



Civil Society Organizations and medicines policy change: A case study of registration, procurement, distribution and use of misoprostol in Uganda



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ABSTRACT

Misoprostol use for postpartum haemorrhage (PPH) has been promoted by Civil Society Organizations (CSOs) since the early 2000s. Yet, CSOs' role in improving access to misoprostol and shaping health policy at global and national levels is not well understood. We document the introduction of misoprostol in Uganda in 2008 from its registration, addition to treatment guidelines and national Essential Medicines List (EML), to its distribution and use. We then analyse the contribution of CSOs to this health policy change and service provision. Policy documents, procurement data and 82 key informant interviews with government officials, healthcare providers, and CSOs in four Ugandan districts of Kampala, Mbarara, Apac, Bundibugyo were collected between 2010 and 2013.

Five key CSOs promoted and accelerated the rollout of misoprostol in Uganda. They supported the registration of misoprostol with the National Drug Authority, the development of clinical guidelines, and the piloting and training of health care providers. CSOs and National Medical Stores were procuring and distributing misoprostol country-wide to health centres two years before it was added to the clinical guidelines and EML of Uganda and in the absence of good evidence. The evidence suggests an increasing trend of misoprostol procurement and availability over the medicine of choice, oxytocin. This shift in national priorities has serious ramifications for maternal health care that need urgent evaluation. The absence of clinical guidelines in health centres and the lack of training preclude rational use of misoprostol. CSOs shifted their focus from the public to the private sector, where some of them continue to promote its use for off-label indications including induction of labour and abortion. There is an urgent need to build capacity to improve the robustness of the national and local institutions in assessing the safety and effectiveness of all medicines and their indications in Uganda.

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1. Introduction

Since the launch of the essential medicine policy by the WHO in the 1970s, many Civil Society Organizations (CSOs) have worked towards assuring access to medicines. Civil society is typically defined as the arena between the state, households and market. WHO defines CSOs as 'non-state, not-for-profit, voluntary organizations formed by people within the social sphere of civil society' (WHO, 2002). These organizations work in diverse areas, such as education, health and social care, environment, human rights, and their activities include service provision, community outreach,

advocacy and resource mobilization. The existing literature on CSOs is generally positive about the role of such organisations in contributing towards health outcomes in developing countries (Lister, 2003; Lowenson, 2003). In Uganda, CSOs have played a crucial role in campaigning for the equitable access and availability of medicines (Lister, 2003; Selvaggio, 2011; Lowenson, 2003) through supporting and influencing the registration and distribution of drugs, and reviewing, formulating and implementing public health policy. On a global level, CSOs have been involved in the renegotiation of TRIPS terms and in securing lower medicine prices (Koivusalo and Mackintosh, 2011).

This study set out to elucidate the role of CSOs in the introduction of the drug misoprostol for prevention of postpartum haemorrhage (PPH) with the aim of reducing the maternal mortality ratio in Uganda. Introduction of a new medicine to public

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health programmes is conditional on three approvals: registration with the national drug regulatory authority, development of treatment guidelines to ensure the rational use of the medicine, and addition to the national essential medicine list (EMHSLU, 2012; UCG, 2010). On a global level, misoprostol has been recommended in the WHO guidelines as a second line treatment for the prevention of PPH since 2007 and its addition to the WHO EML in 2011 was widely supported by CSOs. A study carried out in 2013 identified a network of 238 organizations and individuals who were actively promoting the use of misoprostol for PPH at the time of the 2011 WHO EML application (Millard et al., 2013). This network was global in scope and involved a diverse range of activists, including civil society (NGOs, professional associations, and individuals), government agencies, intergovernmental agencies, funding bodies, research bodies, academic institutions and pharmaceutical companies for which CSOs operating in Uganda are part. This paper contributes to a growing body of literature which takes a more critical view of the public health role of CSOs and the evidence base underpinning the policy change they promote. In affecting health policy, CSOs articulate power which is distributed across multiple locations. It has been argued that within global health arena, NGOs and private foundations with their superior funding are supplanting the role of national governments and eroding democratic accountability for national decision making (Dodgson et al., 2002; McCoy, 2009). Reviews of the involvement of CSOs in health research, and policy and service provision, highlight the absence of frameworks and tools for the systematic evaluation of the impact that these organizations have on health improvement in recipient countries (Kuruvilla, 2005; Thue et al., 2002; Lowenson 2003). There is often lack of transparency in their funding and operations, and accountability remains an issue that needs to be addressed.

We examine a country-specific effort of these CSOs to introduce misoprostol locally and analyse their role in shaping national health policy and influencing national public health priorities. We document the process of the introduction of misoprostol in Uganda, where it was proposed as a solution to the lack of access to oxytocin, the first line treatment for the prevention of PPH. We analyse the role of CSOs, focussing on their involvement in the various stages of approval (registration, treatment guidelines, EML), procurement, distribution and the promotion of misoprostol's use. We assess the extent to which CSOs supported compliance with the national evidence-base requirements for the introduction of a new medicine and the achievement of maternal health policy goals.

