

**15<sup>th</sup>**  
**GENERAL MEMBERSHIP MEETING**  
*of the* **REPRODUCTIVE HEALTH**  
**SUPPLIES COALITION**  
20-24 OCTOBER  
MEXICO CITY

**mexco**  
**2004-2014**  
REPRODUCTIVE HEALTH  
SUPPLIES COALITION

## Investing in High-Quality Maternal Health Products for Low-Resource Settings

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AVAILABILITY



QUALITY



Reproductive Health  
SUPPLIES COALITION



**Jhpiego**  
an affiliate of Johns Hopkins University

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## Introduction

Terms of Reference and Methodology



### Terms of reference

Map known maternal health product manufacturers, market sizes, market dynamics

Build business cases for investing in high-quality products in low-resource settings

Promote reliable production and supply of affordable, quality products

### Methods

Key Stakeholder interviews

Review existing data and published reports

Determine proxy measures for existing data gaps

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Oxytocin, Misoprostol, magnesium sulfate

Available today:

- Nearly final versions of oxytocin and magnesium sulfate
- Excel models and user's guide

Available end of November:


- Completed business cases for oxytocin, magnesium sulfate and misoprostol
- Translations into French and Spanish
- Final Excel models and User's Guide

- Intend to add India to the Excel models

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## Oxytocin

### Challenges



1. Few incentives to procure quality products
  - Many manufacturers
  - No WHO-prequalified products available yet
  - Price-sensitive market
2. Product is sold wholesale for \$0.15 to \$0.20 per 10 IU ampoule, which is fairly inexpensive.
3. Concerns that some products may not be properly manufactured. More concerning is that even high-quality FPP may degrade outside of the cold chain
  - Poor awareness and training in many countries about storage and cold chain requirements
4. Recent studies indicate problems with product registration, product sterility, and physio-chemical assay

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Broad usage of Oxytocin. First line treatment for PPH prevention and treatment according to WHO

PPH is the leading cause of maternal death worldwide, about 70,000 deaths per year.

On WHO Essential Medicines List and UN Commission on Lifesaving Commodities

Oxytocin – use in prevention – 10 IUs, treatment 40 IUs.

Quality issues – these exist in both manufacturing and in the cold chain. Storage requirements are unclear, many presentations say 2-8 degrees, and others will allow higher but it isn't clear if this is properly tested.

- Recent studies done in Indonesia and Ghana. Ghana study was much worse. In Ghana, a study by US Pharmacopeia and the Ghanaian Food and Drug Authority found only 8% of oxytocin samples with market authorization for the country, almost no oxytocin stored in proper temperature (2-8 degrees C), 97.5% of samples failed either assay or sterility testing or both, and over 55% of samples failed their physio-chemical assay. The study concluded that 65.5% of the oxytocin sampled did not meet quality standards, and as a result could have serious implications for the prevention and treatment of PPH. Following the study, there were several product recalls and criminal charges were filed.
- Indonesia: 11.5% of all samples stored in refrigerators failed assays for Active Pharmaceutical Ingredient (API) content, and 15.8% of unrefrigerated samples failed.

- More studies needed.

1. Few incentives to procure quality products
  - Many manufacturers
  - Limited availability of WHO-prequalified products for PPH
  - Price-sensitive market
2. Product is sold wholesale for \$0.15 to \$0.48 per 200µg tablet, with considerable variation. Manufacturers often require large orders.
3. Nine obstetric indications, so the drug is often used off-label
4. Quality concerns about product deterioration, particularly with packaging

Misoprostol is recommended for use where Oxytocin is not available. This is because the cold chain cannot be maintained, or where Oxy isn't available, such as for women who deliver outside of health facilities. This is about half of women in SSA and Southeast Asia.

- Many manufacturers, there are 2 WHO Pre-qualified products, but only one is PQ'ed for PPH.
  - Price varies from \$.15 to \$.48 (Cytotec and a few others). Sold usually in 200 microgram tablets, three needed for prevention of PPH. So cost can go higher.
- Misoprostol has many uses. Originally indicated for gastric ulcers, and still registered for that purpose in many countries. Can also be used to induce and abortion, and for post-abortion care.
- Manufacturing quality still needs more research, but generally not a huge problem. Bigger issue is with packing. With poor packaging, the product deteriorates.

1. Low usage rate by health workers; many not trained to administer the drug properly
2. Various treatment regimens and requirement to mix solutions leads to confusion
3. Health facility availability only 76%; typically not available outside of health facilities, although some pilots are experimenting with loading doses
4. No WHO-prequalified products
5. While the drug is not difficult to manufacture, sterility is essential

Mag Sulfate is the treatment for severe PE/E. 2-8% of pregnancies yearly have PE/E, with some regional variation, 52,000 deaths.

Mag Sulfate is on the WHO's EML and the UN Commission on Lifesaving Commodities list of priority drugs

However, lower usage rates – some health workers are concerned about toxicity to mother and fetus, poor training, requires some training to properly administer, including diluting the medicine and administering different loading and maintenance doses. Different treatment regimens, etc.

Only available in facilities

No PQ'ed products. Generally not hard to manufacture, must be done in a sterile facility, or it can be sterilized after MNFR. Lower quantities needed than for Oxytocin or Misoprostol.

No studies yet on quality of Mag Sulfate in the field, or how it is being administered.

	Approved	In Process	ERP Approved	ERP in Process
Oxytocin	-	1	-	1
Misoprostol	2	-	3	2
Magnesium sulfate	-	1	-	-

\*WHO List of Prequalified Medicinal Products. <http://apps.who.int/prequal/query/ProductRegistry.aspx>.

So how do we assure quality drugs? A few options: Stringent Regulatory Authority (SRA) approval, or WHO prequalification.

WHO PQ process exists to help manufacturers demonstrate the quality of their products in a less expensive way than SRA approval.

TA is available from Concept and others to help, for maternal health drugs.

ERP is a temp approval mechanism.

Mnfrs have been reluctant to go through this process. They say it increases their costs, with no guarantee of additional orders. This is different than with HIV, TB and malaria drugs, which require PQP for Global Fund procurement. That improves likelihood of orders.

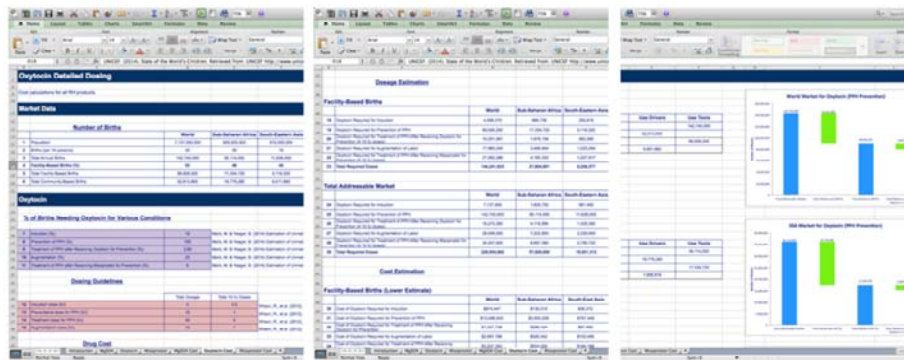
For these three drugs, a lot of the procurement is done by national governments, who do not require PQ.

