

ANALYSIS

Commentary: Evidence versus influence in the WHO procedure for approving essential medicines: misoprostol for maternal health

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In 2002, the World Health Organization changed its procedures for revising the model list of essential medicines as part of a shift to a more transparent and evidence based approach.¹ Barbui and Purgato's analysis highlights how poor quality applications unaccompanied by a systematic review of evidence may lead to the WHO expert committee prioritising reviews of medicines with limited value. Another problem is that the influence of civil society organisations in the application and review process can apparently trump evidence.

A case in point is misoprostol, a synthetic analogue of naturally occurring prostaglandin E1 that was, after six attempts, added to the essential medicine list in 2011 for the prevention of postpartum haemorrhage when oxytocin is not available or cannot be safely used. However, an application to include the drug for the treatment of postpartum haemorrhage was rejected at the same time because it "could divert the attention from or reduce attempts to implement oxytocin availability, a superior treatment."

The drug of choice for preventing and treating postpartum haemorrhage is oxytocin, followed by ergometrine, both of which are heat sensitive and require parenteral administration. Because misoprostol is stable at room temperature and can be administered orally, sublingually, rectally, and vaginally it has been presented as an ideal alternative in low resource settings, where most maternal deaths from haemorrhage occur. However, the evidence in support of using misoprostol is weak despite the large number of trials.

Over 10 years, four successive versions of a Cochrane review of the safety and efficacy of the use of prostaglandins in the prevention of postpartum haemorrhage concluded that misoprostol is not as effective in reducing blood loss as oxytocin and has more side effects, although it adds that misoprostol may be used where no injectable uterotonic is available.² A further separate Cochrane review of the safety of postpartum misoprostol compared with other uterotonics and placebos in 2013 concluded that it increases the risk of fever in doses ≥ 600 μg .³

Ten applications have been made to add misoprostol to the essential medicines list, six for postpartum haemorrhage (table 1). The decision to add misoprostol to the list in 2011 was based on evidence from four randomised controlled trials conducted in low resource settings,^{4,7} which the WHO expert committee said showed that misoprostol was effective and safe when used by traditional birth attendants trained to use it at home deliveries. However, a subsequent review of the four papers showed that the evidence in support of misoprostol in such situations was weak, identifying deficiencies in exclusion criteria, intervention and controls, temporality, and use of outcomes.^{8,9}

Vested interests

The WHO website provides information on applications, including supporting letters. Apart from the submitting organisations, the only supporting documents for the four applications in 2003 and 2005 were from the Population Council. However, the four applications in 2009 and 2011 were endorsed by 89 organisations and individuals working in maternal health (fig 1).¹⁰ This change came about primarily through the activities of the three American civil society organisations that made the applications: Gynuity Health Projects (GHP), Venture Strategies for Health Development (VSHD), and its partner organisation Venture Strategies Innovations (VSI). These organisations have received substantial financial backing for their postpartum haemorrhage programmes and have used those funds to promote the use of misoprostol in developing countries, either through research or through registration and roll-out programmes.¹¹⁻¹⁴

According to information provided on its website, Gynuity's programme began in 2004; the second phase commenced in 2009 with a five year grant from the Gates Foundation of \$25m (£15m; €19m). VSHD was established in 2000, the year that misoprostol came off patent, with the aim of making misoprostol widely available for postpartum haemorrhage; its partner organisation VSI took over these activities in 2008. According to VSI's biennial reports it received \$2.3m in grants and

contracts in 2010-11 and \$12.8m in 2011-12; \$12.4m of this came from the Susan Thompson Buffet Foundation.^{11 12}

The organisations supporting the applications in 2009 and 2011 comprised 34 non-governmental organisations (including Engender Health, Médecins Sans Frontières, Family Care International, and Reproductive Health Technologies Project); 45 experts on women's health; seven professional associations (including the International Federation of Gynaecology and Obstetrics and the International Confederation of Midwives); seven academic institutions; one funding organisation (Susan Thompson Buffet Foundation); and one drug company (Sigma Pharmaceuticals).¹⁰

Some of these individuals and organisations submitted their own letters of support; most were signatories to collective letters—for example, the Prevention of Postpartum Haemorrhage Initiative (POPHI) sent a letter with 20 signatories, and the Reproductive Health Technologies Project sent a letter signed by 36 women's health experts. These letters generally repeat the public health case and evidence on efficacy and safety that is stated in the main application and do not provide any additional evidence.

