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CLINICAL ARTICLE

Cost-effectiveness of misoprostol and prenatal iron supplementation as maternal mortality interventions in home births in rural India

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ABSTRACT

Objective: To determine the cost-effectiveness of prenatal iron supplementation and misoprostol use as interventions to prevent maternal mortality in home births in rural India. **Methods:** A cost-effectiveness analysis depicted three hypothetical cohorts of 10 000 pregnant women delivering at home in rural India: one with no intervention, one receiving standard prenatal iron supplements, and 1 receiving 600 µg of misoprostol in the third stage of labor. **Results:** Misoprostol used to prevent postpartum hemorrhage resulted in a 38% (95% CI, 5%–73%) decrease in maternal deaths, while prenatal iron supplementation resulted in a 5% (95% CI, 0%–47%) decrease. Misoprostol cost a median US \$1401 (IQR US \$1008–\$1848) prenatal iron supplementation cost a median US \$2241 (IQR No Lives Saved–\$3882) per life saved compared with the standard care outcome. **Conclusion:** Misoprostol is a cost-effective maternal mortality intervention for home births. Iron supplementation may be worthwhile to improve women's health, but it is uncertain whether it can prevent mortality after hemorrhage.

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1. Introduction

In India, 83% of rural deliveries occur at home [1]. Researchers estimate that 36% of the annual 540 maternal deaths per 100 000 live births in India are attributable to either postpartum hemorrhage (PPH) or anemia [2–4]. These are both conditions that can be prevented in the home by evidence-based, low resource interventions that do not require institutional access.

Anemia in pregnancy, defined as a hemoglobin (Hb) concentration less than 11 g/dL, is classified as mild (Hb 10–10.9 g/dL), moderate (Hb 7.0–9.9 g/dL), or severe (Hb < 7.0 g/dL) [5]. Anemia can be caused by hookworm infection, malaria, or other micronutrient deficiencies. Globally, 51% of anemia cases are related to iron deficiency [6]. Pregnant women with iron-deficiency anemia (IDA) are at higher risk for poor maternal and fetal outcomes, including low birth weight, cardiovascular stress and perinatal and maternal mortality [6]. In India, anemia prevalence estimates during the third trimester range as high as 88%, with iron responsiveness around 62% [7,8].

IDA was recently nominated as a key risk factor for maternal death. Observational reports have linked IDA to 22% (115 000) of all annual

maternal mortalities attributable to anemia or hemorrhage [9]. Despite several observational studies, there is still insufficient evidence of causality between anemia and maternal mortality [10,11]. In observational studies, unmeasured sociodemographic frailty factors confound the association between anemia and mortality, leading researchers to potentially overstate the impact of anemia. Clinical trials of iron supplementation with maternal mortality as the outcome of interest could offer better estimates of the potential mortality reduction. However, given the rarity of maternal death and common confounding factors, implementing trials with sufficient statistical power is difficult.

Eventually, all women will have access to modern obstetric services, but currently 60 million of 142 million annual deliveries occur without a skilled attendant present at birth [12]. This paper focuses on two of the most promising interventions that could potentially prevent death from maternal hemorrhage for women who deliver outside the formal health system. Skilled providers trained to administer misoprostol after delivery have been shown to lower mean blood loss and reduce PPH incidence for women who deliver outside the health system [13]. Iron supplementation in pregnancy has been shown to lower anemia prevalence [14].

While PPH and anemia are suspected to have independent and interactive effects on maternal death rates, it has not yet been possible to quantify their effects on death rates empirically because of the large sample size that would be required. Death from maternal hemorrhage comes in two forms: (1) the immediate deaths from hemorrhagic shock,

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and (2) the delayed deaths from complications of poor tissue perfusion and oxygenation. Adequate hemoglobin status protects against death from tissue hypoxia after hemorrhagic shock has been resolved.