2. Maternal health in Uganda

2.1. The prevention of PPH and the role of misoprostol

PPH is said to be the most common cause of maternal mortality worldwide (WHO, 2009). Most deaths due to PPH occur in developing countries where the high prevalence of anaemia, poor nutrition, and infections such as malaria, combine with a high proportion of home deliveries without skilled birth attendants and inadequate availability of health services (World Health Organisation, 2012a). Oxytocin is recommended as the first line treatment, together with active management of third stage labour (AMTSL) to prevent PPH (World Health Organisation, 2012b). In situations where the use of oxytocin is not feasible, WHO guidelines recommend the use of misoprostol; this is based on its uterotonic properties, its heat stability, and its range of routes of administration. Unlike oxytocin which requires injection and a cold chain, misoprostol comes in tablet form; it also has a long shelf life and does not require cold chain storage (Tang et al., 2007). However, the evidence base for prevention of PPH in the community has been contested (Chu et al., 2012).

Misoprostol was first registered by the U.S. Food and Drug Administration (FDA) in 1988 for the treatment of gastric ulcers. From the early 1990s misoprostol, a potent uterotonic agent, has been increasingly used for off-label maternal health indications. A large increase is visible in the number of organizations and individuals promoting its use in this area, especially since its patent expiry in 2000. CSOs working in maternal and reproductive health have been involved in research, advocacy, service provision and policies concerned with the use of misoprostol for PPH and other obstetric indications in developing countries.

2.2. Maternal mortality and access to health care services in Uganda

Uganda's maternal mortality ratio remains one of the highest in the world at over 360 for every 100,000, with an estimated 25% of these due to PPH (World Health Organisation, 2013). Uganda's public health system is organized in seven tiers with national and regional referral hospitals, general district hospitals and four levels of health centers (HCs) at community (HC1), parish (HC2), sub-county (HC3) and county level (HC4). Staffing and available services vary across the four levels: HC3 and HC4 should offer Emergency Obstetrics Care (EMOC), whereas HC1 and HC2 serve as low resource referral units which are not able to provide EMOC and have no ambulances and blood transfusion services (Mbonye et al., 2007; WHO/MOH, 2010). CSOs and private providers operate in parallel to the public system and in the case of maternal health, the services of CSOs often cut across several activities at various levels of health care provision.

Overcrowding, understaffing and lack of resources affect all facilities. Basic supplies and equipment for conducting normal deliveries are available in only 33% of facilities offering delivery services with up to 97.2% of health facilities expected to offer EMOC unable to do so (Mbonye et al., 2007). 95% of expectant mothers attend at least one antenatal care visit and 46–54% of the overall deliveries occur in presence of a skilled health worker (WHO/MOH, 2010). This is often a result of user fees, the need to buy medicines and other hospital supplies due to stock outs or irregular supplies, long distances, lack of skilled health providers at HCs and the poor attitude of health workers towards patients which affects their health seeking behaviour. This means that many delivering mothers are unable to access first line treatment for the prevention of PPH as oxytocin can only be administered as an injectable and by trained staff. Misoprostol has been successfully presented as an obvious solution to this problem.

2.3. Medicines selection in Uganda

Medicines procurement is guided by the Essential Medicines and Health Supplies List for Uganda (EMHSLU). EMHSLU is based on WHO's 1999 definition of essential medicines as "those medicines that satisfy the health care needs of the majority of the population at a price patients and community can afford" (EMHSLU, 2012 p.15). Medicines on the list are supposed to be available at all times, in adequate amounts and in appropriate dosage forms. In compiling the list, consideration is given to ease of storage and supply; tablets are also prioritised due to assumed low cost and ease of storage and administration.

The Ministry of Health (MoH) is responsible for the development of clinical guidelines to be used in public and private health facilities. However, private or public prescribers "will still be required to adjust the recommended treatment regimes to meet the particular needs of specific individuals based on clinical judgment and experience" (UCG, 2010 p.V11). These clinical guidelines are of vital importance as they have to be in place before medicines can be listed on the EMHSLU.

Table 1
Chronology of introducing misoprostol in Uganda and the involvement of CSOs.

