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SPECIAL ARTICLE

Assessing the global availability of misoprostol

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ABSTRACT

Objective: To assess the worldwide availability of misoprostol. Documenting the extent of misoprostol use in obstetrics-gynecology is difficult because the drug typically is unregistered for such indications. *Methods:* Data for 2002–2007 on annual sales (measured in weight) to hospitals and retail pharmacies, plus manufacturer prices per 200-μg misoprostol, were analyzed for medications containing misoprostol alone or combined with a nonsteroidal anti-inflammatory drug (NSAID); regional and country-specific trends were identified. Consumer prices per pill are documented for all formulations of registered medications. *Results:* Of the misoprostol sold worldwide, 70% was misoprostol-NSAID-combination drugs; of this, 91% was sold in North America and Western Europe. Asia sold the most misoprostol-only drugs; sales increased dramatically in Bangladesh (by 128%) and India (646%), where various low-price brands are sold. Misoprostol sales decreased in Latin America but increased in the Middle East-North Africa and Sub-Saharan Africa; these regions generally had low amounts sold per population. *Conclusion:* Availability is improving in some low-income regions where misoprostol could significantly reduce maternal deaths due to postpartum hemorrhage and unsafe abortion.

1. Introduction

Misoprostol, a synthetic prostaglandin E_1 analogue, is approved in more than 80 countries for the prevention and treatment of gastric ulcers caused by long-term nonsteroidal anti-inflammatory drug (NSAID) use. A burgeoning literature and experience also support its use in obstetrics-gynecology [1–3]. Effective in labor induction, the treatment of incomplete or missed abortion, the prevention and treatment of postpartum hemorrhage (PPH), and the elective termination of pregnancy, misoprostol is considered potentially lifesaving, particularly in low-resource settings [4–6].

In the United States, most of Western Europe, and several Asian and African countries, misoprostol is part of the approved regimen for inducing abortion; the World Health Organization recommends mifepristone combined with misoprostol as the most effective method of medical abortion [7]. Where mifepristone is unavailable, however, misoprostol alone is being used by providers to terminate unwanted pregnancies and by women to self-induce abortion [8]. Particularly important is the use of misoprostol to prevent PPH, the leading cause of maternal mortality worldwide [9]. In some low-resource settings where other uterotonics are unavailable or cannot be properly stored, or where the skilled attendants needed for intravenous or intramuscular administration are in short supply, misoprostol—a fairly inexpensive, heat-stable drug that can be self-administered—is used to effectively treat and prevent PPH [5,8]. Researchers recently found that making misoprostol readily available in low-resource areas for use in termination of pregnancy and management of PPH would do more than any other realistically achievable, sustainable, large-scale intervention to save the lives of women at risk for death by maternal causes [10].

Although misoprostol's benefits in obstetrics-gynecology are well-established [1–3] and the drug's potential to significantly reduce maternal mortality in low-income countries is clear [5,8,10], in most places misoprostol is available for reproductive health care through off-label use only. Relatively few countries have misoprostol brands registered for obstetric-gynecologic indications (Table 1). Although many medications are used off-label [11], this status for misoprostol severely limits its application and complicates efforts to document its use.

We analyzed sales of all misoprostol-containing drugs sold in a recent 6-year period, identifying trends by region and country. The goals were to assess the availability of misoprostol in high- and low-resource regions and to roughly gauge the amount of misoprostol drug-use for obstetric-gynecologic indications. In assessing the drugs' availability and uses in various regions, we consider pertinent demographic, historical, and legal factors that help explain the observed trends and identify areas of unmet need. Monitoring the availability of misoprostol is an important step toward ensuring continued access to the drug.

2. Methods

Ipas purchased sales data for 2002–2007 on all misoprostol medications from IMS Health (Norwalk, CT, USA). We report annual

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Table 1
Examples of countries with proprietary misoprostol drugs licensed for reproductive health indications.