It is difficult to measure the effect that this support had on the final decision of the committee; it was mentioned only briefly in the final reports in 2009 and 2011.^{15 16} Nevertheless, the individuals and organisations who supported the application must have done so with the view that what they said mattered, and the WHO committee must have been aware of the pressure from institutions of high repute to add the drug to the list.

In 2013 two of us (AMP and PB) submitted an application to delete misoprostol from the list on the basis of the evidence of weakness identified in the review of the four key studies used by the WHO committee.^{8 9} This was vigorously opposed by Gynuity Health Projects, Concept Foundation, and signatories of a Uganda letter.¹⁰ The committee rejected our application because there was no new evidence—that is, no new studies. It did not, however, reassess the existing evidence.

Although the 2002 changes to the list procedures were seen as heralding a more evidence based approach, the 2002 WHO report also said that “in the absence of adequate scientific evidence on current treatment of a priority disease, the WHO Expert Committee on the Selection and Use of Essential Medicines may either defer its decision regarding selection until more evidence becomes available, or choose to make recommendations based on expert opinion and experience.”

Misoprostol highlights how when the evidence base is weak, other factors, including expert opinion, can influence the final outcome. Misoprostol was added to the list for prevention of

postpartum haemorrhage after concerted lobbying by civil society organisations. Given the weakness of the evidence, it seems that such activities influenced the opinion of the committee. It is not clear why the committee reached a different decision about its use for treatment of postpartum haemorrhage or why it refused to review the evidence after weaknesses were identified.

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Table

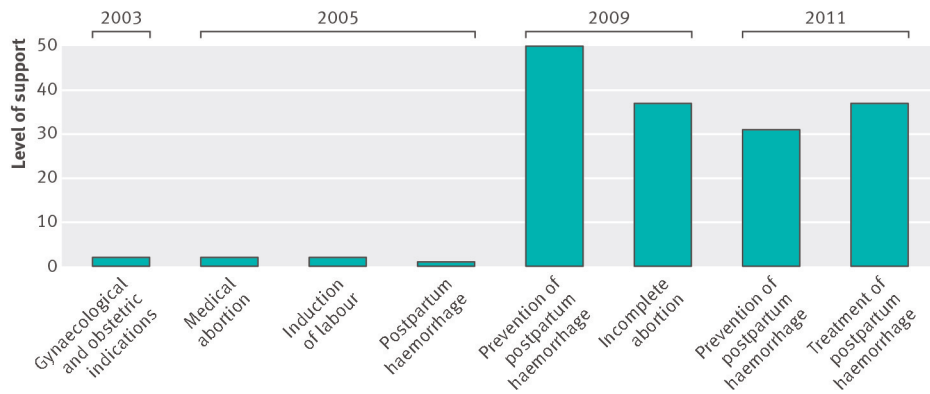
Table 1 | Applications to add misoprostol to WHO essential medicines list

| Year | Indication | Result |
|------|---|---|
| 2003 | Gynaecological and obstetric indications | Not considered because of limited registration for these indications |
| 2005 | Medical abortion | Added to complementary list* |
| | Induction of labour | Added to complementary list |
| | Postpartum haemorrhage | Rejected because of lack of evidence |
| 2009 | Prevention of postpartum haemorrhage | Rejected because of lack of evidence |
| | Incomplete abortion | Added to complementary list |
| 2011 | Treatment of postpartum haemorrhage | Rejected because of lack of evidence of safety when women had received prophylactic misoprostol |
| | Prevention of postpartum haemorrhage | Added to core list‡ |
| 2013 | Treatment of postpartum haemorrhage | Rejected as no new evidence to add to what was considered in 2011 |
| | Application for deletion for prevention of postpartum haemorrhage | Rejected because of absence of new evidence |

* Complementary list includes essential medicines for priority diseases, for which specialised diagnostic or monitoring facilities, medical care, or training are needed.

‡ Minimum medicine needs for a basic healthcare system, listing the most efficacious, safe, and cost effective medicines for priority conditions.

Figure



Number of supporting organisations and individuals for applications to add misoprostol to WHO essential medicines list¹⁰