector, although in a limited way, to the retail pharmacies, clinics, nursing homes and hospitals by medical representatives employed by the manufacturers. The products are [registered as poisons] and therefore are restricted and available only with prescription. It is however possible to get these formulations over the counter from a retail pharmacy without a prescription. Misoprostol is more marketed than the other two medicine categories…."[42]

The SHOPS rapid assessment identified that providers, pharmacists, and even product manufacturers remain largely ignorant of misoprostol's use and dosing to prevent postpartum hemorrhage.[42]

Most national case studies of the public sector showed varying availability of oxytocin, misoprostol, and magnesium sulfate at the facility level, although oxytocin generally had higher availability (as a percentage of facilities stocking the medicine) than misoprostol across the spectrum.[21] Oxytocin and misoprostol are available in the private sector. Magnesium sulfate was most often not available or used by providers because of lack of knowledge and skill in administration.[24, 44] Common among the countries studied was a lack of appropriate knowledge of clinical protocols with respect to timing and dosing.[25] Forty-six percent of health facilities had never stocked magnesium sulfate, according to country reports.

Demand by Consumers

Product and service accessibility refers to the patients' ability to pursue treatment. It includes affordability, location, and socio-cultural acceptability of procuring products and treatments. Accessibility may be impeded by cost, distance to provider or health center, and other barriers to treatment.

Availability

The burden of maternal mortality is highest in Asia and Sub-Saharan Africa. Evidence from Fernandez et al shows increases in the demand for misoprostol in Asia:

> Misoprostol for [obstetric and gynecologic uses] is still in its introductory phase in Asia. This region has the best conditions for a future market expansion….Asia has the largest selection of misoprostol brands, with most products being manufactured locally, and the most products registered for [obstetric and gynecologic uses]. Consequently, misoprostol drugs in Asia are among the least expensive anywhere. …South-Central Asia has the second-highest ratio of [postpartum hemorrhage]-related maternal deaths, after sub-Saharan Africa. Because of these factors and the ongoing programmatic work of several organizations on the continent, we expect that sales of misoprostol in Asia will continue to increase sharply in the future.[13]

The USAID DELIVER PROJECT's procurement strategy adds:

> The global market for oxytocin is highly fragmented on the supply side, with no apparent global market leader in terms of distribution. Similarly, the demand side appears to be highly fragmented, with direct procurement from government agencies and the private sector as well as international donors and other supply organizations. As there are no consolidated sales or distribution data source to quantify value or unit volume, any estimate of market size must be calculated on a per country basis.
>
> Secondary research suggests that there is current, ongoing donor support for the procurement of oxytocin. UNFPA, for example, identifies the drug on its list of procured commodities through public tender. Also, the International Drug Price Indicator Guide, indicates there were at least eight suppliers of oxytocin in 2009, including UNFPA, Missionpharma, Imres, IDA, and others. Sales data provided by UNFPA gives an indication of the sources of their demand, however cannot be taken as an indicator for the market overall, or of the total demand for a particular country (USAID, DELIVER PROJECT, USAID Procurement Strategy: Oxytocin Market Assessment, unpublished data, 2011).

Demand generation and consumer knowledge

Social marketing has helped to "legitimize [misoprostol] for community access in countries where it is present." International organizations contribute significant "marketing efforts for the products—these are not primarily print publicity, but instead rely on consistent and sustained detailing of medical providers, pharmacists, and nursing associations. Often the importance of preventing [postpartum hemorrhage] needs to be explained to private providers that may not be familiar with its health consequences—especially pharmacists…Population Services International (PSI) socially markets misoprostol for [postpartum hemorrhage] in 6 countries (Nigeria, Somaliland, Tanzania, Uganda Myanmar, and Zambia) and contributes to partner programs for misoprostol for [postpartum hemorrhage] in Mozambique…The social marketing organization, DKT International, markets misoprostol for [postpartum hemorrhage] in Democratic Republic of Congo (in pilot phase), Egypt, and Sudan."[43]

Misoprostol for postpartum hemorrhage may be ideal for use outside of health centers where pregnant women are provided with the medicines for self-administration and where mid- and low-level providers may find administration of an oral tablet easier and more compatible to their work environment (i.e., where temperature-controlled storage is not available). Outside of formal pilot programs in which education about misoprostol is emphasized, little is known about patient counseling and/or their comprehension of the importance of the medicine for postpartum hemorrhage and other obstetric uses. It is not fully understood, therefore, where demand for the medicine originates—at the patient, health care worker, health center, department of health level or other. It is also important to understand, at the service provider and patient levels, preferences for and efficacy of oxytocin as compared with misoprostol.