Additional cost is around 5-12% of the price of the drug.



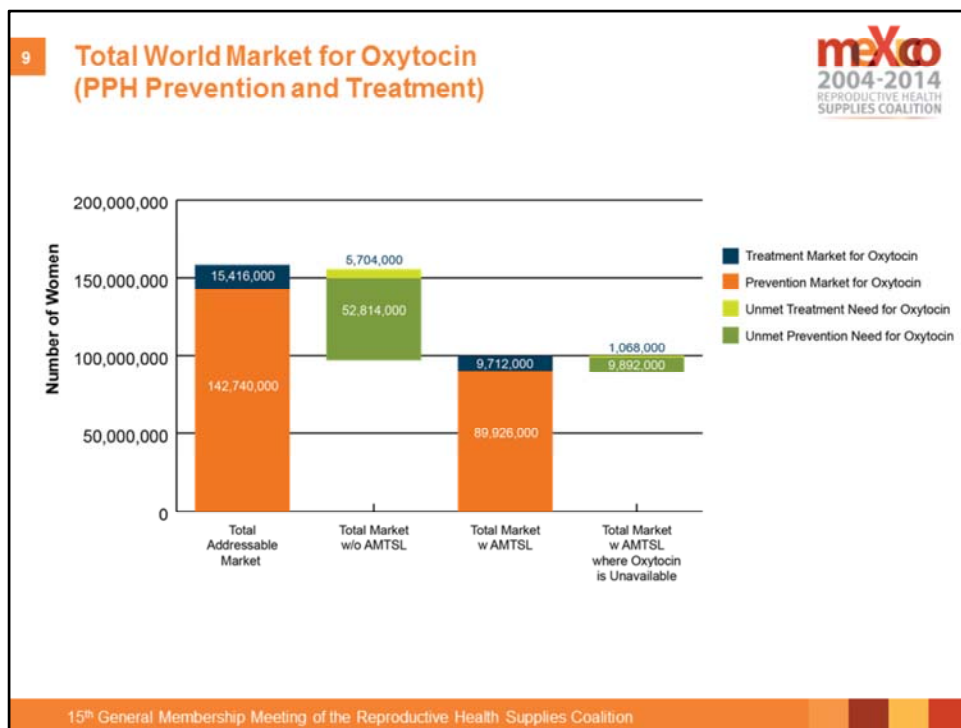
## The RH Assessment Tool

A User-Friendly Tool for Market Estimation



<http://reprolineplus.org/RH-assessments>

Need to add website link when available



**We built a series of tables to understand the size of the market for each drug.**

To interpret this table, start on the right. These smaller numbers are the women who deliver at facilities that do not have Oxytocin. The second from the right is the total market for women delivering in health facilities w AMTSL.

The third bar, in yellow and green, represents the size of the market that is not accessing health care in health facilities, so they have no access to oxytocin. In SSA and SEA, these are half of all women. In this world market table, a higher percentage of women is delivering in health facilities.

Total addressable market is the total size of the market if we removed all of the roadblocks that currently prevent women from accessing Oxytocin. In this case, all women deliver in a facility that has Oxytocin available, and all women worldwide get a preventative dose of Oxytocin when they deliver.

This is the number of treatment doses. For Treatment – light blue and yellow – remember that each of these doses gets four times the amount as the prevention cases, in dark blue.

**Demographic assumptions: Birth rate, PPH prevalence, Facility Based Births, Facility level Oxytocin available**

This graph shows the total number of cases, globally, calling for the use of Oxytocin. The total addressable market for oxytocin is over 142 million prevention cases (dark blue bar) and 15.4 million treatment doses (light blue bar).

The total market for women receiving treatment for AMSTL, or those women delivering in facilities is 90 million prevention cases and 9.7 million treatment cases, although Jhpiego is discounting this by 89% because of lack of availability of oxytocin in health facilities. Where there is no oxytocin available, misoprostol or another drug is administered.

Please note that a treatment dose is 40 IUs of oxytocin, and the chart below only shows cases, not the amount of drug required.

## 10 Total Addressable Market for Oxytocin



		World	Sub-Saharan Africa	Southeast Asia
Induction	Lower limit	\$1,070,000	\$270,000	\$87,000
	Upper limit	\$1,427,000	\$361,000	\$116,000
Prevention of PPH	Lower limit	\$21,411,000	\$5,417,000	\$1,744,000
	Upper limit	\$28,548,000	\$7,222,000	\$2,325,000
Treatment of PPH after Receiving Oxytocin for Prevention	Lower limit	\$2,441,000	\$617,000	\$199,000
	Upper limit	\$3,254,000	\$823,000	\$265,000
Augmentation of Labor	Lower limit	\$4,282,000	\$1,083,000	\$349,000
	Upper limit	\$5,709,000	\$1,444,000	\$465,000
Treatment of PPH after Receiving Misoprostol for Prevention	Lower limit	\$5,138,000	\$1,300,000	\$419,000
	Upper limit	\$6,851,000	\$1,733,000	\$558,000
Total Market	Lower limit	\$35,414,000	\$8,960,000	\$2,885,000
	Upper limit	\$45,791,000	\$11,585,000	\$3,730,000

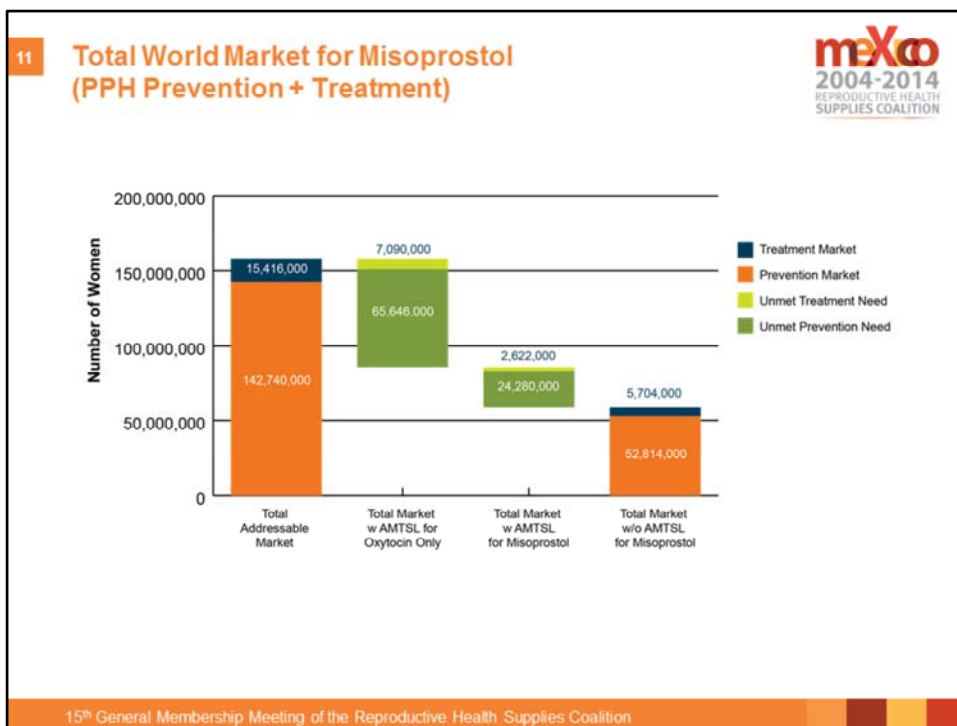
Prices: Lower cost: \$0.15 per 10 IU ampoule

Upper cost: \$0.20 per 10 IU ampoule

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When we figure out the size of the market, we multiplied the number of doses by the cost per dose, and find that the potential size of the Global market is between \$35.4 and \$45.8m.