Year	Misoprostol in Uganda <i>WHO recommendations on misoprostol use for PPH</i>	CSO's involvement
2002	Misoprostol imported by Pfizer's local representatives on special permission from NDA for research purposes under Population Council Unsuccessful attempt to register misoprostol with Uganda's NDA Illegal use of over-priced misoprostol reported (treatment of acute duodenal and gastric ulcers) <i>WHO rejected an application to add misoprostol to its EML. The application by Makerere University stated, "its availability would be potential to dramatically reduce maternal mortality; convinced that national authorities in Africa will find it easier to approve this drug once it is included in WHO's EML"</i>	Population Council n/a Makerere University OB/GYN department
2004	Misoprostol use in Uganda by various health professionals and for various indications reported (Wassberg, 2004)	
2007	<i>WHO guidelines: "In the absence of active management of the third stage of labor, a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH."</i>	
2008	First registration of misoprostol (<i>Misotac</i>) for PPH prevention with NDA	Application by PSI Uganda, supported by VSI
2009	Pilot project introducing misoprostol for PPH management in ten districts designed by MoH and VSI Treatment Guidelines for Prevention and Treatment of PPH Using Misoprostol drafted with assistance from VSI, approved by MoH National Training of Trainers on correct use of misoprostol - Bugiri district Misoprostol pilot project launched in 11 districts Distribution of misoprostol to public health facilities by NMS in 11 districts Distribution of misoprostol to private practitioners and training on its use for safe abortion Second misoprostol product (<i>Kontrac</i>) registered with the NDA	VSI VSI, PSI Uganda VSI, PACE VSI, PACE Ipas
2010	Treatment Guidelines for Prevention and Treatment of PPH Using Misoprostol published by MoH Assessment of misoprostol distribution in Bugiri District Distribution of misoprostol to public HCs by NMS down to HC3 for PPH management Distribution of misoprostol and training providers in private HCs 3 rd misoprostol product (<i>Cytotec</i>) registered with NDA	Supported by VSI VSI PACE
2011	<i>Misoprostol for PPH prevention added to WHO EML</i> Distribution of misoprostol and training providers in private HCs A Randomized Controlled Trial (RCT) in two districts of Mubende and Mityana on impact of availability and distribution of misoprostol to mothers for self-administration/use in community	MSIU Supported by Gynuity Health Projects, University of Liverpool, Makerere University and PACE
2012	4 th misoprostol product (<i>Misoclear</i>) registered by Medical Access Uganda with NDA, supported by PACE and MoH Uganda Clinical Guidelines 2012 approved (not yet published); misoprostol recommended for incomplete abortion and PPH management Misoprostol added to Uganda's EMHSL	PACE, Medical Access Uganda Revision supported by SURE project

3. Methods and analysis

This study is based on interviews and data collected within the EU FP7 funded project on Accessing Medicines in Africa and South Asia (2010–2013). The analysis draws on 82 interviews conducted in Uganda between 20 August 2011 and 22 November 2012 using open-ended questions. Key informants were MoH officials including one commissioner, seven consultants, two Executive Directors of hospitals, four District Health Officers (DHOs), a representative from Securing Uganda's Right to Essential Medicines (SURE) project, Managing Director NMS, Managing Director JMS, 48 health facility managers, 12 prescribers and representatives from five organizations involved in the misoprostol promotion in Uganda (VSI, PACE, MSI, Uganda Private Midwives Organization, Association of Obstetricians and Gynecologists in Uganda) in four districts of Mbarara (South Western Uganda; mid-high ranking), Bundibugyo (Western Uganda; bottom ranking), Kampala (Central Uganda; top performing) and Apac (Northern Uganda; mid-low ranking). Ipas representatives were not interviewed because they are based in Kenya (Nairobi) and Zimbabwe (Harare). Interviews were recorded and transcribed by researchers from Makerere and Mbarara Universities. Transcripts were loaded into MAXQDA V10 to help sort and extract common themes including; misoprostol registration with NDA, its addition on EML, roles of key players involved, development and availability of misoprostol treatment guidelines, evidence base, procurement and distribution of misoprostol in Uganda's health units. Analysis was done by researchers from MUST and Queen Mary, University of London.

Quantitative data on procurement and distribution was

obtained from ten health facility record reviews and 120 pharmacy surveys. Descriptive statistics were obtained using Epi-Info V3.5. We reviewed available documents including WHO and MoH treatment guidelines and EMLs. Triangulation of data was extensively done.

Ethical approval for AMASA as a whole was obtained from the University of Edinburgh (UK), and for the Uganda element from the Mbarara University Institutional Review Committee (IRC) and Uganda National Council of Science and Technology (UNCST).

4. Results

4.1. Chronology of the use of misoprostol in Uganda and CSOs involved

Misoprostol was first imported to Uganda for research use in 2002 (Table 1). In 2004, the use of misoprostol for various maternal health indications was reported (Wassberg, 2004). CSOs and academic practitioners later played an active role in supporting its registration, availability and distribution for its use for PPH and other maternal health indications.

We identified five key CSOs involved in implementing and promoting misoprostol use (Table 2); all part of a larger global network involved in maternal health (Millard et al., 2013). The five CSOs are; Venture Strategies Innovations (VSI), Population Services International (PSI), Programme for Accessible Health Communication and Education (PACE), Marie Stopes International – Uganda (MSIU) and International Pregnancy Advisory Services (Ipas). Ipas differs from the other CSOs in that it does not have a formal office in

Table 2
Key CSO promoting misoprostol in Uganda.

