



Technologies for Health Consultative Meeting: MNCH Pathways

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Maternal Infection



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Clean Delivery

Each year about 60 million women in developing countries give birth with only the help of an untrained attendant or family member or with no help at all.¹ Many of these deliveries take place at home where the risk of infection is high. Some 1,600 women per day die from complications associated with pregnancy or childbirth, and infection is a leading cause.² In developing countries, most women have no access to maternity services due to distance, cost, and local customs; many give birth alone. High rates of neonatal and maternal tetanus and sepsis indicate a need for education and materials focused on clean-birth practices.

For example, expert opinions have estimated that clean-birth practices at home would reduce maternal mortality from infections by a median of 20%. Clean-birth practices with a skilled attendant were estimated to reduce mortality from sepsis by a median of 35% at home and by a median of 55% in a facility. When compared to unattended home birth without clean-birth practices, expert consensus estimated that clean-birth practices at home reduce mortality from neonatal infections by a median of 15% and from tetanus by 30%.

According to the World Health Organization's (WHO) six principles of cleanliness at birth, "The hands of the birth attendant must be washed with water and soap, as well as the perineum of the woman. The surface on which the infant is delivered must be clean. Instruments for cutting the cord and cord care (razor blade, cutting surface, cord ties) should be clean. Nothing should be applied either to the cutting surface or to the stump, with the exception of areas of high infection risk in which the use of topical antiseptics is promoted. The stump should be left uncovered to dry and to mummify."³ The six principles of cleanliness include: clean hands, clean perineum, nothing unclean introduced into the vagina, clean-delivery surface, clean cord-cutting instrument, and clean cord care (including cord ties and cutting surface). The approaches that have been identified to increase uptake of these clean practices are behavior change communication and training at the community level, clean birth/delivery kit distribution, and facility-based interventions including training and improved access to supplies and equipment.

The technologies and solutions included in the tables below are tools with potential to increase access to a clean delivery.

| Supply Information | TECHNOLOGY/SOLUTION | | | | |
|--------------------|--|---|---|--|--|
| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Description | Byotrol delivers broad-spectrum, long-lasting, antimicrobial control in a water-based formulation. Its applications include hand sanitizer and surface/device disinfectant. Byotrol has a backbone of an inert low-surface tension hydrophobic polymer (Amphicelle™) coupled to mild biocides through nonchemical bonding. Various biocides can be coupled to the polymer, which makes Byotrol effective against a wide variety of viruses, bacteria, and fungi. | Autoclaves use heat/steam for sterilization. Some autoclaves use steam heated to 121°–134°C (250°–273°F). To achieve sterility, at least 15 minutes at 121°C (250°F) or 3 minutes at 134°C (273°F) is required. Autoclaves are commonly used for equipment sterilization. In the developed world, large-scale units are also used to manage infectious waste. In recent years, small-scale units have been introduced for health care waste management in low-resource settings. | Chlorhexidine (CHX) at concentrations ranging from 0.05%–1% has been used in several studies to reduce the risk for mothers to develop an infections, and for the newborn to acquire maternal infections (such as HIV or streptococcus) during the passage through the birth canal. | Application of CHX-alcohol has shown to reduce the risk of surgical-site infection by 41% as compared with the most common practice in the United States of using aqueous povidone-iodine. ⁴ Experience in low-income countries is not available. These products are indicated for antisepsis before cesarean section. | Clean delivery kits (CDKs) are defined as only including disposable items for clean-birth practices (e.g., soap, blade, plastic sheet, etc.). CDKs are the focus of achieving the “six cleans” include clean hands, clean perineum, clean delivery surface, clean cord cutting implement, clean cord tying, and clean cord care. |

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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Characteristics applicable for low-resource settings | Unlike alcohol or other conventional biocides, this hazardless, water-based formulation is safe and gentle to the skin, making it more acceptable to service providers. In addition, Byotrol is potentially less expensive than alcohol—which is a petrochemical whose price is significantly affected by oil pricing. It does not require special storage and transport conditions, and birth attendants can refill and reuse the same container, which will likely contribute to further cost reduction. | Stove-top autoclaves are common in the developing world. Small-scale, electric autoclaves are available and becoming more affordable for low-resource settings. Access to power and ability to pay for power are limiting factors to what type of facility can use an autoclave. A number of technologies are in development that look at alternative fuel sources including solar, kerosene, and firewood. | Vaginal cleansing with CHX is feasible to implement in all health care settings, including home-based deliveries. Minimal organizational changes would be required to implement this procedure in delivery settings (e.g., hospitals or clinics) as the required materials would be easily available. Implementation of the procedure in a community setting would require providing an aqueous, alcohol-free, CHX solution (with a concentration between 0.25% and 1%), and training birth attendants. Adequate training and information (including product details, target applications, and methods) should be made available to all birth attendants. | It would be feasible to adapt existing technology that is used in developed countries to a developing-country setting. The combination of CHX and alcohol is more effective than CHX alone. The product does not require extensive training, and it could easily be used preoperatively by nurses. This technology is ideal for hospital settings with capabilities to perform cesarean or obstetric surgeries. | A CDK is an inexpensive, simple kit designed to help create a clean birthing environment, particularly for home births. CDKs are designed for use by skilled birth attendants, family members, and women who give birth unassisted in the home. Community health workers and traditional birth attendants are oriented to the kits, so they can either provide it as part of their birth-delivery services or encourage families to purchase the kit for home deliveries. |

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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Developer and/or manufacturer | Byotrol, Inc. | There are numerous companies and organizations. For example, PATH has developed a compendium of more than 30 small-scale affordable autoclaves manufactured in India. Autoclaves using alternative fuel sources have been developed including those using solar power (with limited success). Aprovecho has developed an institutional stove autoclave. | No commercially available products exist. | Sage Product, Inc. (2% CHX gluconate cloths). Mölnlycke Health Care US, LLC (Hibiclens: 4% CHX gluconate). CareFusion (ChloraPrep: 2% CHX gluconate/70% isopropyl alcohol). Professional Disposable International, Inc. (Chlorascrub: 3.15% CHX gluconate and 70% isopropyl alcohol solution). | There are many companies and organizations that produce CDKs. |
| Status | Various formulations containing Byotrol have been commercialized in the United States, United Kingdom, and other developed countries. Byotrol's Stay Clean™ hand sanitizer is compliant with the US Food and Drug Administration's (USFDA) rules, and Polysphere disinfectant is registered with the US Environmental Protection Agency. | Electric autoclaves have already been commercialized by multiple manufacturers. Steam autoclaves are classified as a class II device according to the USFDA and require 510(k) clearance to be marketed in the United States. | Research phase. | Multiple manufacturers commercialized CHX solution or wipes for preoperative skin preparations in developed countries (e.g., Hibiclens 4% CHX gluconate and Sage's 2% CHX cloths are commercialized in the United States with USFDA approval). The WHO Essential Medicines List (EML) includes 10% polyvidone iodine (equivalent to 1% iodine) and 5% CHX gluconate as antiseptics. | Birth kits are available in more than 51 low-resource countries. ⁵ |

| Supply Information | TECHNOLOGY/SOLUTION | | | | |
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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Efficacy/ effectiveness | Byotrol formulations have been tested against the most stringent test methodologies including the European Standards (EN) 1276 for bacteria, EN 13697 surface testing, EN 1650 against fungi, and EN 14476 against viruses. | Effectiveness of electric and stove-top autoclaves is well established. Effectiveness of technologies using alternative fuel sources varies and is not well documented. | <p>A Cochrane systematic review (five studies; 2,190 term and preterm infants) showed that although vaginal CHX significantly reduces group B streptococcal colonization of neonates, it does not reduce incidence of clinical infections. The authors concluded that current evidence does not support the effectiveness of CHX for vaginal disinfection to prevent the early onset of disease in labor.⁶</p> <p>A second Cochrane systematic review (three studies; 3,012 participants) shows no evidence of an effect of vaginal CHX during labor in preventing maternal and neonatal infections (HIV and streptococcal infections were not assessed). Although the data suggest a trend in reducing postpartum endometritis, the difference was not statistically significant (relative risk 0.83; 95% confidence interval 0.61 to 1.13).⁷ In addition, recent randomized controlled trial studies in Pakistan and South Africa showed that using maternal CHX vaginal wipes were not effective in preventing maternal and perinatal mortality or neonatal sepsis.^{8,9}</p> | <p>CHX-alcohol was significantly more protective than povidone-iodine against both superficial incisional infections (4.2% versus 8.6%, P=0.008) and deep incisional infections (1% versus 3%, P=0.05) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups.⁴</p> <p>The systematic review identified six eligible studies, containing 5,031 patients. CHX reduced postoperative surgical-site infection compared with povidone-iodine (pooled odds ratio 0.68; 95% confidence interval 0.50 to 0.94; P=0.019).¹⁰</p> | Birth kit use was identified in 51 low-resource countries, but evaluations were scarce, with only nine studies reporting effects of intervention packages including births kits. The quality of evidence for inferring causality was weak, with only one randomized controlled trial. In two studies, birth kit use along with co-interventions resulted in a statistically significant increase in the likelihood of the attendant having clean hands. The impact on other aspects of cleanliness was less clear. Intervention packages that include birth kits were associated with reduced newborn mortality (three studies), omphalitis (four studies), and puerperal sepsis (three studies). The one study that considered maternal mortality was not large enough to estimate relative reduction with much precision. ⁵ |