The well-known physiological mortality effects of severe anemia and hemorrhage motivate the use of computer simulation to connect these intermediate outcomes to estimates of lives saved. This paper

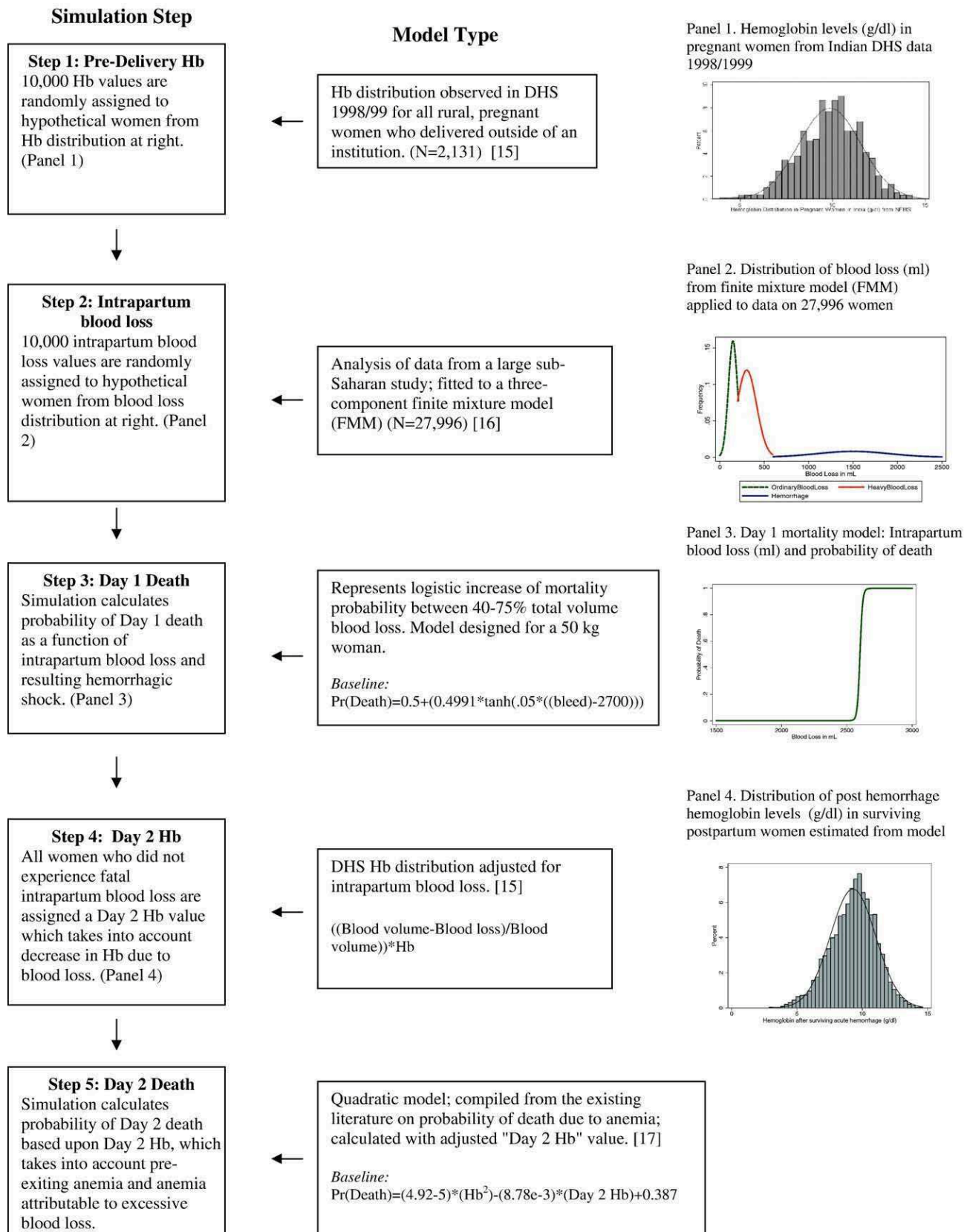


Fig. 1. Conceptual model for basic computer simulation.

introduces the Stochastic Simulator of Hemorrhagic Shock (SSHS), a microsimulation model designed to link changes in hemoglobin level and blood loss to estimates of lives lost. The simulator is applied to home birth interventions to assess the cost-effectiveness of misoprostol and iron supplementation in terms of cost per life saved.

2. Methods

The simulation was designed to reflect the delivery outcomes of 10 000 women in India. Parameters were selected from the literature to mirror conditions in rural Indian communities where women deliver in their homes. The primary outcome of interest was the number of maternal deaths attributable to hemorrhage or anemia that occurred with no intervention, with prenatal iron supplementation, and with misoprostol use immediately after delivery. All parameters and models were based on existing peer-reviewed literature, population-level datasets, and expert consultation in the case of the hemorrhage mortality model. Figs. 1 and 2 describe each simulation step and how it was modeled with information from the literature.