A literature review of the use of uterotonics during home births in South Asia published in 2010 asserted that "descriptive studies suggest that home use of uterotonics before delivery of the baby are predominantly administered by nonprofessionals to accelerate labor, and are not perceived as unsafe." It concluded that "to achieve maximum benefit and minimal harm, programs that increase access to uterotonics for postpartum hemorrhage prevention must take into account existing practices among pregnant women."[45]

Accessibility

National level analysis puts perspective on global market trends and demonstrates that placement of the medicine in the market may not be equivalent with access. Oxytocin, misoprostol and magnesium sulfate, when available at hospitals and health centers, are likely to improve standards of care. User fees for medicines[36] or non-medical products (e.g., hospital bed, food and neonatal care), lack of skilled providers, or poor treatment of women and their relatives may deter patients from seeking care at a health center and opting for home birth instead.[27] Similarly, staffs not trained in the use of magnesium sulfate have doubts about its utility and safety; expressing concerns about the reputation of the hospital in the event of overdose and maternal deaths.[44] Barriers are created when the Ministry of Health does not provide the medicines for free to patients and/or service providers and facilities charge patients a higher price for the medicine than what they paid to the government-operated central medical store.[25] In some countries medicine prices can be a significant portion of the average daily income.[21]

Issues for action

As outlined in this document, there are significant gaps in the data collected to date on maternal health medicines for the developing world. While it is clear that too many women suffer or die during childbirth and that appropriate access to the right medications could save them, more information is needed to better understand where barriers to maternal health lie and how efforts to improve access to effective maternal health medicines can help to overcome them.

Based on the limited data available, a set of reviewers from global institutions (i.e., WHO, UNICEF, and UNFPA), donor governments (i.e. USAID), and international nonprofit organizations, identified potential issues for attention and action by the United Nations Commission on Commodities for Women and Children's Health in the following areas: market-shaping, regulatory environment and best practices and innovations. Cutting across all of the

categories is the need to invest in robust health systems and develop accountability structures to assure adequate procurement of quality maternal health medicines, sufficient human resources and functioning supply chain systems so that essential products reach those who need them most.

Market shaping

Quantify the unmet need for maternal health medicines so manufacturers can adequately scale up to meet that need and cost estimates to achieve universal coverage can be calculated

Ensuring that maternal health medicines are available to all who need them is essential to the provision of maternal health services and saving women's lives. However, there is little understanding of the actual number of women for whom these essential maternal health medicines are not available—that is, women with an unmet need. Additionally, there is no available information about what methods countries are using to quantify medicine needs and whether countries are actually procuring enough to meet their needs. Reviewers strongly believe that quantifying the unmet need for maternal health medicines, both globally and within developing countries, will provide insight as to whether national programs are succeeding at targeting under-served people, responding with products proportionate to actual need, or distributing based on other, more arbitrary factors, and catalyzing appropriate solutions. A better understanding of the women who are not being reached by existing programs will also help to develop cost estimates of the funding necessary to achieve universal coverage.

Identify global and national level expenditures for maternal health medicines so any gaps between necessary and actual funding levels can be determined and filled

In addition to a lack of information on the unmet need for maternal health medicines, there is no comprehensive information on sources, levels, and proportion of funding (donor or national government) for maternal health medications. Without this information, there is limited ability to determine and/or address any potential shortfalls in the availability of resources to satisfy need. Reviewers suggest that the development and tracking of national budget lines for maternal health medicines and associated costs, including supply chain management costs such as storage and distribution, will serve to establish an important baseline for potential future funding. Donor tracking mechanisms should also be considered and pursued.

It is equally important to track private sector financing for maternal health medicines. On the whole, there is little to no specific information on private sector contributions, though it is known that medicines are frequently purchased out of pocket by women and their families. Given indications of private-sector involvement in the availability of medicines at the user level, further examination of financing, policies, and activities relating to the private sector are essential and may ultimately inform the development of strategies for utilizing both public- and private-sector networks and health services for offering maternal health medicines to qualified providers and women in need.

Explore bulk purchasing mechanisms so that prices remain low while at the same time creating more attractive markets for manufacturers

Low profit margin of relatively inexpensive maternal health medicines coupled with the decentralized nature of procurement can result in weak markets for these medicines and provide little incentive for manufacturers to invest in GMP certification or WHO prequalification for their production. It also may deter larger manufacturers from producing these drugs. Reviewers suggest exploring strategies to ensure larger purchase volume, including the potential for facilitating bulk purchase agreements through either multi-country or regional procurement mechanisms. Other strategies may include a globally-consolidated or -managed procurement mechanism that could potentially attract donor support and/or higher purchasing requests for doses and packaging specific to maternal health utilization. This approach may increase incentives for existing manufacturers to meet quality assurance standards and may bring new, larger manufacturers into the market.