CSO	Origins	Focus/activities	Misoprostol related activities/expertise	Involvement in misoprostol rollout in Uganda	Funding
VSI	International Created in 2008 by Venture Strategies for Health and Development	Reducing barriers to accessing essential medicines and health supplies; PPH, safe abortion, family planning	Misoprostol registration, addition to national clinical guidelines and EMLs, training of health providers, and distribution; 20 countries of operation to date	Registration, introduction, development of treatment guidelines, training of health providers and distribution	Susan Thompson Buffet Foundation, Venture Strategies for Health and Development, David and Lucille Packard
PSI	Global Founded in 1970	Family planning, HIV and AIDS, barriers to maternal health (PPH prevention, sepsis, safe abortion), and child health	Advocating misoprostol addition to EML by WHO and LICs; involved widely in procurement, importing, detailing, distribution, training	Registration, purchase, distribution; training health providers; research assessing misoprostol self-administration	Governments –USA, UK, Germany and the Netherlands; GFATM; UN agencies; Susan Thompson Buffett Foundation
PACE	Local PSI Uganda transitioned to PACE on 1st April 2009; an affiliate of PSI	Reproductive Health, HIV, Malaria, Child Health		Distribution under the Women Health Project	USAID, DFID, UNICEF, GFATM, CDC, PEPFAR, NORAD, Civil Society Fund, UNFPA, Youth AIDS, Johnson & Johnson, Merck
MSI Uganda	Local, part of MSI global network	Sexual and reproductive healthcare provision (safe abortion and post-abortion care); family planning, HIV/ STIs	Misoprostol registration for PPH, medical abortion and post-abortion care in several countries; feasibility studies on misoprostol use for post- abortion care and PPH	Advocacy, procurement, import, distribution, use and provider training on misoprostol use for PPH and other indications	USAID, UKaid, Kfw, Susan Thompson Buffett Foundation
Ipas	Global Founded in 1973	Safe abortion	Preventing unsafe abortion	Training providers on misoprostol usage for safe abortion	DFID, Bill and Melinda Gates Foundation, UNPF, Susan Thompson Buffett Foundation

Sources: <http://www.vsinnovations.org/>, VSI 990 forms, <http://www.psi.org>, <http://www.psi.org/uganda>, <http://www.mariestopes.org>, <http://www.ipas.org>.

Uganda, its nearest offices being in Nairobi and Harare. Ipas supports training in the use of misoprostol for abortion care in Uganda.

The US-based VSI, is one of the main organizations involved in promotion and use of misoprostol globally. They played a key role in supporting the addition of misoprostol to the WHO EML in 2011 (Millard et al., 2013). To date, VSI has run misoprostol programmes in 20 countries in Africa and Asia. Their activities include: misoprostol registration, distribution, its addition to national clinical guidelines and essential medicines lists, and the training of health providers. VSI provided financial and material support to the misoprostol rollout programme in Uganda from its outset, helping securing the first misoprostol registration. VSI and PACE worked with the Uganda MoH to introduce misoprostol for PPH prevention in 11 districts in 2009 with the aim of rolling it out across the country by 2010 (VSI, 2011). MSIU and Sigma Pharmaceutical Industries also worked with VSI and PSI/PACE in mapping out distribution and pricing strategies for misoprostol in Uganda. Following the registration of misoprostol in Uganda in 2008, PSI passed on responsibility for implementing its misoprostol programmes to PACE, an independent local organization in Uganda and an affiliate of PSI.

The five CSOs have diverse sources of funding and work independently of each other. Donors for specific misoprostol related activities are typically not declared. PACE programmes are partly funded by USAID and an undisclosed donor who funds maternal health programmes, including access to misoprostol in more than 15 countries (Interview, PACE senior officer).

Although the misoprostol programme in Uganda aimed “to complement other strategies in place to ensure appropriate and timely management of PPH” (MOH 2010 p 3), CSOs activities were not limited only to reducing maternal mortality due to PPH (Table 2). Ipas, for instance, focuses on safe abortion care only. Prescribers and MoH officials indicated that the potential of misoprostol for multiple maternal health indications has attracted its acquisition and use amongst prescribers, supported by these specific CSOs.

4.2. The role of CSOs in the drug approval process: evidence of efficacy and safety

The National Drug Authority (NDA) of Uganda licensed misoprostol for prevention of PPH on the 25 June 2008. PSI Uganda on behalf of Sigma Pharmaceutical Industries, the Egyptian manufacturer of *Misotac*, submitted the application. VSI provided financial and material support during the drug approval process.

Although the NDA approval process requires a medicine to demonstrate quality, safety, effectiveness, suitability and “the evidence of potential benefit of use in Uganda” (NDA, 2006 Pg 10; 10.2 of appendix 4 of NDA: R1), our review of the *Misotac* registration file found evidence only from toxicological, quality and stability tests. The only study that had been submitted on misoprostol which contained data on safety and efficacy was a clinical trial on the use of misoprostol in the treatment of incomplete abortion in Tanzania (Shwekerela et al., 2007); a different indication. The registration file did not state any evidence of the country need for misoprostol in Uganda.