We included here some additional uses for Oxytocin, including induction and augmentation of labor, and treatment of PPH in women who received a first dose of misoprostol. These are women who would likely have given birth at home, and developed PPH, and were then transported to a health facility for treatment.



**For misoprostol, unlike for oxytocin and magnesium sulfate, it is important to remember that we are focusing only on a part of a much larger market. There is a huge effort to increase availability of misoprostol for abortion and postabortion care. So the work we have done here only demonstrates a part of the market.**

Starting again on the right side, we see the global market today for misoprostol for PPH. These are women delivering outside of facilities. These are not actual orders – although our paper starts to approximate that - but rather shows the size of the potential market today. The second bars from right are the women delivering in health facilities that do not have Oxytocin. I wanted to point out that there is a slight deviation from our numbers with Oxytocin here – that is because we based access to Oxytocin on access to a health facility for delivery – a UNICEF statistic – and for misoprostol, be based the numbers off of access to a skilled provider – which is a World Bank statistic. These figures are very similar, but not the same.

The second bars from right show the total market w AMTSL that receives Oxytocin.

And the bar on the right is the same as the Oxytocin table.

**Demographic Assumptions: Birth rate, PPH prevalence, Births attended by skilled provider, misoprostol facility availability**

- The graph below shows the number of cases per year in which misoprostol is called for.
- The total addressable market is the same for oxytocin and misoprostol, because it is the total number of women requiring a uterotonic for prevention or treatment of PPH. (142.7 million cases for prevention, and 15.4 million cases for treatment.)
- The total market for misoprostol that has no access to AMTSL is about 53million prevention doses, and 5.7 million treatment doses.
- There is also a cohort of women representing 24 million prevention cases and 2.6 million treatment cases, who access facilities that sometimes offer oxytocin, and sometimes offer misoprostol.

## Total Market Size for Misoprostol for Prevention and Treatment of PPH\*

		World	Sub-Saharan Africa	Southeast Asia
<b>Prevention of PPH</b>	Lower limit	\$23,766,000	\$8,451,000	\$2,930,000
	Upper limit	\$76,052,000	\$27,042,000	\$9,377,000
<b>Treatment of PPH</b>	Lower limit	\$1,268,000	\$451,000	\$156,000
	Upper limit	\$4,056,000	\$1,442,000	\$500,000
<b>Total Market</b>	Lower limit	<b>\$25,034,000</b>	<b>\$8,902,000</b>	<b>\$3,086,000</b>
	Upper limit	<b>\$80,108,000</b>	<b>\$28,484,000</b>	<b>\$9,877,000</b>

\*Upper limit uses a price of \$0.48 per 200µg tablet

Lower limit uses a price of \$0.15 per 200µg tablet

Prevention dose: 600µg

Treatment dose: 800µg

Upper Cost for one 5g/10mL ampule	\$1.60
Lower Cost for one 5g/10mL ampule	\$0.50
Upper Cost to Treat One PE/E Case with MgSO <sub>4</sub> (Pritchard)	\$12.80
Lower Cost to Treat One PE/E Case with MgSO <sub>4</sub> (Pritchard)	\$4.00
Upper Cost to Treat One PE/E Case with MgSO <sub>4</sub> (Zuspan)	\$9.60
Lower Cost to Treat One PE/E Case with MgSO <sub>4</sub> (Zuspan)	\$3.00

\* Excluding related products and equipment, including IV solution, IV and IM equipment, and calcium gluconate

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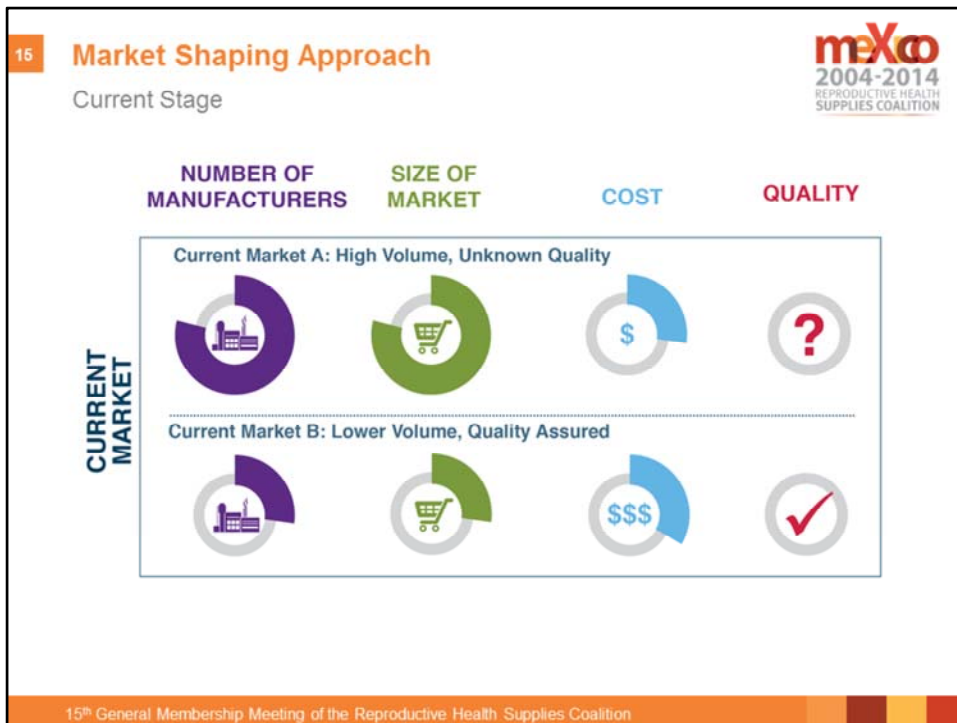
Moving on to Magnesium Sulfate, this is a bit more challenging to model, because there are multiple treatment regimens. We modeled the two most common, Pritchard's and Zuspan. Bangladesh and a few other countries use a lower-dose model.

There are also multiple ampule sizes for mag sulfate. We simplified by focusing on a 5g in 10mL ampule, but we also see lots of 5mL and 20mL ampules. All of these things are potentially complicated for health workers.

