The Role of Misoprostol in the Reduction of Maternal Deaths in Low Resource Settings: A Systematic Review with Recommendations for Action

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The Role of Misoprostol in the Reduction of Maternal Deaths in Low Resource Settings:
A Systematic Review with Recommendations for Action

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Abstract

Objective: The purpose of this systematic review is to determine the role misoprostol currently plays in the reduction of maternal deaths and implications for the future reduction of maternal deaths in low resource settings.

Methods: A comprehensive review of the literature was performed using the following databases: The Cochrane Database, Ebsco, MEDLINE, PubMed, and Electronic Journal Center (EJC). Articles were excluded based upon date published, overt data changes since publication, and setting of misoprostol interventions in tertiary or referral centers that have access to oxytocin. A total of 61 articles were included from 2002-2012 and demonstrated several methodologies and study designs. Review of several program field guides and position statements by key stakeholders were incorporated into this comprehensive literature review.

Discussion: Postpartum hemorrhage accounts for nearly 25% of maternal deaths globally and is most likely to involve the poorest; most underserved, and marginalized women. South Asia and Sub-Saharan Africa comprise the greatest numbers of these women. Widespread use of misoprostol in the treatment and prevention of postpartum hemorrhage remains controversial. The lack of clarity and vigor by the WHO guidelines regarding the use of misoprostol for prevention of PPH at the community level has further impeded efforts aimed at the reduction of maternal deaths due to postpartum hemorrhage. Task shifting strategies will play a crucial role to the successful implementation of community distribution programs that have been proven to save the lives of mothers in low resource areas where maternal deaths are the most profoundly experienced.

Key Words: misoprostol, post-partum hemorrhage, maternal mortality, maternal death, low resource setting, task shifting and skilled birth attendant.
The Role of Misoprostol in the Reduction of Maternal Deaths in Low Resource Settings:

A Systematic Review with Recommendations for Action

Complications during pregnancy and childbirth are the leading cause of death and disability among women in low-income countries. Women’s health is recognized as a fundamental human right in treaties such as the Convention on the Elimination of all Forms of Discrimination against Women [CEDAW], and the International Covenant on Economic, Social and Cultural Rights (Ki-moon, Ban, UN Secretary General, 2010). A maternal death is defined as: “the death of a woman while pregnant or within 42 days of termination of pregnancy, 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 [WHO], 2010). Maternal mortality is widely regarded as a key indicator of population health and of social and economic development, and in many countries in the region of Africa, between 25% and 33% of all deaths of women of reproductive age are the results of a complication of pregnancy or childbirth. Whereas in industrialized countries the risk of maternal death is low, estimated at 1%, the high fertility rates and low contraceptive use in Africa contribute to this high risk (African Regional Reproductive Health Task Force, 2004).

The World Health Organization and other agencies monitor levels and trends closely. This monitoring is a result, in part, by the United Nation's Millennium Development Goals [MDG’s], which call for a three-fourths reduction in the maternal mortality ratio between 1990 and 2015 (Wilmoth et al., 2012).

The Millennium Development Goals are the global objectives for addressing the many facets that define extreme poverty as well as ensuring the basic human rights of each person. The issue of maternal deaths is so pervasive and significant in the global arena that one MDG
specifically addresses this issue. Millennium Development Goal 5 is to improve maternal health. In addition to a three-quarters reduction of maternal deaths, indicators of success include the proportion of births attended by skilled health personnel and the maternal mortality ratio as determined by UNICEF and the WHO (2006). Universal access to reproductive health is the end goal. Such a target implies that the maternal mortality ratio (MMR) should decline at an average rate of at least 5.5% per year over the 25-year interval (Wilmoth et al., 2012).

A maternal death is thought of as one of life’s most tragic ends. The death of a woman who is creating life is profoundly sad, and her death is an immeasurable loss for those living children and other family members who are left behind. Such deaths are almost entirely preventable given proper medical surveillance and timely intervention, and as such maternal mortality is often viewed as a key indicator of the quality of a health care delivery system (Wilmoth et al., 2012). Although maternal mortality rates have fallen in some areas of the world, global attainment of MDG 5 is doubtful (Requejo, Bryce, Deixel, & Victora, 2012). Maternal mortality rates have decreased nearly 47% since 1990, however, nearly 287,000 mothers died in 2010 (Medecins Sans Frontieres, 2012). Of these deaths, approximately 245,000 deaths occurred in Southern Asia and Sub-Saharan Africa (Crowe, Utley, Costello, & Pagel, 2012). These two regions of the world comprise 85% of this global burden.

The areas around the world in which the greatest concentration of maternal deaths occur are often labeled “low resource”. Remote villages in Sub-Saharan Africa and Southern Asia typify this term. Women in these parts of the world often face poverty, discrimination, poor or nonexistent health care infrastructure, lack of access to secure means of communication and lack of reliable and consistent transportation (International Federation of Gynecology and Obstetrics Safe Motherhood and Newborn Health Committee [FIGO SMNHC], 2012). A great percentage
of women in low-resource countries give birth at home or outside a structured health facility without immediate access to emergency obstetric care or a skilled birth attendant, thus making pregnant women more vulnerable to disability and death (Rushwan, 2011). Maternal death rates in these low-resource areas reflect considerable disparities in regards to education, security, income and ultimately access to the most basic of maternal health care services (Lalonde, Daviss, Acosta, & Herschderfer, 2006).

In order to impact the rate of maternal deaths, reduction efforts must be targeted at the most common complications that account for these deaths. These are hemorrhage, sepsis, pre-eclampsia, obstructed labor and unsafe abortion, with the greatest number of deaths as a result of hemorrhage (WHO, 2012a). The focus of my systematic review is postpartum hemorrhage (PPH), as it is the single greatest cause of maternal deaths globally, accounting for nearly one quarter or roughly 71,000 deaths alone in 2010 (Coeytaux & Wells, 2011).

**Purpose Statement**

The purpose of this systematic review is threefold: 1) Determine the role misoprostol currently plays in the reduction of maternal deaths secondary to postpartum hemorrhage, 2) Demonstrate the effectiveness of misoprostol use alone in the efforts to reduce maternal mortality, and 3) Explore implementation opportunities for the future reduction of maternal deaths in low resource settings.