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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Manufacturing quality and capacity | <p>Byotrol does not require special manufacturing equipment.</p> <p>Byotrol licenses its technologies to third parties for manufacturing. The company indicated that it is willing to license its technology to entities in low-resource countries to manufacture and distribute the Byotrol products to the public sector at an affordable price. Byotrol's ease of manufacturing will facilitate the smooth transfer of the technology and the development of manufacturing bases in developing countries.</p> | <p>Multiple manufacturers have commercially available technologies. Quality and availability vary.</p> | <p>It is expected that no special equipment would be required for manufacturing. The active ingredient is easy to obtain at low cost.</p> | <p>As noted previously, there are numerous manufacturers.</p> <p>Both Sage and Mölnlycke are international companies which appear to have manufacturing capacity to meet the current global demand.</p> <p>The active ingredients can be easily obtained at low cost.</p> | <p>Requires assembling and packaging commonly available disposable commodities.</p> |
| Intellectual property (IP) ownership | <p>Patents for Byotrol's composition and application have already been granted in the United Kingdom, the United States, and other member countries of the Patent Corporation Treaty.</p> | <p>Various for alternative fuel designs under development.</p> | <p>There is no IP associated with CHX gluconate. Data on IP associated with wipes are not available.</p> | <p>There is no IP associated with CHX gluconate.</p> | <p>CDKs include only commodities and are unlikely to have IP.</p> |

| Supply Information | TECHNOLOGY/SOLUTION | | | | |
|------------------------------|--|--|--|--|--|
| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Cost and cost drivers | Byotrol does not require special storage and transport conditions, and its primary container can be refilled and reused. The founder of Byotrol told us that it is easy to manufacture Byotrol without any special production equipment. These factors are likely to contribute favorably to the pricing of Byotrol. | <p>The UNICEF Supply Catalog lists several types of autoclaves, ranging from US\$8.20 (drum, sterilizing, 165 mm diameter) to US\$3,699.37 (sterilize, steam, approximately 40 L, electric, with accessories).</p> <p>Autoclaves require a reliable source of electricity (except for a solar-powered one) in order to maintain the pressurization and temperatures necessary to properly disinfect infectious waste.</p> <p>In addition to electricity, other costs include training, drainage for disposal of water runoff from the disinfection cycle, maintenance, spare parts, and consumables.</p> | CHX gluconate, the active ingredient, can be obtained at low cost. | <p>Hibiclens: US\$20.03/32 oz (Amazon.com).</p> <p>Sage chlorhexidine cloths: US\$252.06/96 cloths (Durant Medical Supply.com).</p> <p>The UNICEF Supply Catalog includes: (1) providone-iodine solution 10% in bottle of 200 mL and 500 mL (indicative prices are US\$1.17 and US\$2.64, respectively); and (2) CHX gluconate solution 5% in bottles of 100 mL or 1,000 mL (indicative prices are US\$0.58 and US\$4.98, respectively).</p> <p>The active ingredient can be obtained at a low cost.</p> | The estimated cost of CDKs is between US\$0.17 and US\$0.73 per birth depending on whether they are made locally or whether they are imported. If CDKs are made locally this amounts to a cost of around US\$215 per life saved. ¹¹ |

| Supply Information | TECHNOLOGY/SOLUTION | | | | |
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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Delivery/ procurement channels | <p>Public-private partnership (PPP) is possible for distribution of Byotrol products.</p> <p>Governments could purchase Byotrol products in bulk for use by medical professionals at facilities and by skilled birth attendants in communities.</p> | <p>Several types of autoclaves are listed in the UNICEF Supply Catalog for procurement by public-sector organizations.</p> <p>Autoclaves come with many different features depending on their size, type, and intended use. Procurers need to choose autoclaves that meet/fit their needs.</p> | <p>The current WHO EML includes CHX gluconate as a general antiseptic and for cord care. CHX gluconate for vaginal wipes to reduce maternal and neonatal infections could be added in the EML as a new indication for use to facilitate procurements by public-sector organizations.</p> <p>CHX vaginal wipes could be used for both facility-based delivery and home delivery. However, home delivery could be the primary target due to suboptimal hygienic conditions. The product could be included in midwifery kits.</p> | <p>The current WHO EML includes CHX gluconate as a general antiseptic and for cord care. CHX gluconate for preoperative skin preparation could be added in the EML as a new indication for use to facilitate procurements by public-sector organizations.</p> <p>Also, the product can be distributed to private hospitals through distributors.</p> | <p>Potential delivery channels include social marketing, nongovernmental organization clinics, midwives, and traditional birth attendants for home births.</p> <p>It also has been proposed to distribute CDKs to women during pregnancy. However, this could encourage mothers to give birth at home rather than travel to a health facility. There is some evidence to suggest that provision of CDKs directly to facilities may increase the number of women who choose to deliver there.¹¹</p> |

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| | Non-alcohol-based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | Chlorhexidine gluconate preoperative skin preparation | Clean delivery kits |
| Sustainable business models | <p>Two-tier pricing could be possible. Packaging, volume per package, and dosage forms could be different for public and private sectors.</p> <p>PPP is possible for distribution.</p> | <p>Using manufacturers' sales force or private distribution channels could be costly.</p> <p>Bulk purchases by governments or groups of nongovernmental organizations could be an option.</p> | <p>PPP is possible for manufacturing and distribution.</p> | <p>Two-tier pricing could be possible for this product if there is sufficient demand by private-sector facilities.</p> <p>Large sales volume could be achieved since this product can be used for all types of surgeries.</p> <p>May require different packaging and dosage form (e.g., wipes instead of liquid) to encourage purchases by private hospitals.</p> | <p>Sustainable business models exist in most countries where CDKs have been produced and distributed. Many nongovernmental organizations create and sell them as incentives for community health workers. Examples:</p> <p>Nepal: CDKs are sold and used throughout the country. More than one million kits have been sold since 1994.</p> <p>Bangladesh: BRAC sells their kit through Shasthya Shebikas (community health volunteers).</p> <p>Bangladesh: Social Marketing Company sells their safety kit via social marketing (sold 61,790 safety kits at Tk50 each in fiscal year 2010.)</p> |

| Demand Information | TECHNOLOGY/SOLUTION | | | | |
|------------------------|--|---|---|--|---|
| | Non-alcohol based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | CHX gluconate preoperative skin preparation | Clean delivery kits |
| Existing demand | Buyers include consumers and public and private health care facilities. Referral hospitals and clinics could use this product. The product can also be incorporated in midwifery kits to be used in communities; however, penetration to this level may take a long time since switching from the current practice (using soap and water or nothing at all) to the Byotrol product is likely to take time. | Ministries of health or nongovernmental organizations who have clinics can be buyers. The market size will be driven by the number of facilities and availability of utility at facilities. | No existing demand for CHX vaginal wipes. CHX vaginal wipes can be used both for facility-based and for home delivery. However, home delivery could be the primary target due to its sub-optimal hygienic conditions. | Used at facilities that perform surgeries. The total market size is driven by the number of surgeries performed both at public and private health care facilities. | Primarily used for home births. Demand, therefore, is driven by the number of births that occur at home. An estimated 60 million women each year (worldwide) give birth somewhere other than a health facility. ¹¹ |

| Demand Information | TECHNOLOGY/SOLUTION | | | | |
|--------------------------|--|---|--|--|--|
| | Non-alcohol based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | CHX gluconate preoperative skin preparation | Clean delivery kits |
| Attractiveness | Unlike alcohol or other conventional biocides, this hazardless, water-based formulation is safe and gentle to the skin making it more acceptable to service providers. In addition, Byotrol is potentially less expensive than alcohol—a petrochemical whose price is significantly affected by oil pricing. It does not require special storage and transport conditions, and birth attendants can refill and reuse the same container, which will likely contribute to further cost reduction. | Autoclaves require both a power source and water, which prohibits some facilities from using autoclaves. Requirements for maintenance, repair, and consumables (if any) are also likely to be barriers for uptake. | A study conducted in Pakistan for use of 0.6% CHX indicated that the CHX intervention would be acceptable to women and their providers. Traditional birth attendants had no difficulty administering CHX vaginal and neonatal wipes in a home setting. There were no allergic reactions, vaginal itching, burning, or requests for study termination. The study was not powered to show significant differences in neonatal outcomes between treatment groups. ¹² | CHX gluconate achieves greater reductions in skin microflora than did povidone-iodine and also had greater residual activity after a single application according to some studies. Also, CHX gluconate is not inactivated by blood or serum proteins while iodophors may be inactivated by these substances. | Levels of birth-kit use vary considerably (8%–99%). Higher levels have been reported where kits were distributed for free as part of a research program. ¹³ Research interviews showed that the birth attendants who used the kit perceived it as hygienic, convenient, affordable, and culturally acceptable. The razor blade and thread were the most useful items, and the purpose of the plastic coin was understood. Despite its perceived usefulness, awareness and use of the kit were low. Common reasons for non-use included not knowing about the kit or difficulty in procuring a kit locally. ¹⁴ |
| Price sensitivity | Unknown. | Unknown. There is a very large range in pricing based on the type and size of unit. | Unknown. | Unknown. However, it should be at least equivalent to the antiseptic products listed in the UNICEF Supply Catalog. | The estimated cost of CDKs is between US\$0.17 and US\$0.73 per birth, depending on whether it is made locally or imported. ¹¹ |