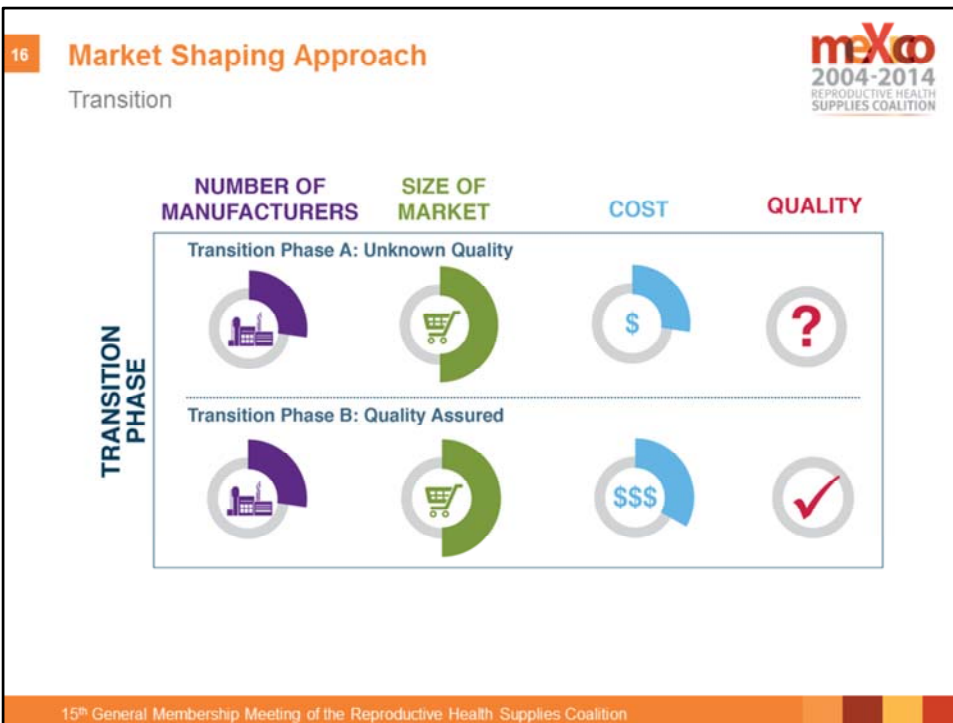
So while the cost per dose is relatively inexpensive, you can see that by the time a full course of treatment is provided, this could be an expensive treatment for a health center, especially including all of the peripherals.



	Pritchard's High Cost	Pritchard's Low Cost	Zuspan High Cost	Zuspan Low Cost
<b>Global high scenario</b>	\$32,230,000	\$10,072,000	\$24,172,000	\$7,554,000
<b>Global low scenario</b>	\$11,511,000	\$3,597,000	\$8,633,000	\$2,698,000
<b>Sub-Saharan Africa high scenario</b>	\$6,213,000	\$1,941,000	\$4,660,000	\$1,456,000
<b>Sub-Saharan Africa low scenario</b>	\$2,219,000	\$693,000	\$1,664,000	\$520,000
<b>Southeast Asia high scenario</b>	\$1,834,000	\$573,000	\$1,375,000	\$430,000
<b>Southeast Asia low scenario</b>	\$655,000	\$205,000	\$491,000	\$153,000



- Work with all procurers of oxytocin, misoprostol, and magnesium sulfate on agreements that they will only procure drugs that are SRA approved, WHO prequalified, or procured from internationally approved procurement agencies that have a quality control and quality assurance process.
- Improve procurement guidelines and procedures, strengthen national drug regulatory agencies and customs functions so that only drugs with Market Approval can enter the country
- Stricter enforcement of national guidelines
- Improve forecasting through technical assistance, which will prevent stockouts and help to promote reasonable drug prices
- Strengthen the cold chain for oxytocin
- Increase awareness about quality issues
- Train health care workers on the administration of these drugs, and promote task-shifting
- Conduct routine quality audits of products in country, at all levels of care
- Ensure manufacturers make reasonable margins and are incentivized to produce quality drugs



- Work with all procurers of oxytocin, misoprostol, and magnesium sulfate on agreements that they will only procure drugs that are SRA approved, WHO prequalified, or procured from internationally approved procurement agencies that have a quality control and quality assurance process.
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## Market Shaping Approach

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Final



1. There is a market for high-quality products
  - Oxytocin: \$4.3-\$5.7m in SSA, \$1.3-1.7m SEA
  - Magnesium sulfate: \$1.5-\$6.2m in SSA, \$430,000-\$1.8m in SEA
  - Misoprostol: \$13.8-\$44.2m in SSA, \$4.5m-\$14.5m in SEA (only for PPH)
2. There are concerns about product quality. It is essential for procurers to only procure SRA-approved or WHO pre-qualified products, or products that are procured from internationally approved procurement agencies that have a quality control and quality assurance process.
3. Procurement of all three products is likely to grow
4. Manufacturers can make a reasonable profit producing quality products, but procurers need to purchase them
5. Improving access to high-quality oxytocin, misoprostol, and magnesium sulfate requires action from many stakeholders

**Support for this project was provided by PATH on behalf of the Reproductive Health Supplies Coalition****Contributors:**

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Jhpiego Accelovate Program:  
<http://www.jhpiego.org/content/accelovate-program>

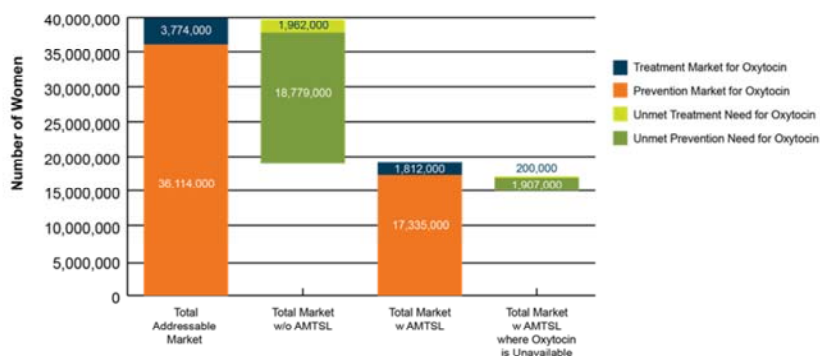
Reproline Plus:  
<http://reprolineplus.org/RH-assessments>

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Additional Slides



## Sub-Saharan Africa Market for Oxytocin (Prevention and Treatment)



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### Demographic Assumptions: Birth rate, PPH prevalence, Facility Based Births, Facility level Oxytocin available