**Methods**

A comprehensive review of the literature was performed using the following databases: The Cochrane Database, Ebsco, MEDLINE, PubMed, and Electronic Journal Center (EJC). Key terms utilized include: maternal mortality, maternal deaths, low resource settings, postpartum hemorrhage, and treatment of postpartum hemorrhage, prevention of postpartum hemorrhage,
misoprostol, cost-effective strategies, and active management of the third stage of labor (AMTSL). Total articles reviewed totaled 141. Articles were excluded based upon date published, overt data changes since publication, and setting of misoprostol interventions in tertiary or referral centers that have access to oxytocin. Articles included were published from 2002-2012 and demonstrated several methodologies with total of 61 references included. Review of several program field guides and position statements by key stakeholders was also incorporated into this comprehensive literature review.

Key analyses include medical efficacy and safety, cost, feasibility, barriers, and implications for public health. Studies were assigned a grade of internal validity utilizing the U.S. Preventive Services Task Force (USPSTF) Criteria for Grading the Internal Validity of Individual Studies (Harris et al., 2001) and conclusions were then determined. It should be noted that evaluation based upon quality of internal validity alone provides only a limited assessment of interventions for the community-based settings in which public health interventions occur. The USPSTF additionally provides a systematic review that assesses external validity, magnitude of effect and certainty to translate the evidence of reviews into suggestions for practice (Brownson, Fielding, & Maylahn, 2009). For the purpose of this systematic review of the literature, this evaluation scheme provided a framework for selection and organization of the data utilized in the compilation that was beneficial to this writer.

**Systematic Review**

**Postpartum Hemorrhage**

Postpartum hemorrhage is defined as the loss of greater than 500ml of blood during the first 24 hours following delivery (WHO, 2007). However, for clinical purposes, any blood loss that has the potential to produce hemodynamic instability should be considered a postpartum
hemorrhage, as clinical estimates of blood loss volumes are often inaccurate (FIGO, SMNHC, 2012). More recent definitions of postpartum hemorrhage make further delineation classified by the period of time following delivery. Primary or immediate PPH occurs immediately following delivery, up to 24 hours. Approximately 70% of cases involving primary PPH are caused by uterine atony (FIGO, SMNH Committee, 2012). Atony of the uterus is defined as insufficient contractility of the uterus following delivery. A less likely type of PPH is known as secondary or late PPH. This type of hemorrhage occurs between 24 hours following delivery up to 6 weeks postpartum. Secondary PPH is most often due to infection, retained products of conception, or both (FIGO, SMNH Committee, 2012). The most likely period at which postpartum hemorrhage occurs is during the third stage of labor. This stage describes the period of time following delivery of the baby, but prior to delivery of the placenta, when the uterus is most likely to experience atony. The third stage of labor is the period of time in which interventions targeted at preventing or treating postpartum hemorrhage becomes crucial. Without immediate medical treatment, a woman that suffers from hemorrhage following childbirth will likely die within two hours (Family Care International, 2006). Intervening successfully to treat postpartum hemorrhage becomes an even greater challenge in the face of such a short window of time. Knowing that postpartum hemorrhage is almost always preventable must not be overlooked.

**Prevention Strategies**

Strategies to reduce maternal mortality in recent years have extended along the continuum of care from low technological, low cost interventions to the high technology, high resource and high cost interventions commonplace in developed areas of the world. Because the environments in which women deliver babies is diverse, the approaches to PPH treatment and prevention will also require diversity (FIGO, SMNHC, 2012). Interventions that might be
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considered high technology range from the reorganization of health systems, the systematic strengthening of midwifery skills, and increasing the number of skilled birth attendants in low resource settings.

Examples of low technology, well-established interventions include immediate breastfeeding of the newborn (within the first hour after birth), which triggers strong uterine contractions and is life saving for the newborn (Edmond et al., 2006; Edmond, Kirkwood, Tawiah, & Agyei, 2008). The WHO-UNICEF Baby-Friendly Hospital Initiative (BFHI) Step 4 states "Help mothers initiate breastfeeding within one hour of birth" (WHO and UNICEF, 2009, Section 4, pg. 11). Further discussion of immediate breastfeeding as a strategy for reducing or preventing postpartum hemorrhage is beyond the scope of this analysis. Additional examples of low technology programs implemented include: the use of pads to accurately measure blood loss following delivery, and the placement of a non-pneumatic anti-shock garment to treat postpartum hemorrhage, have also been noted. Field guides recommend delivery kits with clean cords and plastic pads for use during delivery (Family Care International, 2006). Recent efforts to reduce maternal mortality in low resource countries have prioritized two key strategies: training and deploying skilled birth attendants (SBAs), and improving access to emergency obstetric care. Both strategies have been repeatedly shown to improve maternal and child health outcomes (Prata et al., 2011). Current maternal death rates demonstrate that these strategies alone are insufficient. These strategies do not address the safe-delivery needs of women living in remote communities, who are less likely to have access to either SBAs or emergency obstetric care (Prata et al., 2011).
Safe Motherhood Agendas

While increasing access to a standardized health care structure to include access to skilled birth attendants is an admirable goal, the proportion of births actually attended by a SBA is unlikely to change substantially for several decades (Prata et al., 2012b). The authors report that the omission of TBAs and other lay birth attendants from safe motherhood agendas will result in families that depend solely on SBAs, which remain in short supply. These women will continue to experience increased maternal mortality and morbidity (Prata et al., 2011). Due to weak political commitment and limited infrastructure, large regions exist without effective maternal mortality-reduction efforts in place. Initiatives must include action at the policy level with a widening support base by influential stakeholders in the global effort to reduce the maternal mortality rate. Education initiatives that target an increased utilization of prenatal, antenatal, and postnatal care should continue. Prevention efforts must also continue. The spectrum of agendas currently adopted by the most prominent and resource-rich agencies is broad in depth and breadth and should continue as well. Initiatives that address transportation challenges, accurate measurement of blood loss, promotion of skin-to-skin contact following delivery and community education regarding poor birthing practices and family planning methods hold great merit, and these efforts must also persist.