In the baseline model, each hypothetical woman was randomly assigned a hemoglobin and intrapartum blood loss value from statistical distributions. Each woman was then randomly assigned corresponding mortality probabilities. Hemoglobin measurements from the 1998/99 Indian Demographic and Health Survey (DHS) were used to create a population distribution of Hb in pregnancy [15]. Data on blood loss distributions were drawn from direct observations by physicians at 28 clinics in 6 African countries for 27 996 women (Panel 2; [16]) and used to produce 3 superimposed normal distributions: (1) 54%~N(148, 51); (2) 40%~N(303, 110); and (3) 6%~N(722, 409). The notation “~N(μ , σ)” means “distributed normally with a mean of μ and a standard deviation of σ .” The hemorrhage model can be interpreted to reflect that 54% of women have a modest amount of bleeding averaging 148 ml, 40% have an average amount of bleeding averaging 303 ml, and 6% have hemorrhage averaging 722 ml, but with a wide standard deviation of 409 ml. A recalibration was performed to ensure that this distribution's use resulted in an India-specific expected number of maternal deaths due to PPH. The third distribution was then adjusted to reflect Indian conditions ~N(1700, 409).

Probability of mortality due to hemorrhage was considered a direct function of blood loss and was labeled “Day 1 mortality.” All women who lost more than 75% of their total blood volume in a home delivery were assumed to have died. All women who lost less than 40% of their

total blood volume, had a less than 1% probability of Day 1 hemorrhagic death. All women who lost between 40% and 75% of blood faced a constantly increasing probability of death as reflected by a fitted logistic curve (details available from authors). Probability of mortality indirectly due to anemia was labeled “Day 2 mortality” and was calculated using an existing model in the literature [17]. All deaths attributable to PPH or anemia were calculated by subtracting the number of “Day 1 deaths” from the total number of maternal deaths, modeled by the equation below:

Eq. (1): Equation for calculating cumulative mortality in the simulation

$$\text{Total lives lost} = \text{No. dying on day 1} + ((\text{Pr. dying on day 2}) \times (\text{No. surviving to day 2}))$$

The statistical simulations were performed using STATA 10.0 for Macintosh (STATA Corporation, College Station, TX, USA). The results of the simulation were used to calculate cost-effectiveness of each intervention compared with standard care. In all, 400 iterations of the model were run. The amount of blood lost was kept independent of the pre-existing Hb in each iteration, so that the estimates of lives lost were stochastic and an uncertainty interval was calculated.

Costs of birth attendant training, misoprostol use, and a prenatal iron supplementation program were taken from the literature (Table 1). The cost models were:

Eq. (2): Cost model for standard care arm

C = Birth attendant fee for 10 000 deliveries

Eq. (3): Cost model for misoprostol intervention arm

C = Birth attendant training costs
+ birth attendant fee for 10 000 deliveries
+ birth attendant time cost + misoprostol cost + costs of side effects

Eq. (4): Cost model for prenatal iron supplementation arm

C = Birth attendant training costs
+ birth attendant fee for 10 000 deliveries
+ birth attendant time cost
+ iron supplementation cost for 10 000 women + costs of side effects

In order to provide accurate cost estimates, effort was made to select recent data collected in a similar setting. The majority of the

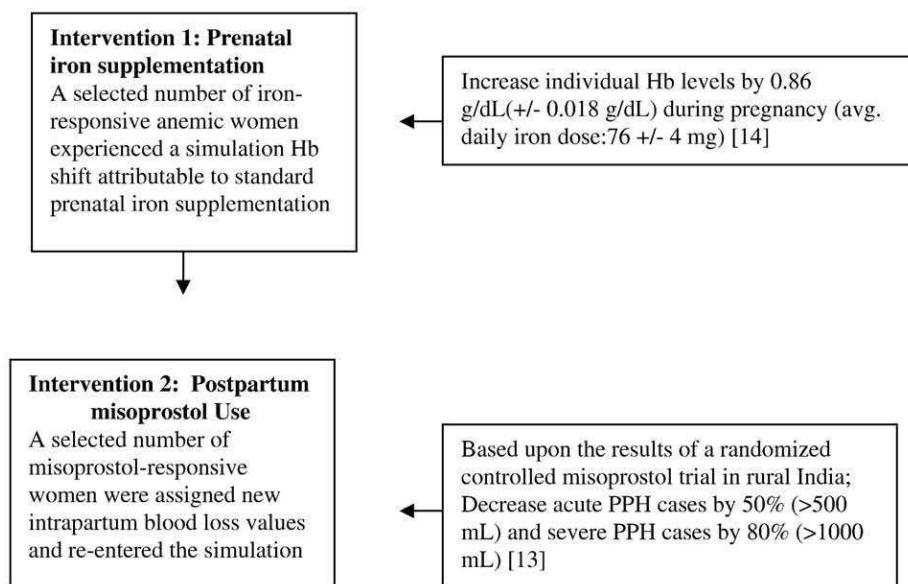


Fig. 2. Conceptual model for intervention simulations.