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| | Non-alcohol based hand sanitizer/disinfectant (Byotrol) | Low-cost autoclaves | Chlorhexidine vaginal wipes | CHX gluconate preoperative skin preparation | Clean delivery kits |
| Policy environment | WHO launched its “Clean Care is Safer Care” campaign in 2005. According to the WHO website, as of November 2011 a total of 14,391 hospitals and health care facilities in 150 countries or areas have registered their commitment to hand hygiene as a part of this global campaign. This clearly indicates strong political support in providing a cleaner environment for improved care for patients. | There are efforts underway to expand the use of more environmentally friendly approaches to health care waste management. Autoclaves are the technology that is being introduced most widely. This is also raising awareness about the use of autoclaves for equipment sterilization. Cost has been a barrier, and more attention is being given to the need for a low-cost, high-quality unit. | Although it would be feasible to implement CHX vaginal disinfection techniques in all health-care settings, including home-based deliveries, studies have shown no evidence to support the hypothesis that vaginal washes with CHX prevent maternal and neonatal infections. | CHX gluconate has been known as an effective antiseptic agent and is already listed in WHO EML, but preoperative skin preparation needs to be added as an indication for use to facilitate the use of the product. In addition, the products currently available in the United States as preoperative skin preparation have different concentration of CHX gluconate. May need to gain a consensus on the concentration level. | Success and support of the CDK varies by country. Different countries have had diverse levels of success. In general there is broad support of kits for many interventions. Efforts to increase facility births may be at odds with expanded use of the CDK. Some have proposed that CDK could also be useful in lower-level facilities. |
| Donors/ stakeholders | WHO, USAID (Byotrol was a finalist in the 2011 Saving Lives at Birth competition). | WHO. | WHO, USAID, CHX Working Group. | WHO, CDC. | USAID, UNICEF, UNFPA. |
| Pre- and post-sales support | No product-specific training or support is required. | Training, maintenance, and repair are required. | Training would be needed to introduce the new practice. | Training would be needed to introduce the new practice. | No specific training or support is required, but the directions for use need to be comprehensible to the user population. |
| Need for demand creation | Requires raising awareness about the need for hand hygiene and the shift from existing alcohol-based product use to the non-alcohol alternative. | Requires raising awareness about importance of proper disinfection. | Further favorable evidence will be necessary to generate demand for vaginal wipes. | Requires raising awareness about the use of CHX gluconate for preoperative skin preparation. | Requires increasing uptake of clean practices, including use of CDKs. Approaches include media and public health messaging, community-based behavior change and training, and facility-based training. |

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Early Detection of pPROM and PROM

Spontaneous rupture of membranes (ROM) is a normal component of labor and delivery. Premature rupture of membranes (PROM) refers to rupture of the fetal membranes prior to the onset of labor¹ and can occur at any gestational age—even at 42 weeks of gestation. It is also referred to as prelabor ROM. PROM can occur either at term or preterm (37 weeks). When PROM occurs before 37 weeks of gestation, it is referred to as preterm PROM (pPROM). PROM complicates 8 percent of all pregnancies and pPROM complicates between 2 percent and 20 percent of all pregnancies.^{1,2} They are both important contributors to neonatal and maternal mortality. Maternal risks of term PROM include chorioamnionitis and postpartum febrile morbidity.^{1,2}

In most cases, ROM can be confirmed by documenting amniotic fluid (AF) leakage from the cervical opening with visualization of pooling in the vagina.³ However, in situations where there is a slow fluid leak or bleeding, the diagnosis of PROM is difficult. In addition, the relatively small amount of AF present early in gestation further challenges the diagnosis of ruptured membranes.^{4,5}

In approximately 20 percent to 25 percent of cases, ROM is not grossly apparent.² A patient's history may suggest ROM, but test results are non-confirmatory, creating an obstetrical dilemma. Early and accurate diagnosis of ROM would allow for gestational age-specific interventions to optimize perinatal outcome and minimize serious complications.⁶ Therefore, the search for an ideal test to definitively diagnose membrane rupture with no delay continues.

Although initial studies may be encouraging, diagnostic techniques are usually subsequently found to be limited by inaccuracies from false positives and false negatives with poorer sensitivities and specificities than originally anticipated. The ideal test should be simple, rapid, inexpensive, and noninvasive. Optimally, the accuracy of the test should not be hampered by the presence of blood, semen, infected urine, or other contaminants. An accurate biochemical marker for ROM should have a high concentration in the AF, a low concentration in maternal blood, and an extremely low background concentration in cervicovaginal discharge with intact membranes.²

The technologies and solutions included in the tables below are tools with potential to increase access to early detection of pPROM and PROM.

| Supply Information | TECHNOLOGY/SOLUTION—TABLE 1 | | | |
|---|--|---|---|---|
| | Phenaphthazine-based pH indicator | Litmus-based pH indicator | Noninvasive absorbent pad | Intra-amniotic dye injection |
| Description | Determines the pH of fluid obtained from the vaginal pool during speculum examinations. | Determines the pH of fluid obtained from the vaginal pool during speculum examinations. | Looks for the presence of amniotic fluid (AF) leak during pregnancy. | Instillation of diluted indigo carmine into the amniotic cavity and confirmation of ROM by documenting dye leakage and staining of tampon within 20 to 30 minutes. |
| Characteristics applicable for low-resource settings | Easy to use. Minimally trained personnel can conduct the test. It is ideal for community and clinic settings. However, confirmation of pPROM and PROM requires the woman to be seen in a hospital setting. | Easy to use. Minimally trained personnel can conduct the test. It is ideal for community and clinic settings. However, confirmation of pPROM and PROM requires woman to be seen in a hospital setting. | Easy to use. Women can use it at home and notify health providers of color change. Applicable for home use, or in community or clinic settings. However, confirmation of pPROM and PROM requires the woman to be seen in a hospital setting. | This procedure requires highly specialized personnel. This is an invasive procedure with inherent risks that include bleeding (placental abruption), infection, iatrogenic PROM, and miscarriage. |
| Developer and/or manufacturer | Nitrazine paper: Bristol-Myers Squibb Co. (distributor: Apothecon), pHizatest™ manufactured by Micro Essential Laboratory. | Apothecary products, Indigo instruments, Whatman. | Amniosense: Home-Based Water Breaking Alarm System (Med-Direct). | Not applicable; this is a technique more than a technology. |
| Status | Commercialized by various manufacturers in the United States. Nitrazine paper is classified as Class I device by the United States Food and Drug Administration (USFDA) and is exempted from the premarket notification procedures. | Commercialized by various manufacturers in the United States. | Commercialized in the United Kingdom and has the CE Mark. | Used in highly specialized centers in the developed world. Use in developing countries is unknown. |
| Efficacy/ effectiveness | Sensitivity: 90.7% Specificity: 77.2% The presence of contaminating substances (e.g., blood, semen, alkaline antiseptics) can also cause nitrazine paper to turn blue, giving a false-positive result. Bacterial vaginosis can produce a similar result. | Similar to nitrazine paper. | Sensitivity: 98% Specificity: 65% | Sensitivity: 100% Specificity: 100% Gold standard for diagnosis of ROM. |

| Supply Information | TECHNOLOGY/SOLUTION—TABLE 1 | | | |
|---|---|--|--|--|
| | Phenolphthazine-based pH indicator | Litmus-based pH indicator | Noninvasive absorbent pad | Intra-amniotic dye injection |
| Manufacturing quality and capacity | Micro Essential Laboratory claims that their product is manufactured in the United States and distributed in 50 countries. Micro Essential Laboratory also recommends that pHizatest® accuracy be validated using the Hydriion® brand buffers or other comparable National Institute of Standard Technologies traceable buffers when circumstances dictate. | Common products are manufactured by multiple companies. It is unlikely that manufacturing capacity and capability will be an issue. | Manufactured by Med-Direct International Ltd. (UK). The technology used for the product is the same as for the phenolphthazine-based pH indicator. It is unlikely that manufacturing capacity and capability will be an issue. | Indigo carmine is produced by multiple manufacturers. Some claim that their product complies with the United States Pharmacopia (USP), but some others do not. Quality control of the drug could be an issue. |
| Intellectual property ownership | No data available. | No data available. | No data available. | Not applicable. |
| Cost and cost drivers | Bristol Myers' nitrazine paper is sold at US\$40 (100 tests, or \$0.40 per test) via Amazon.com. Other internet sites also carry this product. The manufacturers might be using the internet predominantly to minimize distribution costs for this low-cost product. | Indigo instruments' pH strip is priced at US\$14.95 for a pack of 100 strips. Indigo sells the test strips online. | Cost per unit: US\$1.85 per test. This is promoted as a self-test. Instruction for use is provided in the package. When used in low-resource settings, counseling by service providers to women is likely to be required. | Indigo carmine comes in ampoules. The price of indigo carmine (ten 5-mL ampoules), USP, is priced at US\$97 on line. Other cost drivers include training as well as storage for Indigo carmine since it requires a dark room at 15°C to 30°C, which could be challenging in certain countries. |
| Delivery/ procurement channels | These test strips are not included in the United Nations Children's Fund (UNICEF) Supply Catalogue. Also, they could be included in midwifery kits. Since this test is inexpensive, procuring it in bulk might make sense to minimize cost associated with logistics. In addition, the test strips are applicable for nonclinical use. Orders from health care facilities, laboratories, and other facilities could be consolidated to negotiate volume discount. | These test strips are not included in the UNICEF Supply Catalogue. Also, they could be included in midwifery kits. Since this test is inexpensive, procuring it in bulk might make sense to minimize cost associated with logistics. In addition, the test strips are applicable for nonclinical use. Orders from health care facilities, laboratories, and other facilities could be consolidated to negotiate volume discount. | Procurers in the public and private sectors can purchase the test directly from the company. The product could also be listed in the UNICEF Supply Catalogue for bulk procurement and/or could be included in midwifery kits. | Indigo carmine can be procured in bulk by public-sector procurers. It also can be obtained directly from manufacturers. Due to risks inherent to this drug, usage should be carefully monitored. |