However, the use of misoprostol as a standalone intervention when appropriate is a promising approach to help facilitate the reduction of maternal deaths. Improvements in health facilities and training of SBAs often benefit women who live in more developed areas but these advancements are not typically implemented to the scale necessary to reach women living in the most underdeveloped and least served areas (Prata et al., 2011). In regions where there is already a measurable shift towards SBAs and emergency obstetric care, it is certainly prudent to
THE REDUCTION OF MATERNAL DEATHS WITH MISOPROSTOL

target investments with the goal of strengthening health facility access and care delivery. This strategy will continue to augment the positive effects already seen in countries such as Afghanistan and Malawi. Both countries have experienced a significant decline in maternal deaths since 1990 (WHO, 2012b). The appropriate implementation of these interventions should be evaluated on a country-by-country basis.

The impact of attempts to strengthen health systems may be inadequate in areas with the highest incidence of maternal death as a result of postpartum hemorrhage. These are the very regions where the greatest potential exists to improve maternal and newborn survival. As the challenges regarding access to quality care persist, the potential impact of community-based strategies show enormous promise. Such community-based interventions will sustain mothers, promote maternal health and reduce preventable deaths. Without appropriate government supported policy level implementation, such interventions will be difficult to achieve and impossible to maintain. Some stakeholders may consider any diversion of maternal health resources from an agenda that emphasizes an increased use of skilled birth attendants as an improper use of resources, in light of inconsistent support of such strategies by organizations such as the WHO (Sutherland, Meyer, Bishai, Geller, & Miller, 2010).

Access Barriers

Postpartum hemorrhage accounts for nearly 25% of maternal deaths globally and is most likely to involve the poorest; most underserved, and marginalized women. South Asia and Sub-Saharan Africa comprises the greatest numbers of these women. In countries most impacted by maternal deaths, the majority of pregnant women deliver at home without a skilled birth attendant present (Prata, Graff, Graves, & Potts, 2009). Traditionally, births in these isolated,
rural communities occur without access to interventions should complications related to the birth arise.

Transportation and communication systems are rudimentary at best, but more often they are absent altogether. The lack of access to structured health facilities that possess necessary medications, health care worker skill set and supplies, in addition to a lack of skilled birth attendants are all factors which contribute to the complex issues surrounding effective treatment for these women (Geller, Adams, Kelly, & Kodkany, 2006). Intervention programs will continue to have the greatest impact in remote, resource-poor areas in which transportation, geography and antenatal care pose significant challenges for pregnant women. These remote areas are where maternal deaths occur with the greatest frequency. As with many health care initiatives, without government level support, the chance of significantly impacting these statistics is remote.

There are surprisingly significant success stories. For example, the World Health Organization describes maternal mortality transport programs that began in 2006 to meet transportation needs related to access to comprehensive emergency obstetric care in Sierra Leone and Burundi (Medecins Sans Frontieres, 2012). These programs have directly impacted maternal death rates in the above areas. Regions in which maternal deaths are high often have unique challenges representative of the political and socioeconomic climate in their respective countries. In Sierra Leone and Burundi, a major barrier to restoring the health care infrastructure is the lack of qualified medical personnel and poor geographic access to maternal services. The Ministry of Health of Burundi, in collaboration with Medecins Sans Frontieres (MSF), a Belgium-based organization, have targeted these two barriers to access: implementing central referral facilities that provide emergency obstetric care together with an emergency ambulance transfer service in
order to bring women from outlying areas to the central facility. Analysis shows that the introduction of emergency obstetric care and a referral system in regions in Burundi and Sierra Leone have rapidly and significantly decreased the number of maternal deaths. These programs serve as a positive example of a model of care delivery that works for governments, donors and other NGO’s that are contemplating investment strategies (Medecins Sans Frontieres, 2012).

**Active Management of the Third Stage of Labor**

The single most effective strategy for preventing postpartum hemorrhage requires active management of the third stage of labor to include the use of drugs effective at stimulating uterine contraction known as uterotonics (Su, 2012). Uterotonics save lives when administered appropriately to treat postpartum hemorrhage. A recent Cochrane Review described the active management of the third stage of labor as a package that includes the administration of prophylactic uterotonics after birth, such as oxytocin, ergometrine and misoprostol; early cord clamping and cutting, and placental delivery by controlled cord traction. While these techniques are described within the presence of skilled birth attendants, key principles of AMTSL are certainly applicable outside these settings (Oladapo et al., 2009). The prevention of atonic postpartum hemorrhage via AMTSL has been promoted globally and is considered an evidence-based intervention (Oadapo et al., 2009). AMSTL reduces the incidence and severity of PPH and the need for blood transfusion or transfer to a referral facility (FIGO, SMNH, 2012). Any program or intervention targeted at reducing death from PPH must include strategies to address AMTSL (Leduc, Senikas, & Lalonde, 2009). Such programs have greatly impacted maternal deaths in countries such as Pakistan and Afghanistan, where policy-based programs have been undertaken with measurable success (Amowitz, Reis, & Iacopino, 2002). Reductions in maternal mortality rates in these countries reflect these successes. Prior to these programs, Pakistan and
Afghanistan possessed the highest maternal mortality rates worldwide (WHO, 2012b). Such deaths are often preventable with a collaborative approach utilizing a variety of low-cost interventions, notably, the distribution of uterotonics prior to delivery.