Table 1
Cost parameters

Parameter	Quantity	Source
Number of delivery providers to attend 10 000 births	83	^a [28,29]
Cost of 1 home delivery	US \$2	^b [18]
Opportunity cost of provider training time	US \$2	^b [18]
Cost of 1-day training per provider; materials and teachers	US \$2.01	^c [30,31]
Cost of 600 µg misoprostol	US \$0.99	[19]
Cost of prenatal iron supplementation per woman per year	US \$0.87	^d [21]

^a Baseline is the average of a high and low estimate from the literature [331/25].

^b Converted from Indian rupee (Rs) to US\$ using 2008 rates.

^c Baseline is the average of a high and low estimate from the literature [\$3.40/\$.62].

^d Cost calculation for Southeast Asia region assuming 95% coverage. Published in international dollars and assumed to be approximately US \$0.87.

data came from a large-scale intervention that involved training of rural village health workers (VHWs) from 25 districts in Maharashtra, India [18]. Because the simulation is designed for isolated home births settings, it has been assumed that transport to emergency obstetric care (EmOC) facilities is not available. As a result, the cost of care for women who did experience hemorrhage was not calculated.

Misoprostol (CIPLA, Mumbai, India) is manufactured in India and is widely available. Cost for 600 µg of misoprostol is US \$.99 (US \$.33 per 200 µg tablet) [19]. A previous analysis found that the cost of side effects due to misoprostol was negligible [20].

Because VHWs routinely provide prenatal services to women and are only compensated at delivery, it was assumed that all administrative costs for iron delivery were included in this fee [18]. A recent cost-effectiveness analysis (CEA) calculated the cost of iron supplementation in international dollars per woman for a region where both maternal and child mortalities attributable to IDA are high [21]. The calculations were performed with Southeast Asian data. Because the same parameters also apply to South Asia, the results were used in our calculations. Side effects include constipation and nausea [14]. These costs were considered to be negligible in our analysis. See Table 1 for a full list of cost parameters.

Data on the effectiveness of misoprostol for reduction of acute and severe PPH incidence were taken from a randomized controlled trial based in rural India; there was a 50% decrease in acute PPH cases and an 80% reduction in severe PPH cases [13]. In the simulation, of the women in the original blood loss distribution who suffered from acute PPH, 50% were randomly selected and then randomly reassigned an intrapartum blood loss value less than 500 mL. Of the women who suffered from severe PPH, 80% were randomly selected and reassigned a blood loss value less than 1000 mL.

The effect of iron supplementation was dependent on two factors: (1) the percentage of anemic pregnant women responsive to iron; and (2) the average Hb shift experienced by women who completed a prenatal supplementation program. Because the Hb shift is dose dependent, an average pregnant woman who took between 61–90 mg of iron daily would be expected to have a 0.86 g/dL Hb shift over the course of her pregnancy [14]. This dose response estimate was the closest value to the 60 mg/day dosage recommended during pregnancy [22]. In order to determine the percentage of anemia cases responsive to iron, we used a pregnancy-specific rate of 62%, established by a national Indian report [8].

Table 2
Cost-effectiveness of misoprostol and iron supplementation compared with no intervention applied to 10 000 deliveries

	Deaths per 10 000 women (SD)	Lives saved (SD)	Cost per 10 000 deliveries, US\$	D Costs	Incremental cost-effectiveness ratio median ^a and (interquartile range ^a)
No intervention	19.5 (2.0)		\$20 000		
Iron supplementation	18.4 (1.4)	1.1 (4.0)	\$29 032	\$9032	\$2241 (No Lives Saved–\$3882)
Misoprostol	12.0 (0.9)	7.5 (3.3)	\$30 232	\$10 232	\$1401 (\$1008–\$1848)

^a Median and range calculated for positive values only.

Costs, effects, and the incremental cost-effectiveness ratios or ICER (Change in Cost/Change in Lives Saved) were subjected to sensitivity analysis. The greatest uncertainty in the stochastic simulation surrounded overall day 1 and day 2 mortality, so these parameters were subjected to ±20% changes in order to evaluate the effect on the conclusions about cost-effectiveness. Confidence bounds for ICERs and lives saved were generated using At Risk 4.0 software (Palisade Software, Ithaca, NY, USA), and the results of the sensitivity analysis are available from the author on request.