Country	Brand (Manufacturer)	Approved Ob-Gyn indication
Brazil, Peru	Prostokos (Hebron, Caruaru PE, Brazil)	Labor induction, uterine evacuation after fetal death, legal termination of pregnancy
Egypt	Vagiprost (Adwia, El Oubor, Egypt)	Labor induction
France	Gymiso (HRA Pharma, Paris, France)	Legal termination of pregnancy
Russia	Mirolut (Mir-Pharm, Moscow, Russia)	Termination of pregnancy in combination with mifepristone
	Mizoprostol (Beijing Zizhu Pharmaceutical Co., Beijing, China), Beijing, China)	Termination of pregnancy in combination with miferpistone, treatment of PPH
Spain	Misive/Bial (Madrid, Spain)	Medical termination of pregnancy (with or without mifepristone)
	Misofar/Bial (Madrid, Spain)	Dilatation of cervix, treatment of incomplete or missed spontaneous abortion or after intrauterine fetal death.
India	Cytolog (Zydus Cadila, Gujarat, India)	Induction of labor, cervical ripening, termination of pregnancy
	Medabon (Sun Pharma, Mumbai, India)	Medical Termination of pregnancy up to 63 days gestation
	Misoprost (Cipla Pharmaceuticals, Mumbai, India)	Cervical ripening, termination of pregnancy, prevention and treatment of PPH
	Prestakind (Mankind, New Delhi, India)	Induction of labor, cervical ripening, termination of pregnancy
	Zitotec (Sun Pharma, Mumbai, India)	Induction of labor, cervical ripening, termination of pregnancy, prevention and treatment of PPH
Nepal	Isovent (Square Pharmaceuticals, Dhaka, Bangladesh)	Termination of pregnancy, prevention and treatment of PPH
	Misoprost (Cipla Pharmaceuticals, Mumbai, India)	Termination of pregnancy
	Zitotec (Sun Pharma, Mumbai, India)	Termination of pregnancy, prevention and treatment of PPH
Bangladesh	GMisoprostol (Gonoshasthaya Parmaceuticals, Dhaka, Bangladesh)	Labor induction, prevention and treatment of PPH
	Isovent (Square Pharmaceuticals, Dhaka, Bangladesh)	Labor induction, prevention and treatment of PPH
Ghana	Misotac (Sigma Pharmaceutical Industries, Menofya, Egypt)	Prevention and treatment of PPH
Kenya	Isovent (Square Pharmaceuticals, Dhakka, Bangladesh)	Cervical ripening, missed or incomplete abortion, prevention and treatment of PPH
Nigeria	Mizoprostol (Beijing Zizhu Pharmaceutical Co., Beijing, China), Beijing, China)	Prevention and treatment of PPH
Sudan	Misotac (Sigma Pharmaceutical Industries, Menofya, Egypt)	Prevention and treatment of PPH
Tanzania	Misotac (Sigma Pharmaceutical Industries, Menofya, Egypt)	Prevention and treatment of PPH
Uganda	Misotac (Sigma Pharmaceutical Industries, Menofya, Egypt)	Prevention and treatment of PPH
Zambia	Misotac (S Sigma Pharmaceutical Industries, Menofya, Egypt)	Prevention and treatment of PPH
	Mizoprostol (Beijing Zizhu Pharmaceutical Co., Beijing, China)	Termination of pregnancy in combination with mifepristone

Notes:
In several other countries, including the United States, misoprostol is approved for obstetric indications, but no dedicated brand is registered in the country for that purpose.
PPH stands for postpartum hemorrhage. Medabon combines 1 tab of mifepristone 200 mg and 4 tabs of misoprostol 200 μmg.Some of the brands listed above may carry additional indications.

Table 2
Total amount (weight) of misoprostol sold annually, by region and country, according to drug type[a].