Programs aimed at routine use of AMTSL and the use of uterotonics refers to oxytocin as the first drug of choice. Oxytocin, ergotamine and misoprostol are the three most widely recognized uterotonics in PPH treatment. It is well documented throughout the literature that the widely accepted “gold standard” regarding uterotonics utilizes oxytocin, which requires skilled administration by injection as well as specific storage conditions. The WHO specifically states any alternative uterotonic should be administered only when oxytocin is unavailable. Oxytocin becomes an impractical solution due to a widespread insufficient cool/cold chain in low resource areas. Oxytocin, along with other injectable uterotonics, requires refrigeration to maintain patency and injection safety, which is an enormous obstacle. Additionally, ergotamine is contraindicated with pregnancy-induced hypertension (Sanghvi, Zulkarnain, & Chanpong, 2009). The lack of access to skilled care further inhibits the widespread use of oxytocin in low resource areas (Burchett & Mayhew, 2009). It has only been recently that there have been notable strides to recognize the role misoprostol can play in maternal mortality reduction efforts (Derman et al., 2006). Many prominent experts in the field of maternal health have defined the administration of misoprostol in a low resource setting as a best practice for the prevention and treatment of postpartum hemorrhage (FIGO, SMNHC, 2012). Misoprostol is a practical, cost-effective alternative to oxytocin. The safety profile of misoprostol is superb, the cost minimal, and due to thermo stability properties, does not require refrigeration. Additionally, misoprostol has proven to be stable under field conditions (United States Agency for International Development, [USAID], 2010). In addition to treatment of postpartum hemorrhage, prophylactic misoprostol is
a “simple, inexpensive and highly effective therapy to prevent and manage PPH” (Diadhiou et al., 2011). The 18th Expert Committee on the Selection and Use of Essential Medicines approved the addition of misoprostol to the WHO approved model list of essential medicines in 2011, further supporting its systematic distribution and continued use in previously described settings (FIGO, SMNHC, 2012).

**Safety and Efficacy**

Misoprostol is an inexpensive, thermostable prostaglandin E1 derivative. It was originally approved for oral use to prevent and treat peptic ulcers associated with the use of nonsteroidal anti-inflammatory drugs. It is a potent uterotonic and cervical priming agent, available in a tablet that can be administered multiple routes (Hofmeyr et al., 2009). The oral and sublingual route results in the fastest onset of action and strongest initial uterotonic effect. Misoprostol is widely used for induction of abortion, cervical ripening, and induction of labor (Feitsma & Kanahi, 2005). The most common side effects associated with the use of misoprostol include fever, chills, shivering, abdominal pain, nausea, vomiting and diarrhea. Rare but serious side effects include uterine rupture and separation of cesarean scar; however, these effects are typically dose dependent (Burns, 2005). Based on evidence to date, the role that misoprostol can play in the reduction of maternal deaths is significant. This role could be elevated to that of life saving with urgent attention by those positioned to affect policymakers and the coordination of international NGO’s. As illustrated in Table 1, the relative benefits of misoprostol use are substantial when compared to those of oxytocin and ergometrine.
Table 1

Comparison of the Three Most Common Uterotonics and Their Relative Benefits

<table>
<thead>
<tr>
<th>Aspect of PPH</th>
<th>Oxytocin</th>
<th>Ergometrine</th>
<th>Misoprostol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>+++</td>
<td>-/?</td>
<td>++</td>
</tr>
<tr>
<td>Requires Skilled Provider</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Preparation Suitable for Home Birth</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serious Side Effects</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Contraindications</td>
<td>0%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Heat Stability</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost</td>
<td>$0.80</td>
<td>$0.30-$0.50</td>
<td>$0.35-$0.50</td>
</tr>
</tbody>
</table>

Source: Sanghvi, Zulkarnain, & Chanpong, 2009

WHO Position Regarding Misoprostol

It becomes quickly evident that misoprostol is appropriate in both preventative and treatment strategies for postpartum hemorrhage. The WHO has taken an ambiguous and conservative stance regarding the use of misoprostol however, and guidelines updated as recently as 2011 state “there is still some uncertainty regarding the most effective dose and route of administration for the prevention and treatment of PPH” despite evidence to the contrary (World Health Assembly [WHA], 2011, p. 89). In 2009 the Expert Committee requested an Expert Review to include the latest safety data and data from on-going community trials (WHA, 2011). Gynuity Health Projects and Venture Strategies for Health submitted an updated application for
the inclusion of misoprostol as an individual medicine on the WHO Essential Medicines List. The Committee chose not to list treatment of PPH in the list of conditions in which misoprostol is indicated (WHA, 2011). Misoprostol is currently included on the Essential Medicines List for use in induction of labor, for termination of pregnancy in combination with mifepristone, “where legally permitted and culturally acceptable, and for the management of incomplete abortion and miscarriage” (WHA, 2011, pg. 87). The WHO states, “to recommend misoprostol for prevention and treatment of PPH could divert attention or reduce attempts to implement oxytocin availability, a superior treatment” (WHA, 2011, pg. 90). The lack of vigorous support of misoprostol as a key therapy to treat PPH remains a significant barrier in the expansion of misoprostol distribution programs. The WHO also states that misoprostol “should be offered by a health worker trained in its use for prevention of PPH” (WHA, 2010, pg. 1). Furthermore the WHO emphasizes that this recommendation has been misinterpreted as a “recommendation for community distribution during pregnancy (i.e. advance provision) for use when the need arises after birth” (WHA, 2011, pg. 1). The WHO goes on to state that recent data “suggest there may be a benefit from use of misoprostol by traditional birth attendants or assistants provided with training on the use of the product at home deliveries” (WHA, 2011, pg. 88). These statements by the WHO lend to the uncertainty in prioritizing the allocation of already scarce resources by policy makers. Community distribution and administration of misoprostol both singularly and in conjunction with other initiatives has already been successfully implemented and supporting data demonstrates this success. There have been dozens of randomized trials with more than 30,000 women assessing the efficacy of misoprostol for prophylaxis (Sutherland et al., 2010). Previous studies have demonstrated repeated success in the reduction of maternal deaths with programs that include distribution of misoprostol at the community level. Until the WHO offers
resounding support of community based implementation programs, the lives of mothers will be lost.