| Supply Information | TECHNOLOGY/SOLUTION—TABLE 1 | | | |
|------------------------------------|--|--|--|---|
| | Phenaphthazine-based pH indicator | Litmus-based pH indicator | Noninvasive absorbent pad | Intra-amniotic dye injection |
| Sustainable business models | Requires large sales volume to compensate for potentially low profit margin that this strip test brings. | Requires large sales volume to compensate for potentially low profit margin that this strip test brings. | Further investigation of this test is needed. The test costs more than pH test strips; however, value proportion of this test compared to pH test strips is unclear. | Due to the requirement for highly skilled professionals, this method is unlikely to be offered in a sustainable way without proper training programs. |

| Demand Information | TECHNOLOGY/SOLUTION—TABLE 1 | | | |
|------------------------------------|--|--|---|--|
| | Phenolphthazine-based pH indicator | Litmus-based pH indicator | Noninvasive absorbent pad | Intra-amniotic dye injection |
| Existing demand | The market size could be driven by the number of women who are at risk for PROM but do not present apparent symptoms of PROM. These tests can be used in clinics and communities. | The market size could be driven by the number of women who are at risk for PROM but do not present apparent symptoms of PROM. These tests can be used in clinics and communities. | The market size could be driven by the number of women who are at risk for PROM but do not present apparent symptoms of PROM. These tests can be used in clinics and communities. | The market size could be driven by the number of women who are at risk of PROM but do not present apparent symptoms of PROM. Even if this test is adapted by developing countries, it will only be used at referral hospitals. |
| Attractiveness | These products have been widely used in developed countries, are easy to use, and are inexpensive. However, the rate of false positives is high, and there are false negatives in cases of minimal leakage from chronic ROM or “high leak” of the membranes. | These products have been widely used in developed countries, are easy to use, and are inexpensive. However, the rate of false positives is high, and there are false negatives in cases of minimal leakage from chronic ROM or “high leak” of the membranes. | This test might be difficult to be used by women. Service providers’ preference toward this test is unclear. A clear value proposition against pH test strips is required. | Although this method is designated an “unequivocal” diagnostic method for confirmation of ROM, this invasive test carries increased maternal and fetal risk. Inherent risks of intra-amniotic dye injection include trauma, bleeding, infection, and preterm labor. In addition, the test requires highly skilled personnel. Applicability and acceptability of this technique in low-resource settings may not be high. |
| Price sensitivity | Since these test strips are commoditized in developed countries, the price sensitivity is expected to be low. | Since these test strips are commoditized in developed countries, the price sensitivity is expected to be low. | Needs investigation. If this test is self-administered by women, their preference will play a significant role. | Need further investigation for price sensitivity of indigo carmine. |
| Policy environments | Low support for maternal health commodities in general could hinder uptake of new or underutilized tools. | Low support for maternal health commodities in general could hinder uptake of new or underused tools. | Low support for maternal health commodities in general could hinder uptake of new or underutilized tools. | Has not been used in low-resource settings. Potential in women with known risk factors of developing pPROM or PROM. May be cost-prohibited considering it is a disposable technology. |
| Donors/ stakeholders | There are no current global champions advocating for these interventions. | There are no current global champions advocating for these interventions. | There are no current global champions advocating for these interventions. | Policy alignment is necessary. |
| Pre- and post-sales support | This test is disposable. Minimal training is required. | This test is disposable. Minimal training is required. | This test is disposable. Minimal training is required. If this product is self-administered by women, provision of proper counseling will be critical. | This technique requires highly specialized training. |

| Demand Information | TECHNOLOGY/SOLUTION—TABLE 1 | | | |
|---------------------------------|--|--|--|---|
| | Phenaphthazine-based pH indicator | Litmus-based pH indicator | Noninvasive absorbent pad | Intra-amniotic dye injection |
| Need for demand creation | <p>There is a need to understand the reasons for underuse of this technology.</p> <p>Further evaluation of test performance could be necessary since lower specificity might be a concern (i.e., over diagnose).</p> | <p>There is a need to understand the reasons for underuse of this technology.</p> <p>Further evaluation of test performance could be necessary since lower specificity might be a concern (i.e., over diagnose).</p> | <p>There is a need to understand the reasons for underuse of this technology.</p> <p>Further evaluation of test performance could be necessary since lower specificity might be a concern (i.e., over diagnose).</p> | <p>This procedure requires highly skilled personnel. Policy alignment and harmonizations of clinical guidelines are required.</p> |

| Supply Information | TECHNOLOGY/SOLUTION—TABLE 2 | | | |
|---|---|--|---|--|
| | Placental alpha-micro-globulin | Ultrasound assessment of amniotic fluid volume | Insulin-like growth factor binding protein-1 (IGFBP-1) detection test | Alpha-fetoprotein detection test |
| Description | Rapid, non-instrumented, qualitative immunochromatography test for in vitro detection of AF in vaginal secretion of pregnant women. AmniSure detects placental alpha-1 microglobulin (PAMG-1) protein marker of the AF in vaginal secretions and is intended to aid in the detection of ROM in pregnant women greater than 34 weeks gestation with signs, symptoms, or complaints suggestive of ROM. | Can detect oligo-hydramnios suggesting loss of AF due to PROM. | Immunochromatography-based test to detect IGFBP-1. | Based on detection of fetal alpha-fetoprotein in vaginal secretions. |
| Characteristics applicable for low-resource settings | There is no need for speculum examination, additional reagents, or equipment. Samples can be stored in a refrigerator at +4° for six hours. However, confirmation of pPROM and PROM requires the woman to be seen in a hospital setting. | This assessment is time-consuming, requires equipment and expertise, and can only detect significant loss of AF. It cannot confirm the cause of fluid loss. Not all hospital facilities have ultrasound expertise. | Tests are rapid, easy to use, and have no requirement for power. Minimally trained personnel can conduct the test. It can be used in community- and clinic-level settings. However, confirmation of pPROM and PROM requires the woman to be seen in a hospital setting. | This is a rapid test and can be performed at the bedside in 5 minutes. However, confirmation of pPROM and PROM requires the woman to be seen in a hospital setting. |
| Developer and/or manufacturer | AmniSure® (AmniSure International, LLC. Developed by N-Dia, Inc.). | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | Actim PROM®-test (Medix Biochimica, Kauininen, Finland), AMNI Check® (MAST Diagnostica, Germany). | ROM Check (formerly Adeza Biomedical Corporation, now Hologic). |
| Status | Commercialized with the CE Mark. The device received notification as a Class I device from the USFDA in 2009. The product was introduced in Europe, Israel, and Russia as of October 2003. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | This technology has been commercialized. Actim PROM®-test received 510(k) clearance as a Class I device in 2011. | Commercialized in the United States through Matria Healthcare, Inc. and has received USFDA approval. Needs further investigation on the current status of the technology. Adeza was acquired by Cytyc which was subsequently merged to Hologic in 2007. Hologic's web-site currently does not list ROM Check. |