Regulatory environment

Decrease the prevalence of substandard medicines

Maternal health medicines of unknown origin and quality can often be found on the market. To help ensure that quality formulations are widely available and used, reviewers suggest strategies be developed to increase the proportion of manufacturers of oxytocin, misoprostol and magnesium sulfate that conform to internationally accepted and WHO-endorsed guidelines of current GMP. Additionally, reviewers suggest developing a comprehensive list of manufacturers that have been inspected and certified by the WHO or stringent regulatory authority as current GMP-compliant. This may increase the cost of the medicines, but would allow purchasers to have more confidence that the products are of good quality and in accordance with current GMP standards. In order to assist existing local manufacturers in becoming current GMP compliant, reviewers suggest exploring the feasibility and efficiency of a regulatory mechanism to provide additional support and guidance to enhance their capacity to produce quality maternal health medicines. Reviewers also suggest that a qualitative review is needed of why known medicine storage requirements affecting quality are not adhered to. Specific information about manufacturer storage conditions, including temperature-controlled supply chains before and throughout shipping, or the effect of temperature changes on medicine quality may provide valuable insights and lead to systemic improvements.

Improve national regulatory capacity to ensure that only quality medicines are available and that new medicines can effectively enter the market

As reported previously, the capacity of national regulatory authorities to regulate the quality and use of medicines, including oxytocin, misoprostol, and magnesium sulfate, varies widely across countries. Reviewers identified a need for concerted global assistance to and pressure on countries to ensure quality assurance mechanisms are developed and followed, while simultaneously gathering more information on quality control protocols and practices at the country level. Reviewers suggest a technical review of quality assurance mechanisms and identification of model countries exhibiting leadership in the area of quality assurance, including restricting procurements to current GMP-certified manufacturers, exploring regionalization of regulatory functions, and contractually holding manufacturers to high standards, to help

enhance national regulatory authority capacity. Thinking forward, reviewers also identified the need to develop national regulatory capacity specific to assessing combination medicines and devices and conducting post-marketing surveillance as new maternal health products become available.

Promote the national registration of essential maternal health medicines as identified by the WHO

While oxytocin and magnesium sulfate are registered in the vast majority of countries, many countries have not yet registered misoprostol and/or have not approved it for obstetric indications, including prevention of postpartum hemorrhage. The reviewers suggest collecting data regarding the frequency of off-label misoprostol use. Such information would help global advocates to prioritize and focus resources on registering misoprostol for maternal health indications in select countries where off-label use is occurring, so that labeling and instructions are available for appropriate doses and administration by providers.

Best Practices and Innovation

Innovative technologies

Support new product development and delivery innovations

Given the critical importance of maternal health medicines and the known challenges to preservation and use of oxytocin and misoprostol, reviewers believe strong consideration should be given to exploring methods to improve conditions that support their storage and distribution. This includes support for innovations in product development, with special consideration for formulations which create more thermostable products that are less reliant on refrigeration (oxytocin) and innovations in packaging, such as the use of temperature monitoring devices, to indicate when a product, specifically oxytocin, has been exposed to damaging environmental conditions is another suggested area for exploration. In addition, support for innovations in product delivery is critical. Examples for further study and exploration include feasibility of integration of oxytocin with existing public and private sector cold chains or the use of innovative drug delivery technologies (such as oxytocin in pre-loaded, single-use injection devices) to allow lower cadres of health workers to administer medicines. Innovations also may assist in addressing issues with the manufacturing processes and packaging for misoprostol and magnesium sulfate. Reviewers noted it would be important to learn whether mobile technology can be used to assist with diagnosis, treatment, referral, and supply chain management as well.

Strategies to create demand

Strengthen management information systems to ensure medicine availability and avoid stock outs but not too far in advance to risk expiration

M&E is recognized globally across disease portfolios as an area of weakness. M&E within the context of maternal health medicines is no exception. Without performance reports and feedback at each system level—with particular attention on

the service provider and user levels—policies and programs impacting patient outcomes cannot be improved. Reviewers identified M&E system development and strengthening at the country level, including the training of staff to collect, report, and use data to improve availability, quality and access to maternal health medicines as a critical call for action and investment. At the global level, reviewers noted that it is imperative to accelerate and solidify efforts to identify and implement globally-agreed-upon maternal health indicators to inform maternal health service provision and the incorporation of medicines into countries' logistics and health management information systems.