Region and country[d]	Misoprostol-only drugs			Misoprostol–NSAID drugs		
	Sales in 2007 ($\mu g \times 10^6$)	% change 2002–2007	μg/population in 2007	Sales in 2007 ($\mu g \times 10^6$)	% change 2002–2007	μg/population in 2007
Global (Total)	**39 051.0**	**−15**	**3.7**	**90 249.0**	**−4**	**8.6**
North America	**6489.5**	**−29**	**23.6**	**30 580.1**	**−1**	**91.6**
United States	5523.2	−20	18.5	16 806.5	−23	56.3
Canada	951.6	−57	28.8	13 688.9	49	413.6
Puerto Rico	14.7	−47	3.8	84.7	1	21.6
Western Europe	**6020.6**	**−55**	**15.2**	**51 159.1**	**−14**	**128.9**
United Kingdom	536.6	−39	8.9	16 780.7	−9	276.9
France	1848.5	−39	29.5	7782.3	−4	124.0
Spain	427.1	−47	10.6	8386.5	−28	207.6
Germany	149.0	−74	1.8	4490.4	−34	54.5
Netherlands	38.3	−55	2.3	4653.9	3	282.2
Italy	2458.9	−67	42.3	1829.6	−33	31.5
Sweden	121.2	−42	13.4	1237.8	−23	137.3
Denmark	24.0	14	4.4	989.8	38	181.6
Switzerland	56.6	−5	7.5	897.6	8	119.3
Austria	25.8	−64	3.2	1184.2	30	144.6
Portugal[e]	121.8	−37	11.5	1112.1	−5	104.9
Norway	40.0	38	8.7	784.9	11	170.2
Ireland[e]	16.7	−19	4.1	755.2	52	185.9
Finland	37.3	−8	7.1	204.6	−53	39.1
Luxembourg[e]	2.6	4	5.5	39.7	−32	83.6
Belgium	29.8	69	2.9	29.6	−21	2.9
Greece[e]	86.3	33	8.1	0.2	−95	0.0
Eastern Europe	**22.7**	**−53**	**0.1**	**760.2**	**55**	**3.3**
Romania	—[b]	—	—[b]	103.5	70	4.6
Estonia	0.1	−87[c]	0.1	11.9	−64	9.0
Slovenia	0.3	18[c]	0.2	—[b]	—	—[b]
Lithuania	2.5	62	0.7	—[b]	—	—[b]
Latvia	0.1	−69	0.1	0.0	−100	0.0
Czech Republic	0.0	−94	0.0	—[b]	—	—[b]
Slovakia	—[b]	—	—[b]	572.9	160	105.3
Poland	13.0	−17	0.3	71.6	−30	1.9
Russia	6.6	−78	0.1	0.3	−100	0.0
Asia	**21 524.3**	**7**	**6.4**	**4820.6**	**216**	**1.4**
Japan	10 450.0	−3	82.0	—[b]	—	—[b]
India	5494.5	646	5.0	288.8	268[c]	0.3
South Korea	3388.2	−27	69.4	—[b]	—	—[b]
Pakistan[e]	—[b]	—	—[b]	2531.1	254	15.3
Indonesia	223.9	116	0.9	—[b]	—	—[b]
China[f]	1343.4	67	1.0	0.6	—	—[b]
Bangladesh[e]	257.2	128	1.8	1911.3	817[c]	13.0
Malaysia	89.5	0	3.7	—[b]	—	—[b]
Australia	87.0	−47	4.3	40.7	−43	2.0
Hong Kong	46.2	−54	6.7	4.1	−94	0.6
Taiwan	32.3	−58	1.4	44.1	−66	1.9
Thailand[f]	62.8	−42	1.0	—[b]	—	—[b]
New Zealand	35.9	−90	8.8	—[b]	—	—[b]
Singapore	13.6	5	3.0	—[b]	—	—[b]
Philippines	—[b]	—	—[b]	—[b]	—	—[b]
Latin America	**2637.3**	**−17**	**5.1**	**1053.3**	**−30**	**2.1**
Mexico[e]	1157.2	−13	10.8	554.7	−31	5.2
Argentina[e]	—[b]	—	—[b]	362.5	−34	9.1
Venezuela[e]	773.5	26	30.1	105.5	−3	4.1
Central America[e]	147.4	16	3.8	—[b]	—	—[b]
Colombia[e]	92.3	−87	2.1	—[b]	—	—[b]
Ecuador[e]	251.5	25	18.6	20.4	1605[c]	1.5
Dominican Republic[e]	137.6	−10	15.0	10.1	−37	1.1
Uruguay[e]	11.2	261	3.3	—[b]	—	—[b]
Chile[e]	21.6	−2	1.3	—[b]	—	—[b]
Peru[e]	44.8	−10	1.6	—[b]	—	—[b]
Brazil[e]	0.3	16[c]	0.0	—[b]	—	—[b]
Sub-Saharan Africa	**477.2**	**27**	**3.0**	**870.2**	**−9**	**5.5**
South Africa	364.8	30	8.3	870.2	−9	19.7

(continued on next page)

Table 2 (*continued*)

Region and country[d]	Misoprostol-only drugs			Misoprostol–NSAID drugs		
	Sales in 2007 (μg × 10^6)	% change 2002–2007	μg/ population in 2007	Sales in 2007 (μg × 10^6)	% change 2002–2007	μg/ population in 2007
Francophone West Africa[e]	112.4	18	0.7	0.0	−95	0.0
Middle East/ North Africa	**1879.4**	**86**	**8.71**	**602.5**	**585**[g]	**2.8**
Morocco[e]	—[b]	—	—[b]	225.3	—	6.6
Tunisia[e]	—[b]	—	—[b]	177.7	—	17.1
Egypt[e]	856.4	1022	10.9	—[b]	—	—[b]
Lebanon[e]	114.2	5	29.5	5.7	−67	1.5
Jordan[e]	47.4	71	8.0	0.0	−100	—[b]
Israel	4.5	−40	0.7	9.1	−87	1.4
Turkey	856.9	9	12.2	587.7	—	8.4

[a] Unless otherwise indicated, data shown are total annual retail pharmacy and hospital sales. NSAID; nonsteroidal anti-inflammatory drug.

[b] Drug not sold or information unavailable. Sales in 2007 were zero or negligible.

[c] Percentage change from first year for which data are available (2006 for Slovenia, 2004 for Bangladesh, 2005 for the others) to 2007; values of -100% indicate that the drug was not sold in 2007.

[d] North America category excludes Mexico (which is listed under Latin America); United States excludes Puerto Rico. Central America consists of Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, Panama. Francophone West Africa comprises Côte d'Ivoire, Cameroon, Gabon, Senegal, Congo Brazzaville, Guinea, Guinea-Bissau, Benin, Togo, Mali, Burkina Faso.

[e] Sales to retail pharmacies only. *Note:* Hospital sales in Europe, Canada, and the United States vary from 5% to 25% of total misoprostol-only drug sales. We estimate that hospital sales in Latin America and other regions follow similar trends except in Brazil, where a dedicated misoprostol brand for obstetrics-gynecology, Prostokos, is sold exclusively to hospitals and hospital pharmacies.

[f] Sales to hospitals only.

[g] Based on sales data for Tunisia and Morocco for 2007.

sales to wholesalers, retail pharmacy outlets, and hospitals in 64 countries for the two misoprostol-drug categories: (1) products such as Cytotec (Pfizer, New York, USA), containing misoprostol as the sole active ingredient (misoprostol-only drugs); and (2) medications such as Arthrotec (Pfizer), combining misoprostol with an NSAID (misoprostol-NSAID drugs).