| Supply Information | TECHNOLOGY/SOLUTION—TABLE 2 | | | |
|---|--|--|---|--|
| | Placental alpha-micro-globulin | Ultrasound assessment of amniotic fluid volume | Insulin-like growth factor binding protein-1 (IGFBP-1) detection test | Alpha-fetoprotein detection test |
| Efficacy/ effectiveness | Sensitivity: 98% to 99% Specificity: 88% to 100% (Manufacturer’s claim: 98.9% sensitivity, 100% specificity) | Sensitivity: 85.1% Specificity: 78.6% Not a reliable screening test if used alone to detect pPROM and PROM. Used only to help confirm diagnosis. | Sensitivity: 84.9% Specificity: 92.8% | Sensitivity: 90% to 94% Specificity: 95% to 100% |
| Manufacturing quality and capacity | The device was developed by N-Dia, Inc. but is manufactured and distributed by AmniSure International LLC through distributors. AmniSure was established in 2005 and appears to have only one product. ⁷ Their manufacturing capability is uncertain. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | Actim PROM®-test and AMNI Check are manufactured in large European countries. Medix Biochemia, the manufacturer of Actim PROM, has worldwide distribution channels. The manufacturing capacity and capability for these tests are unlikely to be an issue. | No data available. |
| Intellectual property ownership | Patent issued in the United States Patent 7,709,272. The patent is assigned to N-Dia, Inc. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | No data available. | Patent issued in the United States patent 6,267,722. The patent has been assigned to Adeza Biomedical Corporation. |
| Cost and cost drivers | The price of the test is unknown. Cost drivers also include the cost of training and labor to perform the test, although these are likely to be minimal. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | No data available. | No data available. |
| Delivery/ procurement channels | Procurers in the public and private sectors can purchase the test directly from the company. The test also could be listed in the UNICEF Supply Catalogue for bulk procurement. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | Procurers in the public and private sectors can purchase the test directly from the company. The test could also be listed in the UNICEF Supply Catalogue for bulk procurement. | No data available. |
| Sustainable business models | Since the company appears to be small, substantial scale-up in their manufacturing and distribution capacity could be required to achieve sustainable supply of the test. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | Manufacturers appear to have large manufacturing and distribution capacity to sustain the supply of the tests. The test could be incorporated into smaller laboratories in the public sector. Some social franchises offer laboratory services, which could be a potential avenue to offer these tests. | No data available. |

| Demand Information | TECHNOLOGY/SOLUTION—TABLE 2 | | | |
|--------------------------|---|---|--|--|
| | Placental alpha-micro-globulin | Ultrasound assessment of amniotic fluid volume | Insulin-like growth factor binding protein-1 (IGFBP-1) detection test | Alpha-fetoprotein detection test |
| Existing demand | The market size could be driven by the number of women who are at risk of PROM but do not present apparent symptoms of PROM. These tests can be used in clinics. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | The market size could be driven by the number of women who are at risk of PROM but do not present apparent symptoms of PROM. These tests can be used in clinics. | No data available. |
| Attractiveness | <p>The PAMG-1 test has been compared to the amnio-dye test. Preliminary results of this study were published recently and indicate that the PAMG-1 test is as reliable as the amnio-dye test in diagnosing ROM. More studies are needed in low-resource settings to determine the effectiveness and acceptability in those settings.</p> <p>The PAGM-1 rapid strip test seems to be the more accurate bedside test compared with other strip tests. Existing literature suggests that biomarkers (such as PAMG-1, AFP, or IGFBP-1) in the cervicovaginal discharge may be superior to conventional clinical assessment (pooling, nitrazine) in confirming the diagnosis of ROM.</p> | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | User acceptability has not been evaluated for these tests. | User acceptability has not been evaluated for these tests. |
| Price sensitivity | No data available. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | No data available. | No data available. |

| Demand Information | TECHNOLOGY/SOLUTION—TABLE 2 | | | |
|------------------------------------|---|---|--|---|
| | Placental alpha-micro-globulin | Ultrasound assessment of amniotic fluid volume | Insulin-like growth factor binding protein-1 (IGFBP-1) detection test | Alpha-fetoprotein detection test |
| Policy environment | Requirement for highly skilled personnel and ultrasound limit applicability of this technique in low-resource countries. | Test has not been used in low-resource settings, but has strong potential considering scientific data. Uptake in these settings may be affected by the same factors affecting point of care (POC) tests in general (cost, coverage, availability, and correct use). | Refer to low-cost ultrasound in birth asphyxia data sheet. | These tests have not been used in low-resource settings. Uptake in these settings may be affected by the same factors affecting POC tests in general (cost, coverage, availability, and correct use). |
| Donor/ stakeholders | International community has expressed some interest in developing biomarkers and POC tests to diagnose pPROM and PROM. | Refer to low-cost ultrasound in birth asphyxia data sheet. | International community has expressed some interest in developing biomarkers and POC tests to diagnose pPROM and PROM. | International community has expressed some interest in developing biomarkers and POC tests to diagnose pPROM and PROM. |
| Pre- and post-sales support | This test does not require any instrument, and the test kit is disposable. The manufacturer claims that AmniSure® should be used by qualified personnel (physicians, certified nurse midwives, or labor and delivery nurses certified to evaluate ROM). | Refer to low-cost ultrasound in birth asphyxia kit. | This test does not require any instrument, and the test kit is disposable. Training is required, but it might not be intensive. | This test does not require any instrument, and the test kit is disposable. Training is required, but it might not be intensive. |
| Need for demand creation | Involving laboratory technicians and medical professionals might be a key. Lab technicians might appreciate the test as lab capacity-building. | Refer to neonatal asphyxia for information on low-cost ultrasound technologies. | Involving laboratory technicians and medical professionals might be a key. Lab technicians might appreciate the test as lab capacity-building. | No data available. |

References

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Biomarkers for Early Detection of Intra-Amniotic Infection

Intra-amniotic infection (IAI), or chorioamnionitis, complicates up to 10% of all pregnancies and up to 2% of labors at term. There is a significant risk of complications for the mother and the neonate following IAI, including sepsis and pneumonia. In addition, there is a correlation between IAI and premature rupture of membranes (PROM), preterm premature rupture of membranes (pPROM), preterm labor (PTL), and preterm birth. Research in the last decade has also revealed a complex and significant association between IAI and cerebral palsy and other central nervous system damage in both the preterm and term fetus. Timely diagnosis and treatment of IAI can significantly reduce the risk of both maternal and neonatal complications.¹

Approximately 5% to 10% of women with IAI will develop bacteremia. Other maternal complications include labor abnormalities, increased need for oxytocin, and increased risk of cesarean birth. IAI also increases the risk of postpartum hemorrhage and surgical complications such as wound infection, pelvic abscess, and postpartum endometritis.¹ Maternal morbidity is increased with IAI; although maternal mortality is extremely rare in developed countries, this is not the case in societies where pregnant women have limited or no access to medical care.²

The diagnosis of IAI is most commonly made on the basis of clinical symptoms, in particular the presence of maternal fever of more than 38°C (100.4°F) when there are no other identifiable reasons for fever (e.g., urinary tract infection). Other symptoms include maternal tachycardia (≥ 100 -120 bpm), fetal tachycardia (≥ 160 bpm), uterine tenderness, purulent or foul-smelling amniotic fluid, and maternal leukocytosis ($>15,000$ -18,000 cells/mm³). In making the diagnosis of chorioamnionitis, however, providers must keep in mind that research has shown that even in the presence of clinical symptoms suggestive of IAI, the placental pathology often does not support the diagnosis. One such study found that in 38% of cases of clinically diagnosed chorioamnionitis, there was no histologic evidence of infection.³ On the contrary; histologic chorioamnionitis can be present without clinical symptoms. In one study, subclinical infection was present two to three times more commonly than clinical infection.⁴ Subclinical intrauterine infection has been implicated in the development of PTL, PROM and pPROM. Antepartum diagnosis of subclinical chorioamnionitis would, therefore, help providers determine whether the benefits of prolonging pregnancy outweigh the risks in the woman with PTL or pPROM at less than 34 weeks estimated gestational age.

The definitive diagnosis of IAI requires a transabdominal amniocentesis to perform a direct examination of amniotic fluid. However, many health care providers are reluctant to perform amniocentesis because of perceived risks such as bleeding, rupture of the fetal membranes, or increased uterine contractions.⁵

Currently, there is interest in exploring specific biomarkers that could be used for noninvasive, early detection of IAI. The main challenge facing future biomarker research, and in reviewing biomarker studies, is the lack of standard operating protocols for each specific biomarker. In creation of a test to detect IAI, it is important to consider issues such as ease of use, patient's convenience, test performance, levels of predictability, reliability, and cost. The perfect test would be a noninvasive test that could provide clinicians with accurate and fast information to triage women who require clinical management of IAI versus those at low risk that do not require hospitalization and unnecessary interventions.

PATH conducted an extensive review of available and potential host biomarkers as part of a maternal sepsis project. The search revealed no biomarker for the diagnosis of puerperal sepsis with better performance characteristics than stringent clinical criteria. In addition, most biomarkers studied require amniocentesis which is an invasive procedure with potential side effects for the mother and neonate.

The following table lists only a few of the biomarkers that have been studied. The list is not exhaustive and only illustrates the biomarkers for which more information is available. Also, considering the lack of clinical experience of most of the biomarkers listed in detecting IAI, there is no clear definition or recommendation that favors one versus another. Lastly, given the lack of performance of currently studied biomarkers to detect IAI and knowing that development in this area will require substantial financial commitment, it will be important for decision-makers to justify whether investment in this area is a priority over other areas that have shown more promising results.