The Promise of Community Based Programs

In the past, interventions have included an emphasis on increasing access to skilled birth attendants (SBAs). However, in those countries that demonstrate a high maternal mortality ratio, the ratio of skilled birth attendants to women remains low and progress to increase access is slow (Prata et al., 2012). Previous strategies have included the recruitment and retention of SBAs outside the areas that have the highest rate of maternal deaths in order to attempt to address the shortage. Once they are trained, SBAs are often hesitant to work in these areas, and even if they are agreeable to working there, positioning them in these remote areas may not be cost-effective for many programs. Costs related to empowering these communities can be far less than programs designed to place and retain SBAs, and will require no financial incentives in order to retain skilled as well as community birth attendants to remain in their own communities (Prata et al., 2011). The goal of large-scale implementation of such interventions becomes more plausible when such factors are considered and applied to newer strategies. It has only been in recent years that community-based distribution of misoprostol has been evaluated alone for its effectiveness in the treatment of postpartum hemorrhage. Additionally, including community-based birth attendants or traditional birth attendants (TBAs) in the safe motherhood agendas currently underway will assist in ensuring access to life-saving technologies and practices to women in remote areas. Training of TBAs on distribution of misoprostol in conjunction with other interventions such as blood loss measurement tools has great potential to reduce maternal mortality and morbidity in those areas that are most underserved. This task shifting strategy will continue to encounter barriers to its implementation without support by the WHO.
Task Shifting Strategies

Any community-based success will only come with necessary supporting policy considerations at the government level as well as collaboration with those agencies most influential globally, such as the WHO. Because access to SBAs is in the remote future at best for many of these areas of the world, a formal process of intentional and structured task shifting could be explored by agencies positioned to impact maternal deaths the greatest. “According to the WHO, task shifting is the process of delegation whereby tasks are moved, where appropriate, to health workers with shorter training and fewer qualifications” (WHO, 2008, pg. 13). Task shifting can occur within a clinical setting or can be comprised of the shifting of responsibilities from facility-based to community-based providers (Prata et al., 2012a). A recent Cochrane Review called for increased research on low cost, low technological home based management of postpartum hemorrhage (Sibley et al., 2007). Such simple, low-cost methods serve as an interim approach to improving maternal health while longer-term and sustainable strategies are slowly being implemented. Many conventional programs focused exclusively on increasing access to skilled birth attendants with the use of TBAs in the role of advocates for skilled care only. TBAs were utilized in a role that primarily urged women to obtain antenatal, obstetric and postnatal care, with little effort in expanding the knowledge base and skill set of TBAs. Similar interventions have been included in many global initiatives directed at the reduction of the maternal mortality ratio worldwide. These examples highlight the need for a comprehensive approach, rather than the singular focus on agenda items as seen previously.

Task shifting strategies could be considered in order to successfully carry out such wide scale interventions. The development of programs that facilitate the community-based distribution of misoprostol represents just such an opportunity to apply task shifting strategies.
The incidence of maternal deaths can be significantly reduced through the integration of and expansion of the scope of practice of TBAs through task-shifting efforts.

Other healthcare interventions related to HIV and malaria has already revealed substantial gains by incorporating task shifting to improve access to services and mitigate the shortage of health professionals. There are several examples in which task shifting strategies have resulted in success. There have been recent successes that suggest such global collaboration is becoming more prominent. Models used to combat malaria and HIV/AIDS, may provide a successful template for further success, and have demonstrated substantial improvements in patient outcomes, but strategies such as this would benefit from continued research (Brentlinger et al., 2010). Only recently has the attention surrounding such underutilized technologies been redirected from the debates surrounding the knowledge and abilities of trained TBAs and the potential of empowering women to help themselves (Prata et al., 2011).

Task shifting as a strategy has demonstrated a long history of success in Uganda. The Ministry of Health adopted task shifting as a formal strategy as early as 1918. The socioeconomic landscape of Uganda has many similarities related to health care challenges faced by its neighbors, including maternal health. Uganda has a current maternal mortality ratio of 310 per 100,000 live births (WHO, 2012b), which is significantly lower than surrounding countries. For example, Burundi, which is just 300 miles from Uganda, possesses a maternal mortality ratio of 800 per 100,000 live births (WHO, 2012b). Strides in maternal death reduction efforts in Uganda can be attributed to the government’s role in early task shifting efforts. The Ugandan Health Service introduced the use of a core group of medical professionals known as “licentiates,
later medical assistants, and currently known as clinical officers” (Dambisya & Matinhure, 2012).

The arena of pharmaceutical services has also been augmented with the use of such medical support staff in Uganda. Additionally, a second level of task shifting involves the use of patient relatives and/or family members. These individuals are known as “attendants” and often assist with activities of daily living such as feeding and bathing, as well as lab collection and medication retrieval for in-patients (Dambisya & Matinhure, 2012). Task shifting has been demonstrated at the village level in Uganda with the implementation of the National Malaria Control Programme, which introduced the role of the “Community Medicine Distributor” working to manage fevers at the home level. The Community Medicine Distributors are village based volunteers trained to identify and treat simple fevers in children, as well as identify more serious complications associated with malaria such as vomiting and diarrhea, poor feeding and seizure activity (Dambisya & Matinhure, 2012). These volunteers are also responsible for medication administration protocols that have been simplified with pre-packaged, color coded dosing guidelines delineating age-specific treatment. The success achieved at the village level with the home-based management of fever (HBMF) regimen resulted in a modified version of the program implemented in 2009 at the national level (Dambisya & Matinhure, 2012).

A recent study conducted in 2011 in Bangladesh challenged previously held theories regarding the benefits related to the training of TBAs in the use of misoprostol (Prata et al., 2012b). Previous program failures were transformed with the advent of community-level implementation of misoprostol to include education initiatives of TBAs. An evaluation study was conducted in rural Bangladesh from July 2009-January 2011. This study utilized a two-day training period regarding misoprostol use and delivery mats. Training was provided by four
physicians and included information on misoprostol function, dosage, and timing of administration, side effects and their management. The training also provided information on early identification of high-risk pregnancies, danger signs of maternal infection and PPH with particular attention given to PPH.