4.3. The involvement of CSOs in procurement and the availability of misoprostol generics

As indicated in the registration file, VSI, PSI and the MoH had their original contracts with Sigma Pharmaceutical Industries (*Misotac*). Following reports of sub-standard products in 2010, they changed procurement to *Kontrac*, registered by NDA in 2009 by Delmaw Enterprises on behalf of Fourrts Laboratory Ltd. *Misotac* was recalled by mid-2011 and withdrawn from the NDA list. In addition to *Kontrac*, two other misoprostol brands are currently registered with the NDA; *Cytotec* manufactured by Piramal Health Care Ltd (UK) and *Misoclear* produced by ACME Formulation Pvt Ltd (India). PACE is reportedly in the process of registering a Cipla brand of misoprostol. There is no local manufacturer for misoprostol in Uganda.

4.4. The role of CSOs in developing the treatment guidelines

In 2009, VSI, PSI, and the MoH each played a significant role in the development of the *Clinical Guidelines for Prevention and Treatment of Post Partum Haemorrhage Using Misoprostol* which was published in 2010. Misoprostol is presented as “an addition to the arsenal of tools outlined in the Health Sector Strategic Plan and promoted by the Ministry of Health for safe motherhood” (MOH, 2010 p.7). According to the Minister of Health at the time,

“the unacceptably high maternal mortality rate increased a need for new strategies, approaches and innovations in the management of the underlying causes of maternal mortality to be able to achieve a healthy population, a valuable asset in the development process of the country and reducing the maternal mortality by a third by 2015” (MOH, 2010 p.3).

VSI provided financial and material support and their logo features on the cover page of the published guidelines. The document states, “the recommendations contained in these guidelines are evidence-based and are drawn from currently available data” (MOH, 2010 p.6) and refers to WHO's recommendations for the prevention of PPH (WHO 2007), the International Federation of Obstetrics and Gynaecology and the International Confederation of Midwives joint statement on the management of the third stage of labour (FIGO/ICM 2003), one systematic review (Hofmeyr et al., 2005), and two Cochrane systematic reviews (Gulmezoglu et al., 2004; Prendiville et al., 2000). No relevant clinical trials in any low-resource or community setting are mentioned.

The guidelines are directed at “physicians, medical officers, nurses, midwives and any other providers trained in the judicious use of misoprostol to ensure safe administration of misoprostol to mothers with the intention to prevent or treat postpartum haemorrhage” (MOH, 2010 p.6). The guidelines recognize the importance of AMTSL but acknowledge in part, “several providers have not been trained in the use of AMTSL, and that it will take several years before the majority of providers are trained in this technique. For this reason, these guidelines present steps to follow for the prevention of PPH by providers trained in AMTSL and those not initiated yet to this technique” (p. 11).

In 2011, the MoH summarized the document and provided practitioners with, ‘job aids’, short guides on misoprostol use in the management of PPH. Notwithstanding misoprostol's registration only for the prevention of PPH, a one page summary explains how to use misoprostol for both PPH prevention and treatment, and a two page document gives the recommended dosage for both PPH prevention and treatment; also listing possible side-effects and their management, contraindications, the components of AMTSL, and other uses of misoprostol including cervical ripening, induction of labour, incomplete and missed abortion, intrauterine foetal death). Thus, in addition to distributing misoprostol guidelines for the treatment of PPH, an unlicensed indication in Uganda through the job aids, the MoH also included information on other off-label indications. Whereas the currently available Uganda National Clinical Guidelines (UCG) 2010 do not mention misoprostol, their revision, UCG 2012, recommends misoprostol 800 µg sublingually or 1000 µg rectally for treatment of PPH “where oxytocin or ergometrine is not available or appropriate”. The UCG 2012, although still unpublished due to lack of funds and therefore unavailable to practitioners, was the basis on which misoprostol was added to EMHSLU.

4.5. The role of CSOs in the addition of misoprostol to the EMHSLU

Misoprostol was not added to the EMHSLU list until 2012, three

years after its introduction. This list, based on “specialists' experience of the best way to treat vital important conditions and diseases in Uganda” (EMHSLU, 2012 p.18), is said to have followed wide consultation, review, and a 3-day stakeholder's workshop attended by 56 specialists including: MoH Programme Managers, and specialists from the NDA, the NMS, Catholic Relief Services, SURE, UNEPI and WHO Representatives. The EMHSLU 2012 was developed by the Uganda Medicines and Therapeutics Advisory Committee (UMTAC), officially established by the Director General of Health Services in 2011 as the first national committee in charge of appropriate use of medicine, and printed with financial assistance of a USAID supported SURE Project. A scholar at Makerere University and member of the UMTAC, asserted,

“the UMTAC was mandated to revise the Essential Medicines List for Uganda 2007 as one of its first major assignment. It has had to add misoprostol on this list following the evidence that was presented by specialists to stress the country need in terms of challenges in Uganda's health system”.