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|---|---|--|--|--|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Description | Immunoassay for quantitative determination of human Interleukin 8 (IL-8) concentrations in cell culture supernates, serum, plasma, urine, and amniotic fluid (AF). This assay employs the quantitative sandwich enzyme immunoassay technique. | Qualitative immunochromatographic bedside test developed to detect intra-amniotic inflammation based on the detection of an elevated concentration of Matrix metalloproteinase-8 (MMP-8) in AF. | The BRAHMS PCT-Q is an immunochromatographic test for the semiquantitative detection of PCT, which is used for diagnosing and controlling the treatment of severe bacterial infection and sepsis. BRAHMS PCT-Q is a test system with an incubation period of only 30 minutes, which neither depends on apparatus nor needs calibrating. The test uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase). Its effectiveness to diagnose IAI is unclear. | Protein analysis technique to identify protein biomarkers for pregnancy-related complications. ProteoGenix can consistently utilize multiple biomarkers in samples that are attributable to disease, rendering it superior to both conventional single-marker and proteomics-based pattern-recognition technologies. The advantages of a rapid, easy-to-interpret test from serum or other fluids make a compelling opportunity for point-of-care use. |
| Characteristics applicable for low-resource settings | Currently the technology is available for research purposes only. Even if adapted for clinical use, the technology requires highly skilled lab technicians, an ELISA reader, and a regular stock of supplies and reagents. | The test is described as fast, easy to use, does not require laboratory equipment, and results are available in 15 minutes. However, it requires 20 µl of AF obtained through abdominal amniocentesis. Amniocentesis requires highly skilled personnel and must be performed in a hospital with capacity to handle potential procedural complications. | This is a rapid test and is considered a POC test in developed countries. It requires instruments to run the assay and requires use of serum or plasma, which needs centrifugation or separation. Users require training. Storage requirement: 4°C to 30°C. | This technology requires the use of centrifuge for serum separation. It is applicable in clinic settings. Lab technicians require training. |
| Developer and/or manufacturer | Quantikine® ELISA—Human CXCL8/IL-8 Immunoassay (R&D Systems, Inc.). | MMP-8 PTD Check (SK Pharma Co, Ltd, Kyunggi-do, Korea). | B-R-A-H-M-S PCT (Thermo Fisher Scientific). | ProteoGenix, Inc. |
| Status | Currently the test is manufactured for research use only and is not for use in diagnostic procedures. | Status is unknown. This test was mentioned in an article; however, the company's website does not include any information related to this test. | Status is commercialized. | This technology is in clinical trials. |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|---|---|--|--|--|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Efficacy/ effectiveness | <p>In urine:⁶</p> <ul style="list-style-type: none"> -Sensitivity: 53% -Specificity: 91% <p>In cervical fluid:⁷</p> <ul style="list-style-type: none"> -Sensitivity: 69% -Specificity: 63% <p>In amniotic fluid:⁶</p> <ul style="list-style-type: none"> -Sensitivity: 93% -Specificity: 75% | <p>For identification of intra-amniotic infection/ inflammation:⁸</p> <ul style="list-style-type: none"> -Sensitivity: 90% -Specificity: 80% -Positive predictive value: 77% -Negative predictive value: 92% <p>It is also considered an independent predictor of interval to delivery (hazards ratio 3.7; 95% CI, 2.4–5.9) and significant neonatal morbidity (odds ratio 3.1; 95% CI, 1.2–7.9).⁸</p> | <p>Sensitivity: 88.9%</p> <p>Specificity: 65.2%</p> <p>Positive predictive value: 40%</p> <p>Negative predictive value: 95.7%⁹</p> <p>These values are for detection of sepsis at any age or presentation. Values for detection of IAI and puerperal sepsis have not been determined.</p> | <p>Unknown.</p> |
| Manufacturing quality and capacity | <p>Manufactured and distributed in the United States & Canada by R&D Systems, Inc.</p> <p>Distributed in the UK and Europe by R&D Systems Europe, Ltd, and in China by R&D Systems China Co., Lt.</p> <p>Although the manufacturing capacity is unknown for this particular product, it is unlikely to be large, considering that the product has not yet been approved for clinical use.</p> | <p>Manufacturing information is unknown. The company's website does not provide product information. It is likely that the product has not reached its commercialization phase and therefore has not been manufactured.</p> | <p>Manufactured by Thermo Fisher Scientific. B·R·A·H·M·S, the developer of the test, was acquired by Thermo Fisher Scientific, a large US company, in 2009.</p> <p>The PCT assay received USFDA clearance in 2008.</p> | <p>Manufactured by ProteoGenix, Inc. The company was established in 2003, and their products are offered on their web site. The size of the company and its manufacturing capability is likely to be relatively small.</p> |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|--|--|--|--|--|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Intellectual property ownership | No data available. | No data available. | <p>B·R·A·H·M·S owns the IP on PCT and offers the test today along with bioMerieux.</p> <p>Several other immunoassay providers, including Roche Diagnostics and Siemens, have licensed PCT from B·R·A·H·M·S and are offering it or intend to offer it on their immunoassay platforms. (bioMerieux received 510(k) clearance on the use of the assay with their VIDAS system in 2007.</p> <p>Due to acquisition by Thermo Fisher Scientific, it is likely that B·R·A·H·M·S's patents were assigned to Thermo Fisher Scientific.</p> | No data available. |
| Cost and cost drivers | <p>A kit, which contains sufficient materials to run an ELISA on one 96-well plate, is priced at US\$495 per kit.</p> <p>The kit is expensive. Also, additional instruments will be required to run the test.</p> <p>Shipping cost and import duties might increase the price.</p> | The cost is unknown. The company's website does not provide product information. | <p>The cost is approximately US\$23.31 per test.</p> <p>The cost per assay is in the range of US\$30 to US\$50. The cost to a hospital is about US\$40 to US\$45 to run each assay. The PCT test has shown efficacy in reducing both patients' antibiotic duration and also their hospital length of stay; but even with the relatively low cost to hospitals and its benefits for patient care, only an estimated 300 US hospitals currently employ the test.¹⁰</p> <p>Shipping cost and import duties might add to the price.</p> | No data available. |
| Delivery/procurement channels | The test is currently available only for research purposes. | Further investigation is needed. The company's website does not provide product information. | Currently available in developed countries. Procurers can directly contact the company for purchase. | The test has not yet been commercialized. |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|------------------------------------|--|--|--|--|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Sustainable business models | The test is currently available only for research purpose. | Further investigation is needed. The company's website does not provide product information. | <p>Instruments will be required in order to run the test. Due to the complexity of the test, this test is likely to be used in centralized laboratories or private hospitals with relatively sophisticated laboratories in developing countries.</p> <p>Not only training but also post-sales technical support will be necessary. Companies providing this assay with instruments are required to have infrastructure to provide training and technical support.</p> <p>Since sales volume of this test is likely to be small in low-resource countries, companies might be required to price the test high with instruments to accommodate the cost of training and post-sales technical support. Some financial schemes will be necessary to make this assay and instruments more affordable. Alternatively, leasing the instruments could be an option if permitted by regulation.</p> | The test has not yet been commercialized. |

| Demand Information | TECHNOLOGY/SOLUTION | | | |
|-----------------------------|---|---|---|---|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Existing demand | The demand will be driven by the number of women who are suspected with IAI. The number of centralized laboratories and samples that they can process per day also affects the market size. Due to complexity of the test, this test will be used in centralized laboratories. The demand, therefore, will not be large in developing countries. | Further investigation is needed. The company's website does not provide product information. The demand will be driven by the number of women who are suspected with IAI. | The demand will be driven by the number of women who are suspected with IAI. The number of centralized laboratories and samples that they can process per day also affects the market size. Due to complexity of the test, this test will be used in centralized laboratories. The demand, therefore, will not be large in developing countries. | The test has not yet been commercialized. |
| Attractiveness | The product is not available for diagnostic purpose. | The test is described as rapid. However, the test requires amniocentesis and highly skilled personnel. | The test is described as rapid, easy to use and helpful as a supportive test when the quantitative assay is not available. The test has not been used in low-income countries. | The product has potential as a point-of-care test, but requires further clinical evaluation to determine potential barriers and opportunities for uptake. |
| Price sensitivity | No data available | No data available | No data available | No data available |
| Policy environments | Policy alignment is needed. | Policy alignment is needed. | Policy alignment is needed. | Policy alignment is needed. |
| Donors/ stakeholders | There are currently no international donors working on this technology. However, there are some groups such as Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), The Bill & Melinda Gates Foundation, Global Network for Perinatal and Reproductive Health, and academic institutions that may be interested in continuing evaluation of these technologies. | There are currently no international donors working on this technology. However, there are some groups such as GAPPS, the Bill & Melinda Gates Foundation, Global Network for Perinatal and Reproductive Health, and academic institutions that may be interested in continuing evaluation of these technologies. | There are currently no international donors working on this technology. However, there are some groups such as GAPPS, the Bill & Melinda Gates Foundation, Global Network for Perinatal and Reproductive Health, and academic institutions that may be interested in continuing evaluation of these technologies. | There are currently no international donors working on this technology. However, there are some groups such as GAPPS, the Bill & Melinda Gates Foundation, Global Network for Perinatal and Reproductive Health, and academic institutions that may be interested in continuing evaluation of these technologies. |

| Demand Information | TECHNOLOGY/SOLUTION | | | |
|------------------------------------|--|--|--|--|
| | Interleukin 8 in urine, cervical fluid, and amniotic fluid | Matrix metalloproteinase-8 | Procalcitonin (PCT) for bacterial infection | Multiplex biomarker technology to detect IAI |
| | | | | Proteomic biomarkers in vaginal fluid |
| Pre- and post-sales support | Not only training, but also post-sales technical support will be necessary. | The technology needs further investigation. The company's website does not provide product information. | Not only training, but also post-sales technical support will be necessary. | The test has not yet been commercialized. |
| Need for demand creation | Although the need for this test is significant, the need has not yet been translated into demand. Clinical trial data and cost-effectiveness data from low-resource countries are likely to be required in order to first assess the utility of this test in low-resource countries. | Although the need for this test is significant, the need has not yet been translated into demand. Clinical trial data and cost-effectiveness data from low-resource countries are likely to be required in order to first assess the utility of this test in low-resource countries. | Although the need for this test is significant, the need has not yet been translated into demand. Clinical trial data and cost-effectiveness data from low-resource countries are likely to be required in order to first assess the utility of this test in low-resource countries. | Although the need for this test is significant, the need has not yet been translated into demand. Clinical trial data and cost-effectiveness data from low-resource countries are likely to be required in order to first assess the utility of this test in low-resource countries. |