Most tablets contain 200 μg of misoprostol, although some brands use different formulations. Thus, to compare sales across brands and countries, we calculated the total amount of misoprostol in weight (measured in μg) of all misoprostol-containing drugs (rather than the total number of pills) sold annually in each region and country. For each country, we calculated the mean manufacturer selling price for 200 μg of misoprostol by using historical data on misoprostol sales (in US$) divided by the total national weight sold annually. Mean manufacturer selling prices per region were calculated as the average among countries in the region.

Ipas also purchased a global report of 2007 prices for misoprostol pills at the public level (i.e., from pharmacies to consumers).

2.1. Data limitations

IMS tracks pharmaceutical sales globally by auditing distribution channels. Data collection varies by country, depending on how the product is distributed through these channels. Typically, most retail pharmacies and wholesalers (>80%) are sampled. For each country, the collected data are extrapolated to estimate sales nationally across all retail pharmacies. However, IMS normally audits no other channels, such as sales to government institutions and nonprofit organizations. In addition, in some countries IMS lacks permission to collect hospital data; for these countries (noted in Table 2), the data may be understated.

More importantly, IMS does not collect data in countries of potential interest (e.g., Vietnam, Bolivia, multiple African countries). In other instances, they combine data from multiple countries (e.g., Central America). Finally, IMS tracks registered products only; in any given country, sales of unregistered drugs in the black market (although perhaps initially purchased and captured elsewhere) are undocumented.

3. Results and discussion

3.1. United States, Canada, Western Europe

Seventy percent of all the misoprostol sold worldwide is the combination misoprostol-NSAID drugs; and 91% of those sales are to Western Europe, Canada, and the United States (Figs. 1 and 2). Some experts consider misoprostol an outdated drug for its initially approved indication [12]—ulcer prevention for long-term NSAID treatment. However, we believe these findings suggest otherwise. Given that in Western Europe, the United States, and Canada, misoprostol

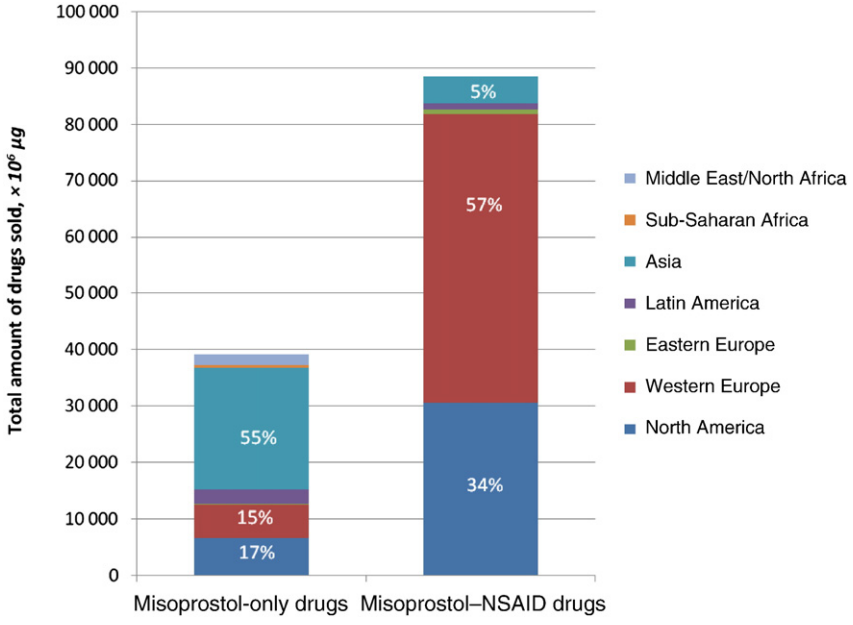

Fig. 1. Global misoprostol market (sales in weight), by drug type, 2007.