We asked for the evidence presented, but this was unavailable. The committee classified misoprostol under oxytocics of the general medicines as a vital medicine (V) to be used by all prescribers down to HC2.

According to another UMTAC member and MoH official, the WHO recommendations had a significant influence on the development of Uganda's EMHSLU and treatment guidelines. The wide availability of misoprostol by different manufacturers following patent expiry coupled with WHO's 2007 declaration on its use for PPH management also helped to build a consensus on the need for its registration in Uganda. Misoprostol's addition on the WHO's model list in 2011 was also highlighted as a major influence:

“The WHO list often has a great input on the NDA and of course the people that review our UCG ... It definitely helps to pool a lot of expert evidence that we might not be able to do ourselves and this addition simplifies people's opinions about it [misoprostol].” (MOH official and member of UMTAC).

4.6. The role of CSOs in training for correct and safe use of misoprostol

VSI had been promoting misoprostol long before its addition to the EMHSLU. Since 2008, VSI had worked with the MoH on a pilot project to introduce misoprostol for PPH management in HC3 and HC4 in the first 10 ‘pilot districts’ of Apac, Lira, Abim, Nakasongola, Bugiri, Masaka, Bushenyi, Kapchorwa, Ibanda and Kiruhura and later added Ntungamo (VSI, 2009). The MoH facilitated a National Training of Trainers (TOTs) in May 2009. The trainers represented development partners and the MoH, and were supported by VSI and PACE.

Later that year, VSI trained 50 public health care providers including doctors, nurses and midwives on the correct and safe use of misoprostol for prevention of PPH in Bugiri district prior to the misoprostol launch in the public sector on 26th June 2009. With wide media coverage, VSI, PACE and the MoH launched the drug and over 600 community members, Members of Parliament, district officials and MoH officials attended.

The effective training and implementation in public facilities have since been affected by high staff turnover. According to a senior DHO,

“we have noticed wide lack of enthusiasm and awareness to use this drug[misoprostol] which has resulted in low utilization and small impact. The staff turnover is still a huge problem, partly due to poor pay in the public sector and heavy workload. This greatly

hampers continuation of the programme, which could be very useful, saving lives and benefiting the communities."

Although VSI left the country in 2011, PACE, Ipas and MSIU have continued to train health care providers in private facilities. A member of the Uganda Private Midwives Organization related:

"I and my colleagues were trained for the first time to use misoprostol by PACE to manage PPH and then later added other indications for use like induction of labour, Post Abortion Care (PAC), medical abortion by MSI ... they periodically call us for refresher trainings and support supervision on its use ... we have also had Ipas training us on safe abortion even though it is illegal in Uganda".

It is noteworthy that the 2009 Misoprostol guidelines (p.6) that were developed by the MoH in partnership with VSI to ensure "judicious and safe use" of misoprostol are not available in HCs. According to our survey, approximately 92% of Health Facility Managers reported no knowledge of these guidelines. Over 60% of managers reported no UCG, 2010. UCG 2012, which outlines misoprostol use, is still unpublished. The job aids, developed in 2011 to guide health workers in management of PPH are also unavailable. Less than 10% of health facility managers had ever seen the job aids and of these fewer than 5% had them displayed on the wall for reference. A senior consultant and MoH official identified high staff turnover and costs as challenges to availability and use,

"these people [VSI, MOH and PACE] trained health workers but the reality is that the staff turnover is very high ... the job aid was drafted by the MoH last year to guide in PPH management and this exercise is surely expensive. These aids are the ones that should be used in health centres. But do you know the process it takes for the job aid to come out from the MoH due to funding? It's a long time."

Some private practitioners however had the WHO and other printed guidelines supplied to them by the various programmes promoting misoprostol use. A member of Uganda Private Midwives Association said,

"MSI is promoting both safe deliveries, family planning and of course their Misoclear for the several indications like PAC, PPH management, labor induction, including what they have conveniently termed as medical abortion with their respective dosage recommendations. We have been trained and given a [wall] chart to guide us on the dosages and administration for these different indications".

Uganda lacks a national formulary and most hospital prescribers indicated using the British National Formulary (BNF), an important additional reference in the use of medicines. The BNF lists misoprostol for PPH as an unlicensed use and does not provide any guidance on dose and route of administration.

4.7. The distribution of misoprostol in pilot districts, impact assessment and scaling up

VSI supported the MoH in the distribution of misoprostol tablets in hospitals and HC3s in the 11 pilot districts from July 2009 to April 2010. On 28 September 2010, the MoH and VSI convened a stakeholders' meeting at Hotel Africana including 45 policy makers from the MoH and representatives from PACE, WHO, and AOGU, to plan a way forward for the misoprostol rollout in Uganda. During this meeting, the VSI national programme coordinator presented the

findings of their "Assessment of Misoprostol Distribution in Bugiri district, Uganda." This study aimed to assess feasibility, safety, effectiveness and acceptability of misoprostol use in the pilot district. It reported an overall increase in uterotonic usage at HCs after the introduction of misoprostol. Wider implications of the programme, like possible replacement of oxytocin or ergometrine with misoprostol were not considered. The MoH re-affirmed and supported VSI's goal to scale up misoprostol availability in Uganda's entire health care system.