Point-of-Care Diagnostic Tests to Detect Sexually Transmitted Infections and Asymptomatic Bacteriuria

There is a great need for simple, cheap diagnostic tests for sexually transmitted infections (STIs) that can be performed at the point of care (POC), enabling treatment to be given immediately. These tests can be incorporated as part of antenatal care visits during pregnancy to decrease morbidity and mortality due to complication of STI during pregnancy.

STIs and reproductive tract infections (RTIs) and their complications are among the most important causes of illness and death for women in poor regions of the world. Infectious complications of pregnancy and their consequences (postabortion and postpartum infections) alone are estimated to cause about one-third of the 500,000 maternal deaths that occur each year. Most of this preventable burden of disease is concentrated in low-income populations.¹ Gonorrhea and chlamydial infection may be 10 to 100 times more common in low-income communities than high-income communities.² Prevalence is higher in South East Asia and sub-Saharan Africa. In such areas, these infections can cause uterine infections. If a woman develops a STI during pregnancy and is not treated, the microorganism causing the disease will stay in the genital track and can cause a uterine infection after delivery. Uterine infections caused by STIs can be prevented by diagnosis and treatment during pregnancy.

STIs and RTIs can also cause poor pregnancy outcomes. Infection within the placenta or amniotic sac (chorioamnionitis) due to endogenous or sexually transmitted organisms is a major cause of late spontaneous abortion and stillbirth. Infection may lead to prelabor rupture of membranes, preterm delivery, and puerperal sepsis. Congenital infection due to syphilis, gonorrhea, chlamydia, herpes simplex virus, hepatitis B, and HIV can cause blindness, disability, and death of the newborn. Other STIs/RTIs, such as HIV and human papillomavirus, may also have serious or fatal consequences. Many regions with high HIV prevalence also have high rates of curable STIs/RTIs.¹

Clinical diagnosis of sexually transmitted diseases (STDs) requires laboratory tests in a majority of patients. Lengthy turn-around time for STD diagnosis is burdensome to patients and clinicians and has led to empirical treatment for several disease presentations. However, resistance to antibiotics commonly used for treating such infections has emerged in many parts of the world³ making it a challenge to do syndromic management of these conditions. More specific tests are, therefore, important in these settings to reduce the amount of unnecessary treatment and to identify asymptomatic infections.

Another challenge in STI control is the high prevalence of asymptomatic gonococcal and chlamydial infections, especially in developing countries where partner notification is difficult. A widely available diagnostic test which allows prompt and effective treatment of asymptomatic patients could reduce the prevalence of these infections, prevent complications, and reduce the incidence of HIV infection, whose transmission they facilitate. Such a test could also play an important part in reducing unnecessary treatment of patients with STI syndromes that are not caused by these pathogens.⁴

Antenatal clinic visits provide opportunities for preventing and detecting STIs and RTIs, and women should be encouraged to attend early in pregnancy. The presence of POC rapid diagnostic tests can facilitate diagnosis and prescription of appropriate treatment during antenatal care.

Point-of-care tests for urinary tract infections and asymptomatic bacteriuria

Urinary tract infections (UTIs) are common during pregnancy. UTIs have three principle presentations: asymptomatic bacteriuria, acute cystitis and pyelonephritis. The diagnosis and treatment of UTI depends on the presentation. Asymptomatic bacteriuria (defined as bacterial colonization of the urinary tract without urinary tract symptomatology) is the most prevalent of these infections.⁵

Asymptomatic bacteriuria during pregnancy has serious consequences. Untreated asymptomatic bacteriuria leads to the development of symptomatic cystitis in approximately 30 percent of patients and can lead to the development of pyelonephritis in up to 50 percent.⁶ Asymptomatic bacteriuria is associated with an increased risk of intrauterine growth retardation and low-birth-weight infants. The relatively high prevalence of asymptomatic bacteriuria during pregnancy, the significant consequences for women and for the pregnancy, plus the ability to avoid sequelae with treatment, justify screening pregnant women for bacteriuria.⁷

Routine screening and antimicrobial treatment of confirmed positive cases is recommended. Although there is no doubt that formal urine culture is the best method to confirm presence of bacteria in urine samples, this method is not feasible for many areas of the world, especially in developing countries. A POC diagnostic test is needed in those rural areas where specialized laboratories are not available. Patients at risk of having bacteriuria could be referred to central hospitals for further analysis to confirm the disease. These tests have to be sensitive with high positive predictive value in order to detect all patients that should be referred without missing positive cases.⁵

The ideal test

The ideal screening test for STIs and asymptomatic bacteriuria would be 100 percent sensitive and 100 percent specific. The World Health Organization (WHO) launched a STI Diagnostics Initiative (SDI) in 1998. The current priorities of this initiative are to improve the detection of chlamydia (screening of a high-risk population), gonorrhea (supporting syndromic management in high- and low-disease prevalence settings), and syphilis (specifically the screening of pregnant women). In conjunction, the initiative promoted the development and evaluation of STI diagnostics that meet specific criteria known by the acronym ASSURED. ASSURED stands for: Affordable—by those at risk of infection; Sensitive—few false negatives; Specific—few false positives; User-friendly—simple to perform (three to four steps required with minimal training necessary); Rapid and Robust—to enable treatment at first visit (rapid) and does not require refrigerated storage (robust); Equipment-free—easily collected non-invasive specimens (e.g., saliva, urine); Delivered—to end-users.⁹

The ASSURED criteria also emphasize the benefits of POC testing. POC testing allows for a quick and noninvasive ways to detect infection. Noninvasive tests are tests that do not require a pelvic exam, such as self-obtained vaginal swabs, oral swabs, or urine tests. Some patients find the pelvic exam uncomfortable, and some providers who care for young adults lack the resources and experience to perform a pelvic exam.¹⁰

Barriers to the use of point-of-care tests in clinical settings

Potential barriers to use and adoption of POC tests in clinical settings include patient acceptability, clinician knowledge and acceptance, cost, and technology requirements. Although patients might be comfortable collecting self-swabs, they might not trust the results of the POC test as much as they would a standard testing method such as nucleic acid amplification testing (NAAT) of samples from a pelvic exam or urine specimen.¹¹ Clinicians may sometimes fail to adopt new technologies and prefer testing methods they are comfortable with and are considered the gold standard (i.e., wet mount for trichomoniasis and NAAT for chlamydia). In addition, there can be a wide variation in the time between product development and adoption of new technology, which depends not only on the costs of the new technology but also on how well information and support is distributed over the network of potential users.¹²

The technologies and solutions included in the tables below are tools with potential to increase access to point-of-care diagnostic tests to detect sexually transmitted infections and asymptomatic bacteriuria.