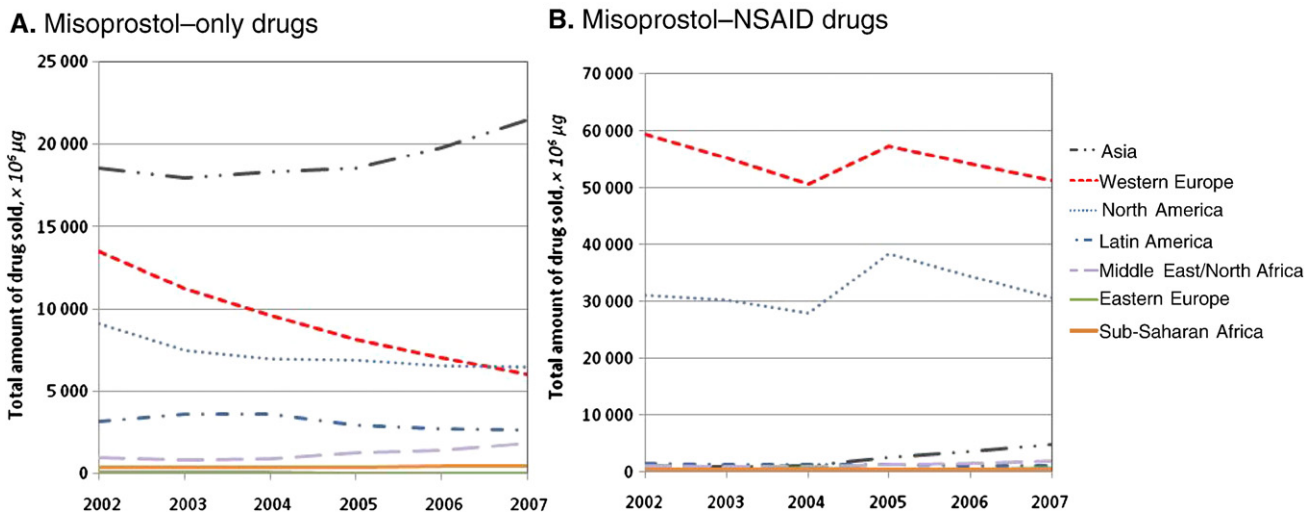

Fig. 2. Total amount (weight) of misoprostol sold per year, by drug type, according to region, 2002–2007.

medications can be obtained explicitly for obstetric-gynecologic uses with relative ease, there is no need to purchase combination misoprostol-NSAID drugs under the guise of needing the medication for gastrointestinal-related purposes. Moreover, misoprostol-only drugs often cost less than misoprostol-NSAID products do in these countries (Fig. 3). Thus, we conclude that the bulk of misoprostol drugs purchased worldwide is probably used for its initially approved indication.

In these locations, sales of misoprostol-NSAID drugs initially declined, reflecting a decreasing need for misoprostol's gastroprotective properties since the introduction of cyclooxygenase-2 (COX-2) inhibitors, a new generation of arthritis medications with reduced gastrointestinal complications, in the 1990s. Sales of misoprostol-NSAID drugs then spiked beginning in late 2004 (Fig. 2B), coinciding with the withdrawal of rofecoxib (VIOXX; Merck and Co., Whitehouse Station, NJ, USA), a popular COX-2 inhibitor, from the market [13].

Western Europe, Canada, and the United States combined had the second-highest sales of misoprostol-only drugs, after Asia, accounting for one-third (32%) of the global misoprostol-only market. Sales of drugs in this category decreased over the 2002–2007 period.

Although misoprostol has been used in Western Europe for early termination of pregnancy since the late 1980s, no misoprostol brand registered for obstetric-gynecologic indications had been available until 2004, when Gymiso (HRA Pharma, Paris) was launched in France. Gymiso's sales in 2007 were 0.5% of the total misoprostol-only drug market in France. Two other brands were registered in Spain in March 2008 (Table 1). In the United States and Canada, no misoprostol brand has yet been registered for an obstetric-gynecologic indication.

3.2. Asia

Asia consistently had the highest amount (total weight) of misoprostol-only drugs sold during 2002–2007 (Fig. 2), largely because of relatively robust sales in Japan. However, while the sales in Japan have declined slightly, total sales of misoprostol-only drugs increased by 7% in the region since 2002 (Table 2). We suspect that in Japan, where the population is aging and abortion services have long been accessible, misoprostol is being used mainly as it appears to be used in the United States, Canada, and Western Europe—as prophylaxis for NSAID-induced ulcer disease, its registered clinical indication. And, as in North America and Western Europe, misoprostol sales in Japan have declined.

The real growth in Asia occurred in India, where sales of misoprostol-only drugs increased by 646% since 2002; Bangladesh (128% rise); and Indonesia (116% rise) (Table 2). The market growth in these countries is probably related to the increased use of misoprostol in obstetrics-gynecology. In India, misoprostol is approved for PPH, termination of pregnancy, and cervical ripening. Most pill packages in India have 4 pills, each containing 200 µg—the precise initial dose recommended with mifepristone for first-trimester abortion