By September 2010, the NMS had started pushing misoprostol in HC3's kits to supplement ergometrine and delivering it to ordering health facilities from HC4 upwards. The Joint Medical Stores (JMS), established in 1979 as a joint venture between the Uganda Protestant Medical Bureau and the Uganda Catholic Medical Bureau, procures and sells essential medicines to most private health facilities; misoprostol is not listed in its catalogue, possibly due to its association with abortion.

4.8. Role of CSOs in procurement and distribution

PACE (*Kontrac*) and MSI (*Misoclear*) supply misoprostol to private facilities. PACE previously worked directly with public facilities but now within its reproductive health programme it has established partnerships with private providers, to which it distributes misoprostol at a subsidized price to make it more available and affordable to the community. This was confirmed by data from facility records and prescriber interviews. According to a PACE reproductive health official,

"because those are private clinics and they are profit oriented, that is why we subsidize these supplies and we do not want them to overcharge clients ... we do for them community mobilization through available media. We also do regular CMEs to support our providers on usage [of misoprostol]"

A senior medical official with PACE added,

"our big anonymous funder directly facilitates the acquisition and distribution of misoprostol for maternal health to private health workers who need them at a very subsidized and affordable price even on credit ... we do not supply to the public HCs. We supply the private health facilities or workers and the faith based facilities and give out at least 40,000 pills per region per quarter"

MSI has a distribution target of 1,200,000 pills of misoprostol annually and procures misoprostol through Medical Access Uganda (LTR) (Interview, MSI programme coordinator). MSI only distributes to private skilled medical practitioners and other clinics which manage their innovative 'Blue Star', a social franchise network that has several health care providers in Uganda aiming at "offering voluntary family planning and reproductive healthcare services to the underserved community" (MSI, 2012). This programme is supported by USAID and UKaid. It was noted that through reimbursement of services, MSI motivates health care providers to promote their programmes, including the use of *Misoclear* for several indications.

"We work with WHO and MOH towards meeting the MDGs for reducing maternal mortality ... We mainly work with private midwives because we realized they were very important in administering this product in the private facilities and AOGU members that run our Blue Star programmes. For public midwives, we were very sceptical because of lack of motivation to implement these programmes and that's why some of these products like misoprostol are expiring from their stores even when they are available there. It's hard to train, supply and monitor their activities"

due to stringent public policy issues ... private sector usually have major impact on Uganda's health care outcomes and we reimburse them for our promoted programmes they offer. We have already caused big impact and the rate of consumption of misoprostol and other products have increased". (Senior MSI programme Official)

A Senior UPMA member and private prescriber also referred to the lack of direct incentives in the public sector as a cause of CSOs turning to private prescribers. She argued,

"They [PACE, VSI, MSI] first went to the public health centres to train and distribute misoprostol before they came to work with private practitioners due to existing stringent policies in public sector and lack of accountability. They had lost a lot of money in the public centres. After training, their programmes were implemented slowly or not at all due to lack of incentives for the health workers. The private facilities do benefit directly because like we charge for every service offered and have all these indirect incentives which isn't the case for public facilities ... MSI reimburses us for these services ... we are also given other incentives like sterilizers, beds and instruments by PACE, which is not particularly interesting for public facilities where everything is supposed to be provided free of charge. The health workers therefore weigh their effort in doing something with no direct benefits and this was affecting the programme targets. We improved coverage of their services at a low fee ... these are output-based programmes and targets are very important to them for continued funding".

The third available brand of misoprostol, *Cytotec*, is distributed through private pharmacies and is priced significantly higher than generics.

4.9. Misoprostol substitutes for oxytocin in public HCs

Since the enforcement of the MoH procurement policy in 2010, all HCs procure all their medicines from the NMS. This meant that ergometrine (the only uterotonic agent previously listed as an essential medicine for HC3s) and misoprostol (added on HC3 health delivery kit in 2010) are the current drugs of choice and are delivered quarterly to HC3s by NMS. Quantitative data also showed a noticeable increase in quantities of misoprostol delivered to HC4s and hospitals. A MoH official emphasized the complementarity of misoprostol to the already existing methods,

"as a ministry, we are not promoting misoprostol in place of oxytocin. We are only using it as a supplement for PPH management because of its many benefits like ease of use, stability and its less stringent requirement for supply chain that pose a big challenge for other injectables ... Overcoming these health system challenges is long term and misoprostol could help with the maternal mortality in Uganda".