Prior to the training, very few TBAs identified misoprostol as means to prevent PPH and 88.5% stated that they did not have any knowledge regarding the prevention of excessive bleeding (Prata et al., 2012b). Post training of the TBAs found the training to be highly effective and the vast majority of TBAs attending home births safely and correctly utilized the two interventions. Follow-up data eighteen months after the training showed adherence to protocols and knowledge retention remained high (Prata et al., 2012b). A similar task-shifting model as seen with malaria programs can easily be translated for use with a misoprostol distribution program and efforts to do so should be explored (Cruz & McPake, 2011). Incorporating the use of relatives and local village volunteers additionally ensures that traditional practices and beliefs are incorporated into any community-wide intervention. This integration ensures that local customs surrounding birthing practices and the long-accepted knowledge held by TBAs is incorporated into any education programs and initiatives undertaken as recommended (Byrne & Morgan, 2011). Such examples of success provide a roadmap (Harper, 2010) for similar task shifting efforts related to misoprostol distribution and administration programs. Task shifting is not without challenges however. Identified barriers related to the implementation of task shifting programs include the disparity between the knowledge base held by policy makers and front-line health workers in regards to the meaning and purpose of task shifting initiatives. These barriers included front-line workers resistance to change (Teela et al., 2009), protection of role delineation by professionals, professional boundaries and regulations, high disease burden, heavy
workload, poor planning strategies and lack of clear cut guidelines regarding task shifting at the
formal and policy level. Many of these barriers have been overcome with the well-documented
examples of other successful task shifting programs at the village or community level (Dambisya
& Matinhure, 2012). Because it is unlikely that the majority of women will have access to care
from skilled birth attendants in the near future, governments, international agencies and local
efforts need to bring interventions such as the community-based distribution of misoprostol to
these women. Future strategies should include TBAs as well as other community members who
attend births, and delivering mothers themselves. If both community and home-based
management strategies for postpartum hemorrhage are to be implemented to the scale necessary
to impact current maternal mortality rates, the approach surrounding effective interventions must
be broadened.

Cost Effectiveness

Health planners in low-resource settings face overwhelming funding constraints (Geller
et al., 2008) and public health interventions, even lifesaving strategies, are often considered on
the cost per life saved. The cost-effectiveness of maternal health interventions is no exception
and is a necessity for policy-makers. An analysis conducted in 2010 evaluated the cost-
effectiveness of misoprostol for treatment versus prevention of PPH at the community or home
level. A simulation model was applied to portray mortality and morbidity caused by PPH among
3 settings of 10,000 women delivering at home in rural India. This setting is comprised of a
large state in India with a high MMR and high home birth rate. At the time of this simulation
study, it was estimated that 71% of births in rural India occur at home (Sutherland et al., 2010).

The simulation model included cost of drugs, birth attendant training and transport for
women to obtain further emergency care if they did not respond to misoprostol. The 3 scenarios
described were: 1) standard management as defined by delivery attendance by a TBA without medication availability, 2) standard management plus 800 micrograms of sublingual misoprostol for PPH treatment, and 3) standard management plus 600 micrograms of prophylactic oral misoprostol. Results demonstrated a 70% lower mortality in the second setting and 81% lower mortality in the third setting (Sutherland et al., 2010). The study results were used to calculate the cost-effectiveness of each intervention compared to no intervention. Results showed the misoprostol treatment package saved 9.4 lives per 10,000 women when compared to standard management. The prophylactic treatment package saves an additional 1.4 lives for a total of 10.8 lives saved per 10,000 women. The disease burden from maternal hemorrhage is calculated as 325 DALY’s per 10,000 women with standard management with a reduction noted as low as 76 DALY’s with misoprostol use. The cost difference between standard management and treatment would be $1,212 per 10,000 women, while expansion to prevention would add another $5,721 per 10,000 women (Sutherland et al., 2010). Few public health interventions can prevent DALY’s as inexpensively.

If incorporated with existing programs, the training of traditional birth attendants and mothers regarding the administration of misoprostol need not be costly (Bradley, Prata, Young-Lin, & Bishai, 2007). A cost-effectiveness study completed in 2007, determined the cost to train traditional birth attendants in the use of misoprostol for the treatment of postpartum hemorrhage per trainee, including teacher and materials. The training and subsequent cost analysis occurred in Afghanistan in 1999 and in India in 2005. Cost ranged from US $3 to $17 per trainee (Prata et al., 2011). This study further substantiates the benefits of misoprostol use when the considerations center on training and program implementation cost containment. When evaluating cost containment strategies related to treatment, again there are very few obstacles
identified. The cost of a complete course of therapy utilizing misoprostol is approximately US $0.30 per woman (Rajbhandari et al., 2010).

A recent cost-effectiveness modeling study of community-based distribution of misoprostol for home deliveries in a south Asian setting found it to be a cost-effective intervention, with a cost per death averted of $1,401 (Hussein, Newlands, D’Ambruoso, Thaver, Talukder & Besana, 2010). Further support of such initiatives was demonstrated when, in 2006, The International Federation of Gynaecology and Obstetrics and the International Conference of Midwives jointly recommended the use of misoprostol for home births without a skilled attendant (Hussein et al., 2010). A recent empirical study conducted in five communities near Zaria in the northwestern region of Nigeria (Prata et al., 2012a) demonstrated the feasibility and safety of the distribution of misoprostol on a large scale, in part, due to the well-executed community mobilization in order to implement a pre-determined health intervention.

An operations research study conducted in Nepal from January 2006 through June 2008 (Rajbhandari et al., 2010) implemented a misoprostol distribution program at a district level within the government health system. The goal was to determine if high coverage, specifically among those at greatest risk, was feasible. The components of disadvantage assessed included literacy, income and geographic isolation. Program monitoring data concluded that program feasibility was established with relative ease. Ending survey data showed that 18,761 women, over 74 percent of women previously identified as high risk that underwent vaginal births, received misoprostol. Overall uterotonic coverage increased from 11.6% at the beginning of the study to 74.2% at its conclusion.