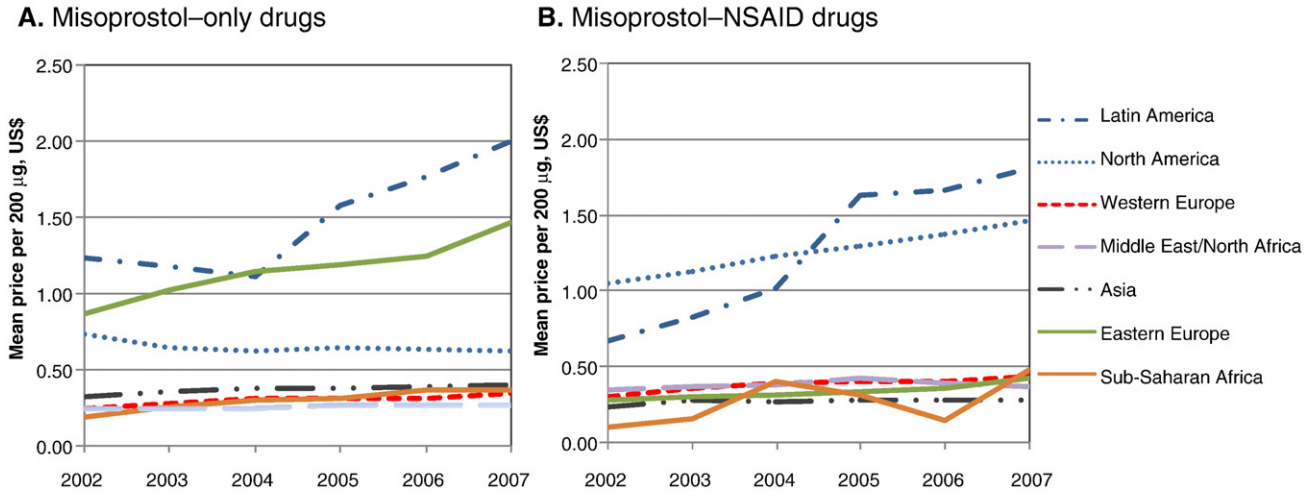

Fig. 3. Mean annual manufacturer prices for 200 µg of misoprostol, by type of drug, according to region, 2002–2007.

Table 3
Registered misoprostol drugs with only 200 μg misoprostol in their formulations sold in 2007 in Asia, Latin America, and Africa[a].

Country and brand name	Manufacturer	Presentations	Consumer price/pill, US$
Asia			
Japan			
Cytotec	Kaken Seiyaku	100, 500, and 1000 pills	0.36
India			
Misoprost	Cipla	4 pills	0.36
Cytolog	Zydus Cadila	4 and 10 pills	0.48 and.0.36
Zitotec	Sun Pharma	2 pills	0.39
Prestakind	Mankind	4 pills	0.41
Kontrac	Fourts India	2 pills	0.37
Miso	Bestochem	4 pills	0.40
Misogon	German Remedies	4 pills	0.35
Misotrax	Genetica	4 pills	0.35
Misogent	Aristo Pharma	4pills	0.38
Mizolast	FDC	4 pills	0.31
Safegaurd	Pulse Pharma	10 pills combined with diclofenac	0.14
Mesopil	Nicholas Piramal	4 pills	0.33
Midiclo	Macleods Pharma	6 pills combined with diclofenac	0.28
South Korea			
Cytotec	Pfizer Korea	120 and 250 pills	0.28 and 0.29
Alsoben	Unimed	100 and 500 pills	0.26 and 0.21
Misel	Shin Poong	30, 100, and 250 pills	0.25
Misoprostol NLS	Nelson Korea Pharma	100 and 500 pills	0.34
Sintec	Sam Chum Dang	100, 250 and 300 pills	0.27
Gastotec	JRP	500 pills	0.25
Cystol	Korea United Pharma	100 pills	0.27
Gastec	Samchully Ph-Chung Gei	100 and 500 pills	0.26 and 0.24
Cirotec	Yoo Young	500 pills	0.26
Gistol	Withusmedipharm	300 pills	0.25
Misoplus	Walse Korea	500 pills	0.23
Pakistan			
Arthrotec	Searle (Pfizer)	20 pills combined with diclofenac	0.23
Cytopan	Getz Pharma	20 pills combined with diclofenac	0.16–0.19
Indonesia			
Noprostol	Novell Pharm	50 pills	0.83
Gastrul	Gastrul	30 pills	1.19
China			
Cytotec	Pharmacia Corp	20 pills	0.46
Arthrotec	Pharmacia Corp	10 pills combined with diclofenac	0.49
Misoprostol	Sh.Hua Lian Pharma	3 and 30 pills	0.34
Misoprostol	BJ. Pharm.FTY No.3	3 and 30 pills	0.31 and 0.39
Bangladesh			
Asotec	Square Pharmaceuticals	30 pills	0.22
Isovent	Square Pharmaceuticals	30 pills	0.22
Cytomis	Incepta Pharma	30 pills	0.22
Miclofenac	Square Pharmaceuticals	30 pills combined with diclofenac	0.16
Ultrafen-plus	Beximco	30 pills combined with diclofenac	0.16
Erdon Super	Aristo Pharma	10 and 50 pills combined with diclofenac	0.15 and 0.09
Misoclo	General	20 pills combined with diclofenac	0.15
Profenac plus	Popular Pharmaceuticals	20 pills combined with diclofenac	0.15
Misofen	Somatec	30 pills combined with diclofenac	0.15
Dix Extra	Apex Pharma	30 pills combined with diclofenac	0.15
Arthrofen	Healthcare Pharma	30 pills combined with diclofenac	0.15
Malaysia			
Cytotec	Pfizer	100 pills	1.05
New Zealand			
Cytotec	Pfizer	120 pills	0.38
Singapore			
Cytotec	Pfizer	100 pills	1.25
Thailand			
Cytotec	Pfizer	140 pills	0.41
Australia			
Cytotec	Pfizer	120 pills	0.36
Artrotec	Pfizer	60 pills combined with diclofenac	0.50
Hong Kong			
Cytotec	Pfizer	100 pills	0.62
Artrotec	Pfizer	10 and 20 pills combined with diclofenac	0.60 and 0.82
Taiwan			
Cytotec	Pfizer	30, 28, 112, and 120 pills	0.53
Artrotec	Pfizer	60 pills combined with diclofenac	0.43
U-miso	U-Liang	28 and 1000 pills	0.43
Latin America			
Mexico			
Cytotec	Pfizer	28 pills	4.90
Artrotec	Pfizer	10, 20 and 30 pills combined with diclofenac	2.19, 1.76 and 1.09
Cyrux[b]	Serral	28 pills	1.01
Argentina			
Oxaprost	Beta	16 pills combined with diclofenac	3.01
Venezuela			
Cytotec	Pfizer	28 pills	0.79
Artrotec	Pfizer	20 pills combined with diclofenac	0.97–1.23
Central America			
Cytotec	Pfizer	28 pills	1.41
Colombia			
Cytotec	Pfizer	28 pills	2.80
Cytil	Tecnoquimicas	14 and 28 pills	1.41 and 1.38
Ecuador			
Cytotec	Pfizer	28 pills	0.48
Dominican Republic			
Cytotec	Searle (Pfizer)	20 and 28 pills	1.57 and 0.99
Artrotec	Searle (Pfizer)	20 and 30 pills combined with diclofenac	1.84 and 1.23
Uruguay			
Misoprostol	Servimedic	28 pills	5.52
Chile			
Misotrol	Sanofi Aventis	28 pills	3.32
Peru[c]			
Cytotec	Searle (Pfizer)	28 pills	1.40
Misoprolen	Intipharm	28 pills	0.98
Brazil			
Prostokos	Hebron	50 pills	15.80
Sub-Saharan Africa			
South Africa			
Cytotec	Pfizer	60 and 120 pills	0.55 and 0.49
Artrotec	Pfizer	20, 30 and 60 pills combined with diclofenac	0.42–0.49
Francophone West Africa			
Cytotec	Pfizer	28 pills	0.59
Middle East/North Africa			
Tunisia			
Arthrotec	Pfizer	20 and 30 pills combined with diclofenac	0.50 and 0.40
Morocco			
Arthrotec	Pfizer	20 pills combined with diclofenac	0.57 and 0.40
Egypt			
Misotac	Sigma	20 pills	0.19
Lebanon			
Cytotec	Pfizer	28 pills	0.50
Arthrotec	Pfizer	20 pills combined with diclofenac	0.63