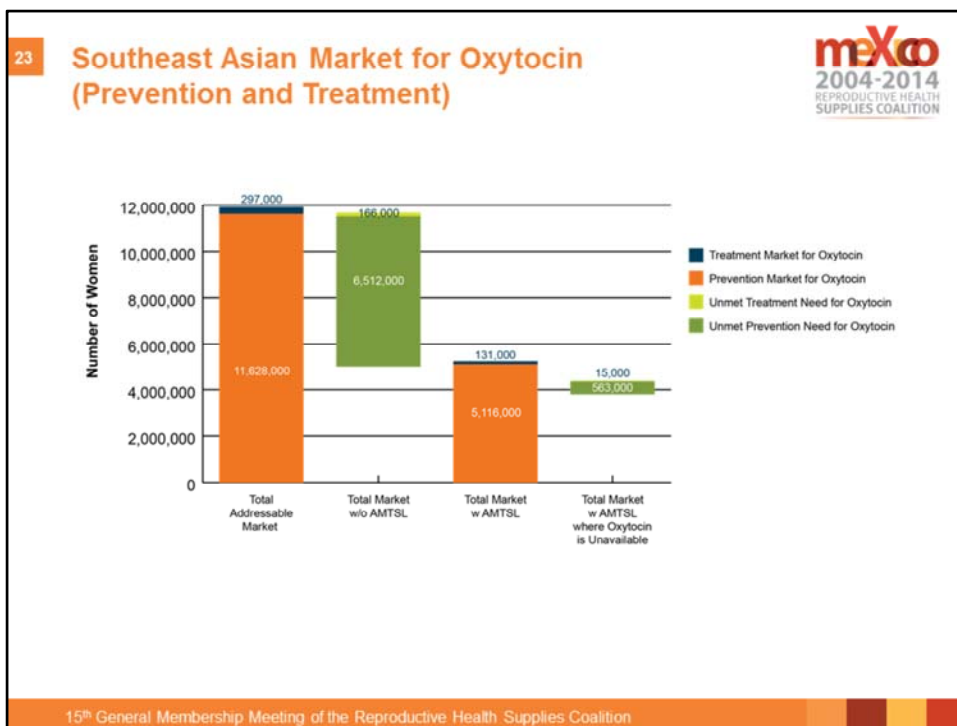
This graph shows the total number of cases, in SSA, calling for the use of Oxytocin. In Sub-Saharan Africa, there are 36 million annual births, each one of which should receive a preventative dose of oxytocin.

However, because just over half of African women deliver outside of a health facility, the total market for preventative doses is half the total addressable market, or 17.3 million cases

The total market without AMTSL, or that delivers outside of facilities, is 18.8 million cases.

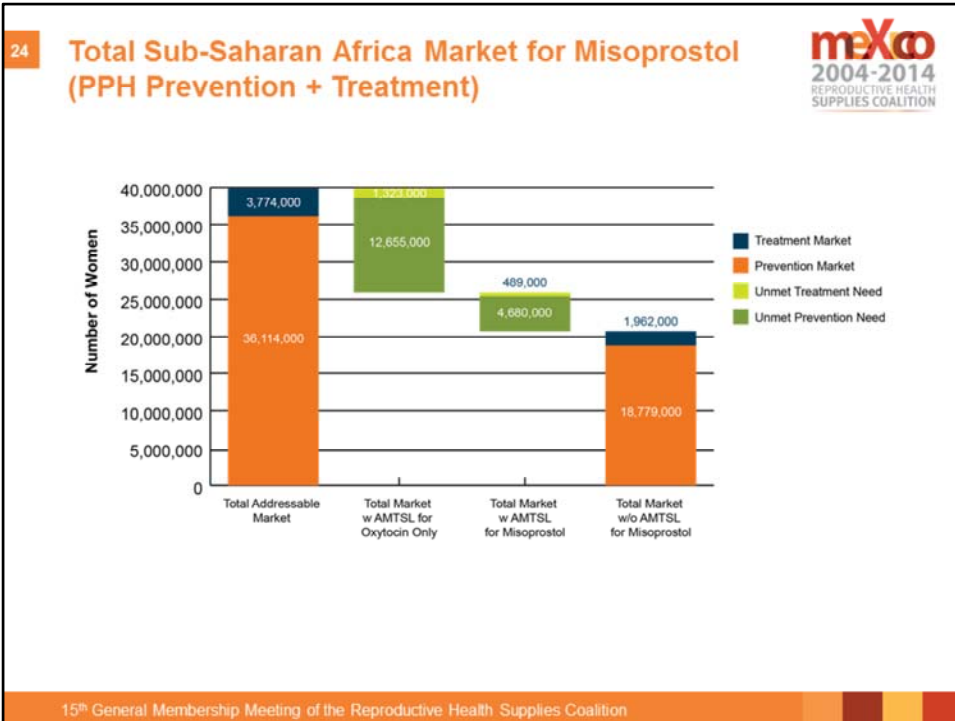
The number of prevention and treatment doses in health facilities is also reduced because only 89% of health facilities have oxytocin available.

For treatment, there are 3.8m cases in the total addressable market, although it is important to bear in mind that these cases require four times the prevention dose.



**Demographic Assumptions: Birth rate, PPH prevalence, Facility Based Births, Facility level Oxytocin available**

- In Southeast Asia, there are 11,628,000 births annually.
- The rate of PPH is significantly lower, about 2.6%, so the number of treatment doses in the total addressable market is 300,000.
- According to the World Bank, fewer than half of Southeast Asian women deliver at health facilities with access to AMTSL, while over half deliver at home.
- The total market without AMTSL is 6.5m preventative doses, and 166,000 treatment doses.



- **Demographic Assumptions: Birth rate, PPH prevalence, Births attended by skilled provider, misoprostol facility availability**

In Sub-Saharan Africa, there are 36 million annual births, half of which take place outside of health facilities.

There is a need for 19 million prevention doses, and nearly 2 million treatment doses, as well as a percentage of the cases in the third column. It should be noted again that there are other uses for misoprostol, and this paper is only quantifying the need for the postpartum uses of the drug.

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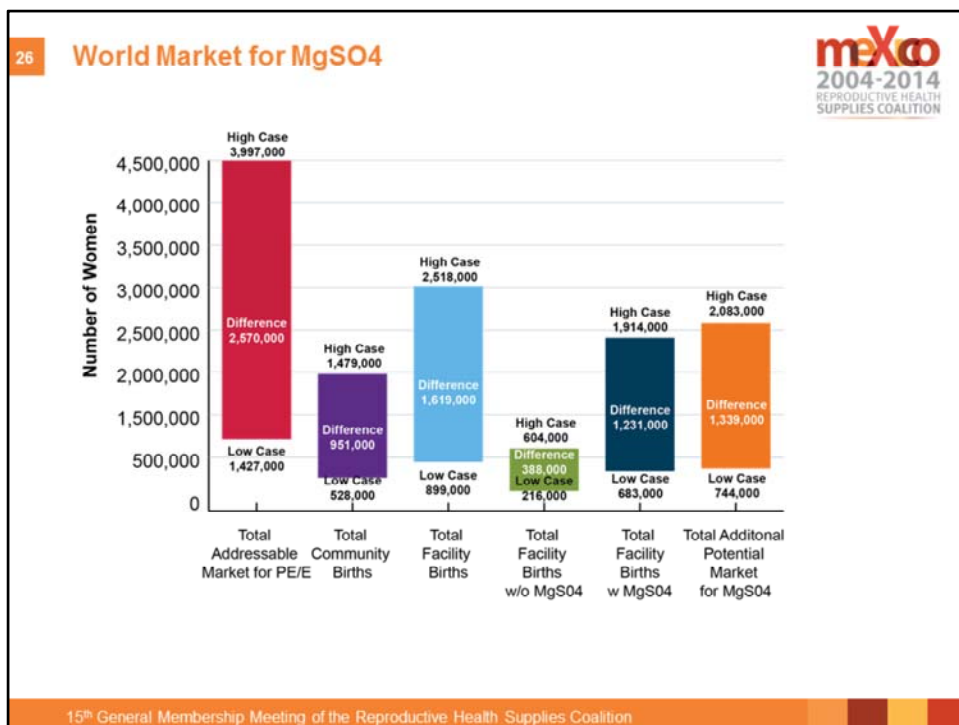
## Total Southeast Asian Market for Misoprostol (PPH Prevention + Treatment)