A recent study conducted in Senegal further illustrates the ease of implementing a program to include misoprostol distribution at the community level. This particular study
provides further evidence that the presence and supervision of skill birth attendants is unnecessary to successfully reduce maternal deaths with misoprostol administration for postpartum hemorrhage. Senegal has a maternal mortality rate of 401 in 100,000 live births and only 33% of deliveries in the country are assisted by skilled attendants that would be considered qualified to prevent or treat obstetric complications (Diadhiou et al., 2011). Data as recently as 2011 states that 38% of women in Senegal deliver in their own homes or in the home of a friend or other family member (Diadhiou et al., 2011). This study was conducted in two sociodemographically distinct poor regions of Senegal, where births seldom occur within the walls of health facilities or in the presence of skilled birth attendants. The aim of the study was to demonstrate the effectiveness of a simple, low cost training program that would promote the safe and accurate administration of misoprostol by trained traditional birth attendants for prevention of postpartum hemorrhage. Correct administration was clearly defined regarding oral dosing and timing during delivery. Results were so overwhelming that the second planned study was cancelled on the basis of the results of the first study. All study participants, whose deliveries were assisted by the traditional birth attendants that were trained for the purposes of the study, received correct and safe administration of misoprostol for postpartum hemorrhage prevention. Training consisted of just one day supplemented by practicum as defined by attendance at ten deliveries at health centers and three deliveries at maternity huts (Diadhiou et al., 2011). Additionally, the training incorporated education regarding the benefit or harm of controlled cord traction and uterine massage, as evidence related to these practices is sparse. Study participants were instructed to avoid both uterine massage and controlled cord traction during deliveries, with mixed compliance noted.
This illustrates the additional opportunities for the incorporation of adjunct interventions targeted at education related to poor birthing practices. It is also feasible to incorporate protocols to include immediate arrangement of transportation and referral to available health centers for women requiring treatment for postpartum hemorrhage to include the use of misoprostol. The support of simple training programs and unencumbered access to adequate supplies of misoprostol will make great strides to advance postpartum hemorrhage prevention and treatment in the community setting.

**Distribution Barriers**

There are several unique challenges related to misoprostol access for women that are underserved and high risk (Burns, 2005) as illustrated in Table 2. Misoprostol has a complicated history and has been informally utilized for use in a diverse and broad sense, most notably associated with abortion. As a result, despite the increasing body of evidence in support of the use of misoprostol, this proof has yet to result in consistent and effective policies, programs and clinical practice around the globe (Burns, 2005). Its widespread policy implementation and use may provoke resistance among policy makers and providers and unwanted opposition and exposure from anti-abortion activists. For example, the Ministry of Health in Brazil increased regulations in order to restrict the use of misoprostol as an abortifacient. Several states enacted additional restrictions, with the state of Ceara issuing a complete ban on its use. In countries where misoprostol is approved only for the prevention of gastric ulcers, use for obstetric or gynecological purposes is considered “off label” (Burns, 2005).
Table 2

*Perceived Barriers to Misoprostol Distribution at the Community Level Ranked in Order of Importance and Suggested Strategies*

<table>
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<th>BARRIER</th>
<th>SUGGESTED STRATEGIES</th>
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| 1. Lack of global consensus regarding evidence-based protocols and guidelines | 1. Expand WHO guidelines related to misoprostol for PPH to include its use for treatment, not just prevention as well as more definitive statement regarding use at the community level.  
2. Use of evidence-based advocacy; urge countries to think independently of WHO to make individual evidence-based decisions.  
3. Encourage NGO coordination and cooperation; synchronize agendas and avoid duplication of efforts. |
| 2. Association with abortion                                           | 1. Focus messaging on value of misoprostol, lives saved.  
2. Add misoprostol to safe delivery kits.  
3. Control distribution of misoprostol to prevent “misuse”  
4. Consider legal challenge in countries with high MMR that restrict access to misoprostol.  
5. Go “under the radar”. Introduce misoprostol for noncontroversial uses, with unspoken understanding that it may be used for abortion. |
| 3. Concerns about safety and side effects                             | 1. Conduct additional, targeted research to include dosing, route of administration, and cost and benefit analysis. |
2. Ensure availability through private sector. |
| 5. Controversy over who can administer misoprostol at the community level | 1. Conduct research to address concerns regarding safety and effectiveness of community level administration.  
2. Increased emphasis on prevalence of home births.  
3. Engage professional organizations as advocates. |
| 6. Fear of women’s empowerment                                        | 1. Target women as providers of their own care.  
2. Utilize women’s organizations’ networks regarding availability and uses. |

Source: Coeytaux, & Wells, 2010

**Global Availability**

Challenges related to pharmaceutical strategies to reduce maternal deaths are not only related to access and the lack of development of new drugs in obstetrics. Millennium Development Goal Eight encourages “global partnerships in cooperation with pharmaceutical companies provide access to affordable essential drugs in developing countries” (Fisk & Atun, 2008, p. 22). Although there have been record amounts invested by wealthier developed
countries in pharmaceutical research and development, as well as global initiatives to impact disease burden in less developed countries, there is still a marked lack of new drugs for diseases of pregnancy. Only one new class of drugs has been licensed in the past two decades, and no new class of drug is in clinical trials for primary obstetric uses (Fisk & Atun, 2008). Although the effects of this shortage are noted in countries with readily available resources, the impact is much greater in resource-poor settings where the brunt of the disease and death burden is felt. Pregnancy is a temporary condition, thereby creating a relatively small market size. Unfortunately, without collaboration by pharmaceutical companies in research and development efforts, there is less likelihood of gaining the attention of international donor agencies. The distribution of misoprostol should not be hampered, as the above challenges have been addressed successfully.

![Global Misoprostol Registration by Indication](image)

**Figure 1**

Global Misoprostol Registration by Indication. (Venture Strategies for Health and Development, 2004)
Discussion and Recommendations

Despite data demonstrating its effectiveness and cost-savings benefit, the widespread use of misoprostol especially in very low-resource locations remains controversial. The lack of clear, evidence-based policies and guidelines has hindered policy makers in making sound decisions regarding the introduction of misoprostol at the national level. The continued lack of clarity and vigor by the WHO guidelines regarding the use of misoprostol for prevention and treatment of PPH at the community level has further impeded efforts aimed at the reduction of maternal deaths due to postpartum hemorrhage. This lack of clarity and guidelines has been cited as the single greatest barrier in community-based implementation programs (Coeytaux & Wells, 2011). There is little research that has reported on the use of misoprostol used solely in the treatment or prevention of postpartum hemorrhage. The few studies that have implemented misoprostol as a stand-alone strategy have all demonstrated its effectiveness in the treatment and prevention of PPH as well as its safety and usability in low resource areas. This evidence has been shared along all appropriate academic, professional and clinical channels; yet progress in implementation remains slow. The many studies that incorporated the use of misoprostol with other pharmacologic and non-pharmacologic interventions further substantiate the promise of expanding the role of misoprostol in PPH treatment and prevention. Current strategies are fragmented and politicized, although access to misoprostol in recent years has shown a dramatic increase. Task shifting strategies will play a crucial role to the successful implementation of community distribution programs and must be fully embraced by the international agencies best positioned to impact program implementation. Such programs have been proven to save the lives of mothers in low resource areas where maternal deaths are the most profoundly experienced.
This systematic review has clearly identified the next steps if the global community is to achieve a significant reduction in maternal deaths.