Monitor policy implementation so gaps may be addressed

Reviewers indicate that more qualitative and quantitative information is needed on the existence and content of standard treatment guidelines for medicines used to manage postpartum hemorrhage and pre-eclampsia and eclampsia in alignment with international standards and guidelines. They suggest a priority focus be on improving tracking of the presence of maternal health medicines and health workers permitted and trained to use them in national and sub-national policy, including standard treatment guidelines, budget lines, national procurement and logistics management systems, and programmatic guidance and pre-service education. Reviewers also note the presence of standard guidelines and other policies do not guarantee availability and appropriate use for the patients who need these medications. They further recommend that tracking of policy implementation at the point of service delivery should be part of regular monitoring and evaluation and audits.

Improve knowledge and skills of health care providers and supply chain managers

A significant gap exists between policy and practice. In places where oxytocin, misoprostol and magnesium sulfate, are in fact integrated into standard treatment guidelines, limited provider knowledge and skills relative to the medicines may limit demand and availability, particularly at the community level. Examples of this are unfamiliarity by providers with dosing and administration of magnesium sulfate, as well as preferences for one uterotonic or another.

Ensuring adequate competency through training, supervision and accountability of providers regarding the administration of maternal health medicines, and supply managers regarding resupply of those medicines is critical to increasing the medicines' utilization by ensuring their continuous availability. Reviewers suggest more information is needed about health provider knowledge, attitudes and practices to identify challenges and develop recommendations for strengthening their capacity. To build competency of supply chain managers, existing curricula, procedures, standards and guidelines for supply chain management should be strategically implemented to address the known gaps in knowledge, attitudes and practices of these equally important health system workers.

Innovations for scale up

Build the evidence base and human resource capacity for administration of maternal health medicines by lower-level workers so that women may receive appropriate care when delivering in their community

Given the high number of births that occur in the developing world in rural environments and with limited access to skilled attendants, reviewers identified the need to conduct studies and generate evidence to inform global and national

policies enabling increased administration of maternal medicines at lower levels of the health system. In particular, more research and evidence is needed on distribution of misoprostol for home use and magnesium sulfate at lower-lever facilities to inform development of international policies, standards and recommendations.

At the same time, reviewers acknowledged that while many countries restrict maternal health medicines administration to a particular health care worker skill level, task shifting may still occur safely and successfully. Therefore, they suggest a dual focus on accumulating evidence to strengthen policy and regulatory frameworks and providing human resources capacity-building opportunities through piloting initiatives. Strengthening systems to support both facility-based care and home use is key to ensuring that essential medicines are available and accessible to those who need them.

Conclusion

Expanding access to quality, affordable maternal health medicines is critical to making progress in reducing maternal mortality. However, significant challenges often impede such access. Chief among them is a lack of data on the needs, gaps, systems and financing for maternal health medicines. Inconsistent quality of medicines and lack of skills among providers on their administration also create considerable barriers to appropriate maternal care.

This report provides a review of the current conditions and available evidence on maternal health medicines as well as potential actions and areas for continued study for the United Nations Commission on Commodities for Women and Children's Health to explore. Attention to the areas noted in Box 4 will improve women's health worldwide.

In addition to these key areas related to maternal health medicines, the need for strong health systems and accountability mechanisms to strengthen governance will be critical to assure that medicines get to those who need them. With concerted effort and strong political will, access to safe and effective maternal health medicines can increasingly protect the lives of women around the world.

Box 4: Issues for action

- Quantify the unmet need for maternal health medicines so manufacturers can adequately scale up to meet that need and cost estimates to achieve universal coverage can be calculated.
- Identify global and national level expenditures for maternal health medicines so any gaps between necessary and actual funding levels can be determined and filled.
- Explore bulk purchasing mechanisms so that prices remain low while at the same time creating more attractive markets for manufacturers.
- Decrease the prevalence of substandard medicines.
- Improve national regulatory capacity to ensure that only quality medicines are available and that new medicines can effectively enter the market.
- Promote the national registration of essential maternal health medicines as identified by WHO.
- Support new product development and delivery innovations.
- Strengthen management information systems to ensure medicine availability and avoid stock outs but not too far in advance to risk expiration.
- Monitor policy implementation so gaps may be addressed.
- Improve knowledge and skills of health care providers and supply chain managers.
- Build the evidence base and human resource capacity for administration of maternal health medicines by lower-level workers so that women may receive appropriate care when delivering in their community.

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