3. Results

Birth attendant training to correctly administer misoprostol after delivery and to support prenatal iron supplementation would result in significant decreases in the total number of maternal deaths attributable to either PPH or anemia. In our simulation, misoprostol use after delivery led to a 38% (95% confidence interval [CI], 5%–73%) reduction in maternal deaths with an incremental cost per life saved of US \$1401 (interquartile range [IQR], US \$1008–1848). Prenatal iron supplementation resulted in a 5% (95% CI, 0%–47%) decrease in maternal deaths compared with the standard care outcome with an incremental cost of US \$2241 (IQR, No Lives Saved–\$3882) per life saved (Table 2).

A univariate sensitivity analysis (available from the author on request) provided high and low estimates of the misoprostol and iron incremental cost effectiveness ratios based on alternative estimates of the mortality probabilities. This was performed because the conditional probabilities of death as a function of blood loss and day 2 hemoglobin are known with the least certainty. The sensitivity analysis essentially rendered these probabilities 20% lower and 20% higher to see how the change affected the conclusions. The sensitivity results show that the general conclusions of cost-effectiveness for misoprostol are robust to uncertainty about the mortality rates. However, the conclusion that iron supplementation is effective or cost-effective is not robust. Iron supplementation leads to non-zero estimates of lives saved in only 57% of iterations tested, meaning that with 43% probability a program of iron supplementation for 10 000 women would not lead to any lives saved from maternal hemorrhage.

4. Discussion

Recent studies have demonstrated that certain maternal mortality interventions can be safely applied in low-resource areas. Cost-effectiveness is another critical element in shaping national and international donor policy and subsequent intervention distribution and use. The Disease Control Priorities Project (DCPP) has already published a comprehensive CEA of institutional maternal mortality interventions [23]. This analysis seeks to take the DCPP one step further by performing a CEA to address the plight of women who deliver at home in rural areas and by determining the impact of two non-institutional maternal mortality interventions.

This simulation is promising in the sense that it permits one to estimate mortality as a function of blood loss and hemoglobin for a virtual population. It is the first of its kind and differs from prior maternity mortality models because of its exclusive focus on death from hemorrhage [24]. The parameters that were used to design the present simulation were either regional or national estimates relevant to South

Asia. Because of the nature of the mortality parameters, blood loss distribution, and necessity of limiting hemorrhage deaths to those attributable to PPH, there is uncertainty over the absolute number of lives saved by each intervention. The sensitivity analysis demonstrated that when mortality rates were higher, the cost-effectiveness of both interventions was more attractive. Moreover, the baseline cost-effectiveness estimate of US \$1401 for misoprostol per life saved compares favorably to other public health interventions; in comparison, the estimated cost of improving comprehensive emergency obstetric care per life saved is US \$10 532 [23]. However, one limitation of the misoprostol cost is the assumption that providing misoprostol and training birth attendants to administer misoprostol will produce the same results as a previous misoprostol trial that utilized skilled birth attendants [13].

Any time that one transfers results to a population, there is uncertainty over the population-level effectiveness. While iron supplementation is critical to maternal health and fetal development, India's existing iron supplementation programs have a long history of failure due to gastrointestinal side effects and resulting noncompliance [25]. The results of our simulation showed that iron supplementation may have a minor effect, if any, on maternal mortality reduction, and these results may be difficult to detect in a randomized trial. In addition, anemia may lead to death due to causes other than tissue hypoxia. It is important to emphasize that the effects of iron, with regard to promotion of good maternal and infant outcomes, are known to be worthwhile aside from any effect on mortality [11].

It is notable that the unregulated use of misoprostol for multiple indications has been contested because of instances where it was improperly administered and adverse outcomes resulted [26]. However, one large-scale trial in Indonesia found that misoprostol can be safely distributed to women by local VHWs, who also counsel women on misoprostol use after delivery [27]. Advocates of misoprostol use after delivery emphasize the use of caution and promote correct use by careful training and clearly differentiated packaging [27].

Both iron supplementation and misoprostol are evidence-based interventions that improve pregnancy outcomes and can be safely delivered by providers in rural areas. The present model shows that misoprostol is cost-effective. With greater use, misoprostol could save the lives of tens of thousands of women each year at a potentially low cost.

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