Table 3 (*continued*)

Country and brand name	Manufacturer	Presentations	Consumer price/pill, US$
Israel			
Cytotec	Pfizer	28 pills	0.52
Arthrotec	Pfizer	20 pills combined with diclofenac	0.60–0.78
Jordan			
Cytotec	Pfizer	28 pills	0.47
Turkey			
Cytotec	Aliraif Searle	28 pills	0.28
Arthrotec	Pfizer	20 pills combined with diclofenac	0.38–0.50

[a] Comprehensive list of all formulations worldwide available at http://www.ipas.org/miso-by-country.

[b] Consumer prices for Cyrux were calculated on the basis of manufacturer selling prices by using conversion factors provided by IMS Health.

[c] Another misoprostol drug—Cytofine (Master Farma)—is also being sold in Peru, but sales data are unavailable.

(Table 3); additional strengths and packaging are available for other indications (data available at http://www.ipas.org/miso-by-country). In Bangladesh, misoprostol is approved for PPH management. Menstrual regulation is legal in Bangladesh and Indonesia [14].

In China, where misoprostol has long been approved for medical termination of pregnancy and cervical softening, and where 9 million of the continent's 26 million abortions occur annually [15], sales increased by 67% since 2002. The country's overall level of misoprostol sales seems low, however, given China's population size and induced-abortion rate.

Misoprostol for obstetric-gynecologic indications is still in its introductory phase in Asia. This region has the best conditions for a future market expansion. Misoprostol is already approved for PPH in Bangladesh, India, and Nepal; medical abortion is available in countries such as India, China, Nepal, and Vietnam [16–18]. In addition, Asia has the largest selection of misoprostol brands, with most products being manufactured locally, and the most products registered for obstetric-gynecologic uses. Consequently, misoprostol drugs in Asia are among the least expensive anywhere (Fig. 3, Table 3). Asia has the largest population and the most induced abortions of all the continents [14], and among all regions South-Central Asia has the second-highest ratio of PPH-related maternal deaths, after Sub-Saharan Africa [9]. Because of these factors and the ongoing programmatic work of several organizations on the continent, we expect that sales of misoprostol in Asia will continue to increase sharply in the future.

3.3. Latin America

Brazil and Peru are the only Latin American countries with misoprostol registered for obstetric-gynecologic indications. In Brazil, misoprostol was reintroduced in 2005 as Prostokos (Hebron, Caruaru PE, Brazil); its distribution is restricted by law to hospitals, where the drug can be used for approved indications only (Table 1). Prostokos recently received registration approval for the same indications in Peru, where it will soon be sold to hospitals.