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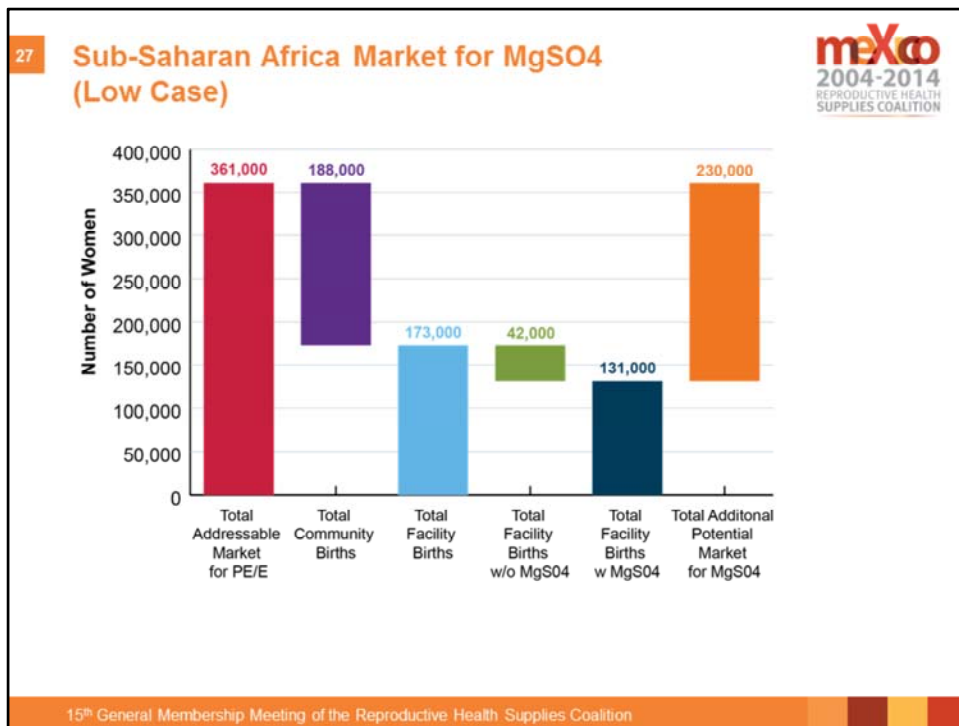
- **Demographic Assumptions: Birth rate, PPH prevalence, Births attended by skilled provider, misoprostol facility availability**
- In Southeast Asia, there are 11.6 million births annually.
- The rate of PPH is significantly lower, about 2.6%, and half of women deliver outside of a health facility.
- The total addressable market for misoprostol for PPH is 166,000 treatment cases, and 6.5 million prevention cases.



### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

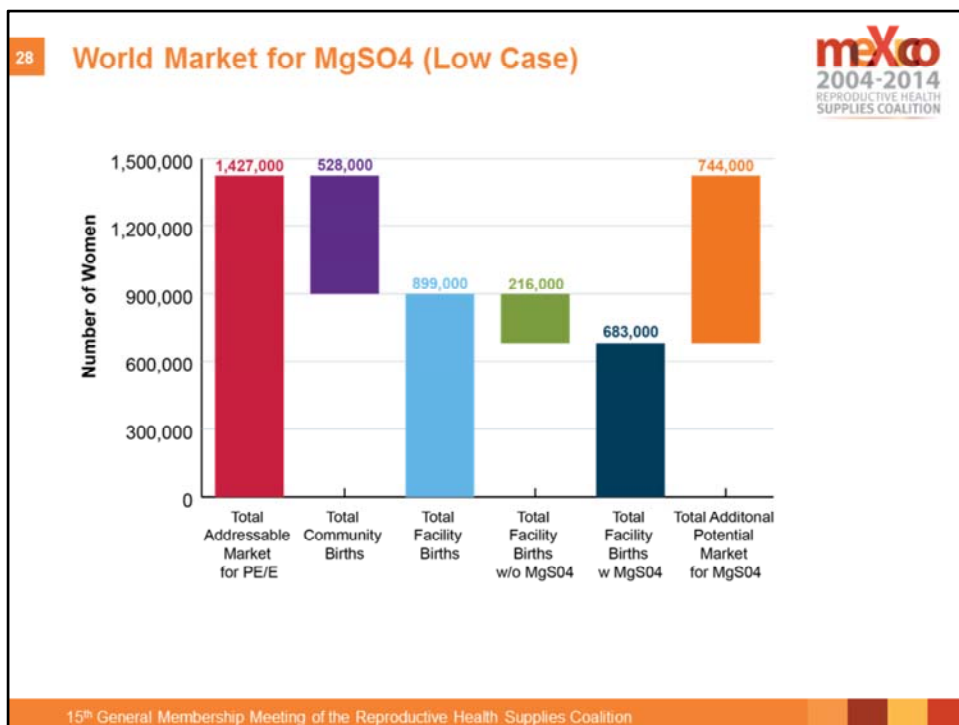
This graph shows the difference between our high and low scenario estimations. In the low case scenario, the total addressable market is nearly 1.5 million cases, whereas in the high case, the total addressable market is 4 million cases. The true market size is likely somewhere between these estimations. The total additional potential market for manufacturers is between 743,000 cases and 2 million cases.

If countries can increase the availability of MgSO<sub>4</sub> and increase the rate of facility based delivery, the market size for the drug could increase and be sufficiently large enough to incentivize manufacturers to produce the product.



### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

In SSA, the lower case scenario estimates 361,000 cases per year requiring MgSO<sub>4</sub>. Because half of the women in SSA deliver outside health facilities, and many facilities do not have MgSO<sub>4</sub>, only 132,000 cases of women needing the drug have access to it.