- The revision of the WHO position regarding indications for use of misoprostol to include PPH prevention and treatment.

- The revision of the WHO position regarding community based distribution of misoprostol for PPH prevention with resounding advocacy for structured implementation of programs aimed at the training of TBAs in appropriate and timely misoprostol use.

- Collaboration between the WHO, NGOs, the pharmaceutical industry and the governments of previously identified low resource countries and regions to develop and standardize the approach to addressing maternal deaths. This approach should include community based distribution programs utilizing task shifting strategies discussed in this systematic review.

- Continue the expansion of long term and sustainable strategies to reduce maternal deaths while simultaneously promoting policy advocacy related to community based misoprostol programs.

The knowledge that maternal deaths can be averted with well-established evidence-based public health interventions is disturbing. Yet, these deaths continue. Quantifying losses when a mother dies goes beyond money or DALY’s prevented. The fundamental human right of a woman’s health has been overlooked in favor of other high profile, palatable and often costly initiatives in the past. The World Health Organization is urged to provide critical guidance to governments where maternal deaths continue unchecked. With global alliances firmly in place and transparent policy development and implementation underway, maternal mortality initiatives
must now be scaled up to make a population level impact (Dieleman, Shaw, & Zwanikken, 2011). Such an impact is long overdue. Although attainment of MDG 5 by the stated target dates is doubtful, global efforts must be increased to save the lives of mothers.

**Limitations**

This analysis is a unique exploration of the use of misoprostol to reduce deaths from postpartum hemorrhage in low resource settings because it addresses both treatment and prevention strategies. The progression and expansion of this analysis expanded far beyond the original scope of the investigation. A comprehensive analysis of the pharmaceutical industry, specifically the sluggish development of obstetric drugs and the effects of the current business model employed by pharmaceutical companies would be beneficial; such analysis was beyond the scope of this systematic review. Further examination of the political implications related to the implementation of maternal mortality intervention programs, specifically including conflict areas might have yielded more insights into public health outcomes. Religious and cultural factors probably have significant implications in the development of any community based programs as well as deeply entrenched gender-based disparities, all which are often unique to global regions and political climate (Buse, Mays, & Walt, 2005) and also were not explored in depth as part of this investigation. Further exploration of these crucial determinants is recommended.
References


Current methods of the U.S. preventive services task force: A review of the process.

*American Journal of Preventive Medicine, 20*(suppl. 3), 21-35.


Appendix A: Tier 1 Core Public Health Competencies Met

<table>
<thead>
<tr>
<th>Domain #1: Analytic/Assessment</th>
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<tr>
<td>Identify the health status of populations and their related determinants of health and illness (e.g., factors contributing to health promotion and disease prevention, the quality, availability and use of health services)</td>
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<td>Describe the characteristics of a population-based health problem (e.g., equity, social determinants, environment)</td>
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<tr>
<td>Identify sources of public health data and information</td>
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<tr>
<td>Recognize the integrity and comparability of data</td>
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<td>Identify gaps in data sources</td>
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<tr>
<td>Use information technology to collect, store, and retrieve data</td>
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<td>Describe how data are used to address scientific, political, ethical, and social public health issues</td>
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<th>Domain #2: Policy Development and Program Planning</th>
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<tr>
<td>Gather information relevant to specific public health policy issues</td>
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<td>Describe how policy options can influence public health programs</td>
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<tr>
<td>Explain the expected outcomes of policy options (e.g., health, fiscal, administrative, legal, ethical, social, political)</td>
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<tr>
<td>Gather information that will inform policy decisions (e.g., health, fiscal, administrative, legal, ethical, social, political)</td>
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<tr>
<td>Identify mechanisms to monitor and evaluate programs for their effectiveness and quality</td>
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<th>Domain #3: Communication</th>
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<tr>
<td>Communicate in writing and orally, in person, and through electronic means, with linguistic and cultural proficiency</td>
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<tr>
<td>Participate in the development of demographic, statistical, programmatic and scientific presentations</td>
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<th>Domain #4: Cultural Competency</th>
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<tr>
<td>Recognize the role of cultural, social, and behavioral factors in the accessibility, availability, acceptability and delivery of public health services</td>
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<th>Domain #5: Community Dimensions of Practice</th>
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<tr>
<td>Describe the role of governmental and non-governmental organizations in the delivery of community health services</td>
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<th>Domain #6: Public Health Sciences</th>
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<tr>
<td>Identify the basic public health sciences (including, but not limited to biostatistics, epidemiology, environmental health sciences, health services administration, and social and behavioral health sciences)</td>
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<tr>
<td>Describe the scientific evidence related to a public health issue, concern, or, intervention</td>
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<tr>
<td>Retrieve scientific evidence from a variety of text and electronic sources</td>
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<tr>
<td>Discuss the limitations of research findings (e.g., limitations of data sources, importance of observations and interrelationships)</td>
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<th>Domain #7: Financial Planning and Management</th>
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<tr>
<td>Describe how cost-effectiveness, cost-benefit, and cost-utility analyses affect programmatic prioritization and decision making</td>
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<th>Domain #8: Leadership and Systems Thinking</th>
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<tr>
<td>Identify internal and external problems that may affect the delivery of Essential Public Health Services</td>
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<tr>
<td>Describe the impact of changes in the public health system, and larger social, political, economic environment on organizational practices</td>
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