A common assumption has been that use of misoprostol-induced abortion was widespread in Latin America, where legal abortion is highly restricted and the induced-abortion rate is relatively high. Although pharmaceutical purchases in Latin America have often required no prescription and misoprostol's abortifacient properties are believed to be well-known by women in the general public, we found that the amount of drug sold per population was lower than that for Asia and more-developed countries (Fig. 1, Table 2). Moreover, pharmacy sales declined over the past 6 years (Fig. 2).

Our findings may not mean that the rate of medically induced abortion has decreased; however, we cannot explain this seeming contradiction without analysis of further data. Of note, our findings reflect only registered products commercially available in each country, not unregistered products available over the internet or in the black market [19]. The black market is believed to play an important role in the region, especially in Uruguay and Brazil [19,20], where the legal market prices are expensive and access is highly restricted.

Although the total drug amount sold has decreased, sales measured in US dollars grew continuously since 2002 because of steadily rising prices. Prices increased sharply during 2004–2005; both categories of misoprostol-containing drugs (Fig. 3) were more expensive in Latin America than anywhere else since 2004. Prostokos is the most expensive misoprostol brand (US $15.80 for a 200-μg pill), followed by generic misoprostol in Uruguay; both products are manufactured by local companies (Table 3). In contrast, Venezuela and Ecuador, with the highest sales per population in Latin America, have the lowest prices in the region (US $0.48 for a 200-μg pill in Ecuador).

Argentina has only one commercially available brand—Oxaprost (Beta, Buenos Aires), which combines 200 μg of misoprostol with the NSAID diclofenac. According to the College of Pharmacists of Buenos Aires, women are using this medication for self-induced abortion; approximately 80% of all Oxaprost prescriptions in Argentina are written by obstetrician-gynecologists [21]. In a recent study, misoprostol retained its effectiveness as an abortifacient when combined with an NSAID [22].

Mexico has the largest absolute sales of misoprostol in the region, although the amount sold annually decreased steadily since 2002. Because Mexico City recently liberalized its abortion law and multiple organizations are disseminating information in Mexico on misoprostol use in reproductive health [19], misoprostol use for obstetric-gynecologic indications will likely increase in the future.

3.4. Eastern Europe

Since 2007, Russia has been the only Eastern European country with misoprostol brands registered for an obstetric-gynecologic indication (Table 1); sales of these brands represent 37% of the total sales of all misoprostol-only containing drugs in Russia. Total misoprostol sales in Russia and throughout Eastern Europe generally have declined since 2002. Among all regions, Eastern Europe consistently had the lowest drug amounts sold—and, for the misoprostol-only drugs, the lowest amounts sold per population (Table 2). In Romania and especially Slovakia, where misoprostol-only drugs are unavailable, misoprostol-NSAID–drug sales increased substantially.

Several factors discourage misoprostol use for obstetric-gynecologic indications in the region. For example, in Eastern Europe, where induced-abortion rates remain high [15], surgical abortion services historically have been provided free-of-charge—as a primary method of family planning—in the public sector in all the former Soviet-bloc countries except Slovakia and Poland, whereas medical abortion services generally are not covered. In addition, Eastern Europe had the second-highest prices worldwide for misoprostol-only medications. Prices in the region rose by 47% over the study period; Poland, Slovenia, and Russia drove the prices high in the region.

3.5. Middle East–North Africa

In the Middle East–North Africa region, sales of misoprostol-only drugs increased during 2002–2007. Lebanon had the highest sales per population of misoprostol-only drugs in 2007 (Table 2).

Misoprostol is approved in Tunisia for termination of pregnancy. In Egypt, the only country in the region with a registered brand for labor induction (Table 1), retail pharmacy sales increased by 1022%.

3.6. Sub-Saharan Africa

Unfortunately, the sales data for Sub-Saharan Africa are limited. Data are available for South Africa and the Francophone West Africa region only.

Until recently, misoprostol products were registered in few African countries, even for gastrointestinal indications. In the past few years, however, misoprostol has been registered or approved for obstetric-gynecologic indications in several countries, including Ghana, Nigeria, Sudan, Ethiopia, Kenya, South Africa, Tanzania, Uganda, and Zambia [23,24].

This region has the highest rates of maternal mortality and morbidity worldwide, largely resulting from PPH and complications of unsafe abortion [9]. In this region, increasing the availability and accessibility of misoprostol could significantly reduce the maternal death rate. We therefore expect that sales of misoprostol products will rise in the coming years as a result of the efforts of organizations in various countries to have misoprostol included on essential medications lists and to register misoprostol products for PPH management or/and termination of pregnancy.

4. Conclusion

While the bulk of sales of misoprostol worldwide continues to be in high-resource countries, and therefore primarily used for gastric-related indications, the use of misoprostol in obstetrics-gynecology is growing worldwide, as indicated by its introduction and registration in an increasing number of countries [23,24]. Securing access to misoprostol for a range of lifesaving obstetric-gynecologic uses is important, particularly in countries with scarce resources, where the drug should be made available at both the hospital and community levels [10,24,25].

This report marks the start of an Ipas initiative to track longitudinally and analyze the availability and sales of misoprostol products globally. This information should help increase awareness of, and ultimately access to, this lifesaving drug for women.

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