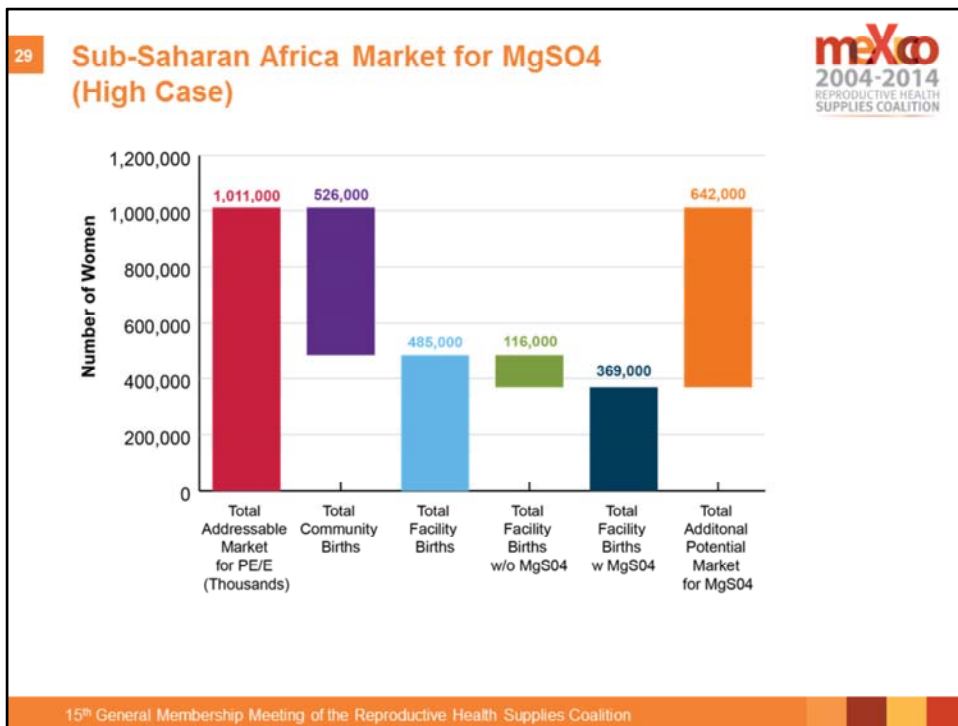


### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

Here, we project the world market for MgSO<sub>4</sub>, assuming the lower prevalence rate of PE/E among pregnancies.

Total addressable market is nearly 1.5 million cases, but we adjust with discounts for women delivering outside of facilities and for facilities where MgSO<sub>4</sub> is unavailable.

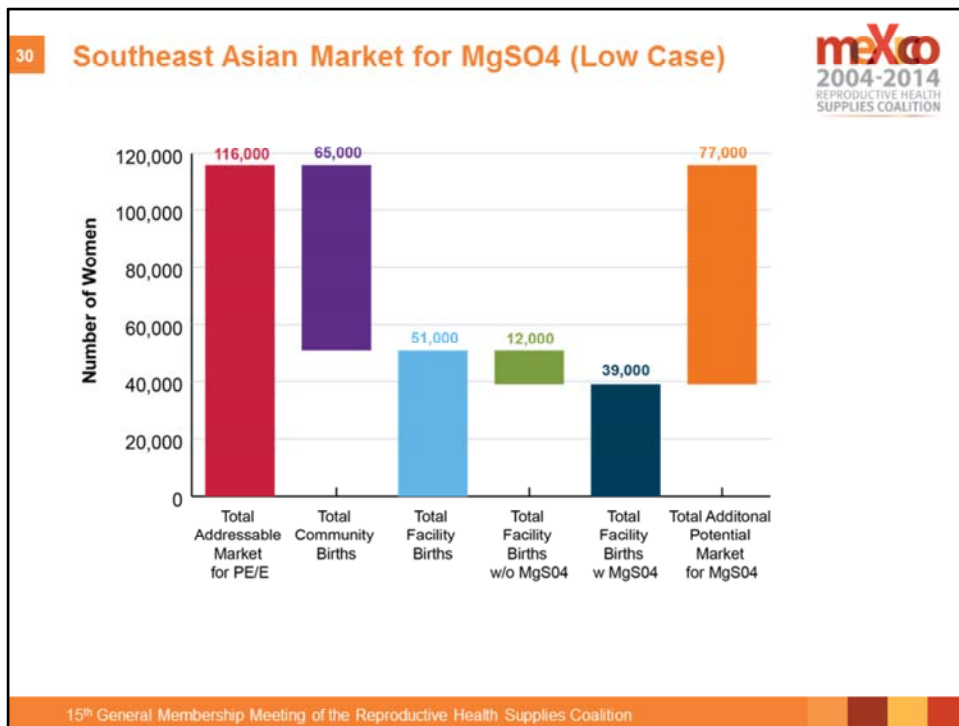
We arrive at the final green bar, which shows that even in the low case scenario, nearly 750,000 cases of severe PE/E remain treated with MgSO<sub>4</sub> per year.



**Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability**

In our high case, the total addressable market in SSA is over 1 million cases, with reality being that only 368,883 women needing the drug having access to it. An additional 642,309 treatments may be needed each year.