Nevertheless, the health facility record reviews show that the last oxytocin and ergometrine supply for the HC4s was in the second half of 2011 and 2009 respectively. No supplies of oxytocin to HC3s were reported although it is listed for that level in the EMHSLU (EMHSLU, 2007). This finding was supported by prescriber and HFM interviews that revealed that the NMS frequently supplied less medicine than was ordered. According to some facility managers, misoprostol is often pushed in higher quantities even to non-ordering facilities. This coupled with low awareness of use among health workers, causes stock piling and expiry due to non-utilization within many of these centres. 10 of the 15 HC4s reported having not been supplied with oxytocin or ergometrine by

the NMS for at least one quarter of the previous year and instead having been urged to pull surplus supplies from the lower HCs.

5. Discussion

This case study documents how CSOs operate on a local level in Uganda to facilitate access to medicines and change the national medicines policy. By focussing on the reduction in maternal mortality, these CSOs followed evidence for management of countries' priority conditions (WHO, 2013) and made a major contribution to the introduction and use of misoprostol in Uganda. Their traditional role in advocacy, coordination, advice, funding, and medicine distribution has been extended to other government functions. For example, we show the direct involvement of the CSOs in product registration with the drug regulatory authorities and in the development of clinical guidelines; two tasks that used to be in the domain of the pharmaceutical industry and health experts respectively. The CSOs were also indirectly involved in misoprostol's addition to EMHSLU through the misoprostol treatment guideline supported by VSI.

The weaknesses of institutions for the medicine approval in low-income countries are well documented (WHO, 2010). In the introduction of misoprostol in Uganda, the active participation of and support by CSOs did not help to overcome these weaknesses. The registration of misoprostol with the NDA occurred without meeting minimum NDA requirements for safety and efficacy. The development of the misoprostol treatment guidelines also failed to consider current evidence base for misoprostol use in low-resource settings, for which it was introduced in Uganda.

The current WHO guidelines (WHO, 2012b) and Cochrane review (Tuncalp et al., 2012) both highlight weaknesses in the available evidence for misoprostol use in low-resource countries, which has since been supported (Chu et al., 2012). The most current research concluded that oxytocin is the preferred uterotonic drug of choice for prevention of PPH where AMTSL is practiced (Atukunda et al., 2014; Tuncalp et al., 2012). The Cochrane review additionally recommended that oxytocin be made widely available for use in all health centres (Tuncalp et al., 2012). Although the misoprostol programme in Uganda aimed to introduce an additional medicine to tackle maternal mortality in Uganda (MOH, 2010), the evidence suggests that this goal has been significantly expanded: (1) misoprostol was being pushed to all public and private HCs and replacing oxytocin especially in lower health centre settings with fair capacity to enable oxytocin use; and (2) some CSOs actively encourage misoprostol use for unapproved indications including induction of labour and abortion. This study documents that scrutiny paid to evidence and efficacy was insufficient, which is of concern when science and evidence appear not to play a strong role in a health policy change.

Although the literature acknowledges CSOs' wide involvement in coordination and monitoring public programmes (Kruse, 2004; Thue et al., 2002), there was no report of direct involvement of the CSOs in the monitoring and evaluation of the public misoprostol rollout programme in Uganda. There is also no evaluation report available on CSOs' activities in private sector. One pilot project in one district was evaluated by VSI before scaling up (VSI, 2011). This pilot showed an increased use of all uterotonics after training on misoprostol use, which suggests previous overall lack of training on PPH management rather than a necessity to introduce an alternative easy-to-use drug. There has been no evaluation of wider implications of the programme including the impact on availability and use of uterotonics after misoprostol's introduction. Whereas the initiative aimed at reducing maternal mortality rates in Uganda, it was not clear whether the mothers unable to access skilled health professionals were targeted and the impact of this

program is still unknown.

National clinical guidelines play a vital role as they are required before medicines can be listed on Uganda's essential medicine list, and this listing informs medicine procurement for public health system through the NMS (EMHSLU, 2012). The insufficient evidence base in support of a medicine, coupled with unregulated national rollout of misoprostol to all facilities (private and public) prior to its addition in the Uganda clinical guidelines (UCG) and EMHSLU has serious negative implications for drug usage in Uganda. Guidelines and job aids are not available and lack of and inadequate training in misoprostol's use could lead to patient harm and wasted resources in terms of procurement costs and unused medicines.

6. Conclusion

Civil society organisations accelerated misoprostol rollout in Uganda, playing an active role in its registration, piloting, distribution and use. In the absence of strong evidence and despite its introduction as a complementary treatment to injectable uterotonics, evidence suggests an increasing trend of misoprostol procurement and availability over the medicine of choice—oxytocin, two years prior to its addition to the national clinical guidelines and EMHSLU. This has implications for maternal health care when the policy focus and financial resources are shifted from the first line prevention and treatment strategies to those that are easier to implement. The aim of the misoprostol programme has been expanded by pushing misoprostol to health facilities with fair capacity to use oxytocin, including some CSOs promoting it for off-label indications. Ramifications of these changes for maternal health care need urgent evaluation. There is also an urgent need to build capacity to improve robustness of the national and local institutions involved in registration, procurement, distribution and use of new medicines.

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