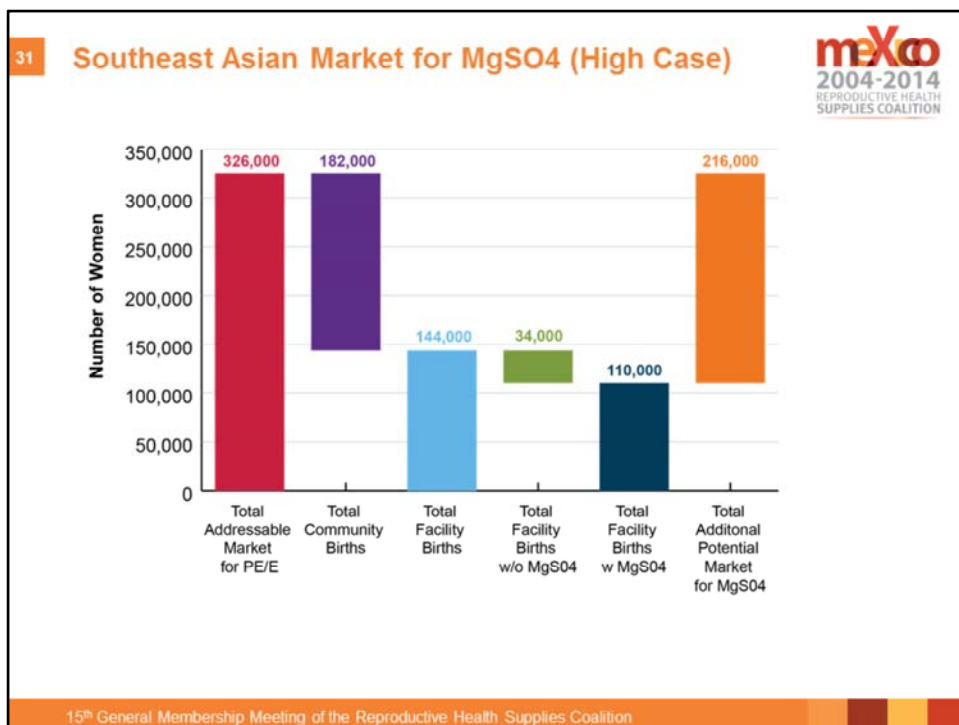




### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

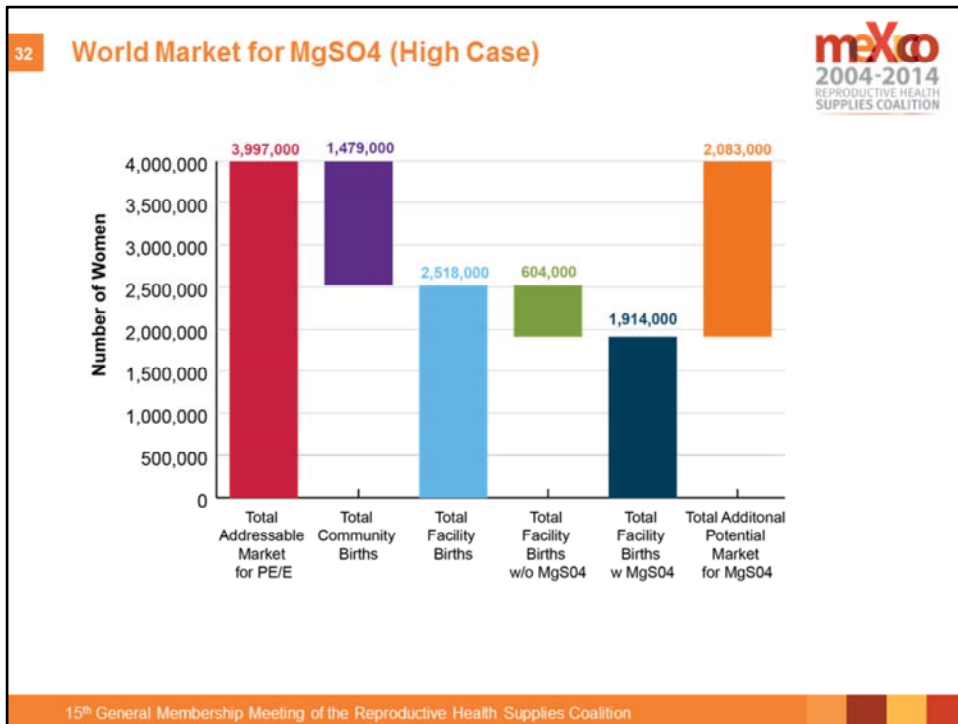
Southeast Asia has a smaller market size compared to SSA, with 11.6 million annual births, compared to 26 million births in SSA. As a result, we'll see fewer cases of severe PE/E requiring treatment with MgSO<sub>4</sub>

Using the lower PE/E assumption, we estimate a total addressable market of 117,000 treatments, with 77,000 not being currently met. There still is a large gap for manufacturers to fill.



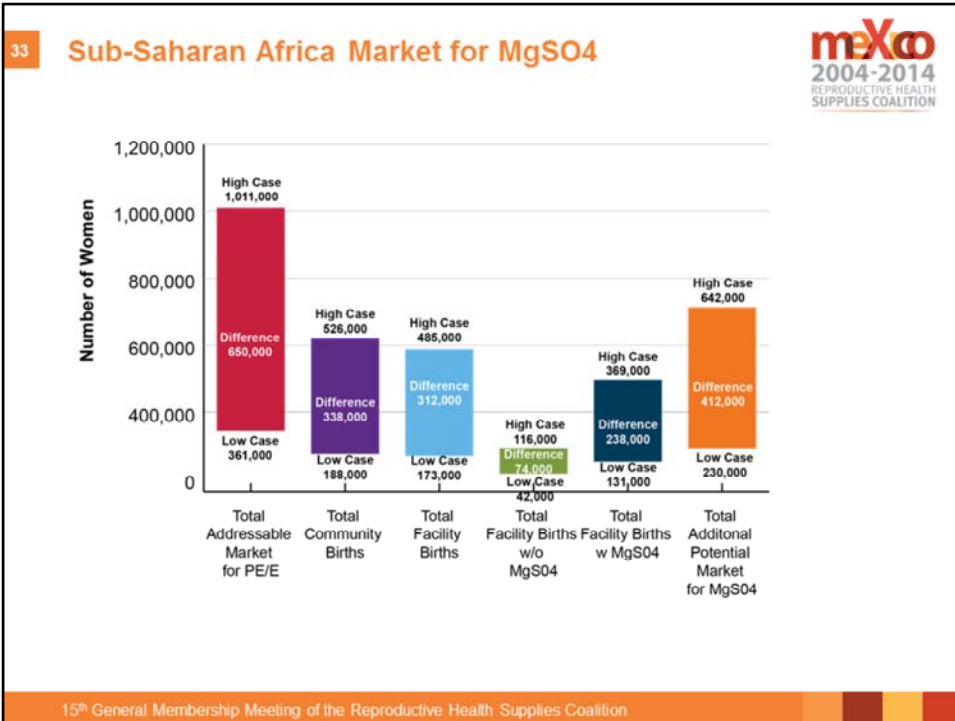
**Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability**

In the high case scenario, more than 325,000 women require treatment with MgSO<sub>4</sub> each year. The unmet need is 216,000 treatments.



- **Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability**

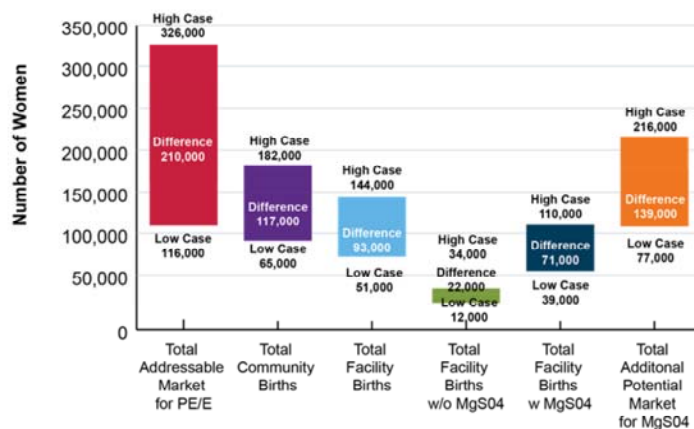
This graph uses the same methodology, but estimates the total addressable market given the higher PE/E prevalence assumption of 2.8% of all pregnancies. We see the potential global market is nearly 4 million treatment cases per year, with just over 2 million cases remaining untreated by MgSO<sub>4</sub>, representing a large additional potential market.



### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

Here we show the gap between our high and low scenarios (the difference in PE/E prevalence during pregnancy).

The total addressable market for severe PE/E is between 361,000 and 1 million cases, with unmet need between 229,000 and 642,000 cases, representing a considerable additional need for the drug in Sub-Saharan Africa.


 15<sup>th</sup> General Membership Meeting of the Reproductive Health Supplies Coalition

### Demographic Assumptions: Birth rate, Facility births, PE/E prevalence, MgSO<sub>4</sub> availability

Here we show the difference in market estimations, between the high and low scenarios. The real need is likely somewhere between these estimates. The additional market potential is between 77,000 and 217,000 cases.