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|--|---|---|
| | Single Antigen Detection—TABLE 1 | | |
| | Syphilis | Chlamydia | Gonorrhea |
| Description | Immunoassay to detect specific antibodies against <i>Treponema pallidum</i> antigen. | Immunochromatographic strip (ICS) tests to detect chlamydia antigen. | ICS tests to detect gonorrhea antigen. |
| Characteristics applicable for low-resource settings | <p>Easy to use and interpret results. Can obtain test results typically within 15 to 20 minutes. Can use whole blood (some tests require serum/plasma).</p> <p>No need for centrifuge and sophisticated laboratory equipment (for testing whole blood). No need for power supply. Can be used by minimally-trained personnel. Tests need to be accompanied with appropriate treatment.</p> | <p>Easy to use and interpret results.</p> <p>Can obtain results in short time (12 minutes or less for QuickVue®, 15 minutes for SD BIOLINE).</p> <p>No need for power supply.</p> <p>Can be used by minimally-trained personnel.</p> <p>Tests need to be accompanied with appropriate treatment.</p> | <p>Easy to use and interpret results.</p> <p>Can obtain results in short time (10 to 20 minutes for One Step Gonorrhea Test).</p> <p>No need for power supply.</p> <p>Can be used by minimally trained personnel.</p> <p>Tests need to be accompanied with appropriate treatment.</p> |
| Developer and/or manufacturer | <p>Multiple. Examples include:</p> <p>Determine® Syphilis (Alere)</p> <p>Syphilis Fast (DIESSE diagnostica)</p> <p>Espline TP (Fujirebio, Inc.)</p> <p>Syphicheck-WB (Qualpro Diagnostic)</p> <p>SD BIOLINE Syphilis 3.0 (Standard Diagnostics, Inc.)</p> <p>VisiTect syphilis (Omega Diagnostics, Ltd.)</p> | <p>Multiple.</p> <p>Examples include: QuickVue® chlamydia test (Quidel Corporation)</p> <p>SD BIOLINE chlamydia test (Standard Diagnostics Inc.)</p> | <p>Multiple.</p> <p>Examples include:</p> <p>One Step Gonorrhea Test (Atlas Link Co., Inc.)</p> |
| Status | Commercialized. Some of the tests are CE marked. | Commercialized. Quidel’s QuickVue® is marketed in the United States. The device is classified as Class I. | Commercialized. One Step Gonorrhea Test is produced by Atlas Link (China) and does not have United States Food and Drug Administration (USFDA) clearance. |
| Efficacy/effectiveness | <p>Sensitivity: 92.8% to 98%.</p> <p>Specificity: 84.5% to 97.7%.</p> <p>Many immunoassays are available for testing syphilis. Some of the tests’ sensitivity and specificity are different from manufacturers’ claims.</p> | <p>Although numerous ICS tests are commercially available, ICS tests for chlamydia generally suffer from lower sensitivity (25% to 65%), compared to the gold standard NAAT.</p> <p>However, Quidel’s QuickVue®, which has USFDA clearance, has overall sensitivity of 92% and specificity of 98%.</p> <p>SD BIOLINE manufactured in South Korea claims in their package insert that its test has sensitivity of 93.1% and specificity of 98.8%. This test does not have USFDA clearance.</p> | <p>Atlas Link does not claim sensitivity and specificity for its One Step Gonorrhea Test.</p> <p>Some other commercially available tests for gonorrhea have sensitivity of 71% and specificity of 99%. ICS tests for gonorrhea generally have lower sensitivity compared to culture, the gold standard for gonorrhea.</p> |

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|--|--|---|
| | Single Antigen Detection—TABLE 1 | | |
| | Syphilis | Chlamydia | Gonorrhea |
| Manufacturing quality and capacity | <p>There are many manufactures; some of them have very large capacity to produce rapid tests.</p> <p>Regulatory mechanisms to evaluate quality of diagnostic tests are generally weak in developing countries. Proper quality control mechanisms are needed. Also, individuals who are involved in procurement at the country level should identify high-quality tests.</p> | <p>Quidel has manufacturing facilities in three locations in the US. It is a large manufacturer of ICS tests.</p> <p>Regulatory mechanisms to evaluate quality of diagnostic tests are weak in developing countries. Proper quality control mechanisms are needed and individuals who are involved in procurement at the country level should identify high-quality tests.</p> | <p>Manufactured by Atlas Link in China.</p> <p>Regulatory mechanisms to evaluate quality of diagnostic tests are generally weak in developing countries. Proper quality control mechanisms are needed. Also, individuals who are involved in procurement at the country level should identify high-quality tests.</p> |
| Intellectual property ownership | <p>Patents related to ICS tests in developed countries are predominantly owned by two companies: (1) Becton Dickinson and (2) Inverness (now Alere). Abbott's lateral flow business was acquired by Inverness in 2007, and Quidel licenses its lateral flow technology from Inverness.</p> | <p>Patents related to ICS tests in developed countries are predominantly owned by two companies: (1) Becton Dickinson and (2) Inverness (now Alere). Abbott's lateral flow business was acquired by Inverness in 2007, and Quidel licenses its lateral flow technology from Inverness.</p> | <p>ICS tests patents in developed countries are predominantly owned by two companies: (1) Becton Dickinson and (2) Inverness (now Alere). Abbott's lateral flow business was acquired by Inverness in 2007, and Quidel licenses its lateral flow technology from Inverness.</p> |
| Cost and cost drivers | <p>Determine® Syphilis: \$1 per assay.¹³</p> <p>SD Bioline Syphilis: \$0.45 per assay.¹³</p> <p>Eight rapid syphilis tests evaluated by SDI are included in WHO Bulk Procurement. The economic cost of the intervention is \$1.44 per woman screened, \$20 per woman treated, and \$187 per adverse birth outcome averted. The cost per disability-adjusted li \$10.56 per DALY saved. The cost per DALY saved from all syphilis screening studies ranged from US\$3.97 to US\$18.73.¹⁴</p> | <p>Quidel's QuickVue® is available online at \$255 per kit (25 tests).</p> | <p>Price information for the One Step Gonorrhea Test not available.</p> |
| Delivery/procurement channels | <p>All the tests listed here are on the United Nations Children's Fund's (UNICEF's) Supply Catalog for purchasing.</p> <p>Eight tests are in WHO's bulk procurement schemes.</p> | <p>Except for syphilis and HIV tests, POC diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations.</p> <p>Buyers need to purchase the tests from manufacturers or commercial distributors directly.</p> | <p>Except for syphilis and HIV tests, POC diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations.</p> <p>Buyers need to purchase the tests from manufacturers/ commercial distributors directly.</p> |
| Sustainable business models | <p>POC tests for STIs can be used in STI clinics, antenatal care programs, or surveillance programs in both the public and private sectors.</p> <p>There are also social franchise clinics that provide testing and treatment for STIs.</p> | <p>POC tests for STIs can be used in STI clinics, antenatal care programs, or surveillance programs in both the public and private sectors.</p> <p>There are also social franchise clinics that provide testing and treatment for STIs.</p> | <p>POC tests for STIs can be used in STI clinics, antenatal care programs or surveillance programs, in both the public and private sectors.</p> <p>There are also social franchise clinics that provide testing and treatment for STIs.</p> |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|--------------------------------------|--|---|--|
| | Single Antigen Detection—TABLE 1 | | |
| | Syphilis | Chlamydia | Gonorrhea |
| Existing and potential demand | <p>The market size will be driven by the number of women who receive antenatal care services as the priority market segment.</p> <p>STI clinics and surveillance programs will also be buyers/users for the tests.</p> | <p>The market size will be driven by the number of women who receive antenatal care services as the priority market segment.</p> <p>STI clinics and surveillance programs will also be buyers/users for the tests.</p> <p>Each country's STI prevention/control strategy and prevalence of STIs and HIV are likely to affect implementation of STI screening. This in turn will affect the demand for STI tests.</p> | <p>The market size will be driven by the number of women who receive antenatal care services as the priority market segment.</p> <p>STI clinics and surveillance programs will also be buyers/users for the tests.</p> <p>Each country's STI prevention/control strategy and prevalence of STIs and HIV are likely to affect implementation of STI screening. This in turn will affect the demand for STI tests.</p> |
| Attractiveness | <p>Mozambique's experience was that syphilis testing increased to 93 percent in all facilities due to introduction of the ICS test.</p> <p>The greater numbers of women tested and treated likely contributed, along with other factors, to a drop in the antenatal prevalence of syphilis from 12 percent in 1988 to 5 percent in 2005.</p> <p>In addition to having a positive impact on women and their children, this project also helped to bolster primary health care and the supporting systems in government health facilities.</p> | <p>POC testing allows for a quick and noninvasive ways to detect infection.</p> <p>Noninvasive tests are tests that do not require a pelvic exam, (e.g., self obtained vaginal swabs, oral swabs, or urine tests). Some patients find the pelvic exam uncomfortable, and some providers who care for young adults lack the resources and experience to perform a pelvic exam.</p> <p>In a study conducted evaluating POC chlamydia tests, participants were asked about acceptability of self-collecting vaginal swabs; 95.9 percent felt comfortable collecting self-swabs. In addition, over 99 percent participants in the study by indicated they were willing to wait up to two hours for rapid chlamydia test results.¹⁵</p> | <p>A study by Benzaken, et al.¹⁶ evaluated patient acceptability for a rapid gonorrhea test, and 98.8 percent of participants said they would be willing to wait up to an hour for test results.</p> |
| Price sensitivity | <p>No data available.</p> <p>The current tests listed on UNICEF Supply Catalog are priced between US\$0.45 and US\$2 per test.</p> | <p>No data is available.</p> <p>Quidel's QuickVue®, approved by the USFDA is available online at US\$10.2 per test.</p> <p>Tests manufactured in China could be less expensive.</p> | <p>No data is available.</p> <p>Price information for the One Step Gonorrhea Test is not available.</p> <p>Tests manufactured in China could be less expensive.</p> |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|------------------------------------|--|---|---|
| | Single Antigen Detection—TABLE 1 | | |
| | Syphilis | Chlamydia | Gonorrhea |
| Policy environment | <p>In 2009, countries of the Americas, in collaboration with WHO, UNICEF, and others, agreed to eliminate mother-to-child transmission, of HIV and congenital syphilis by 2015.</p> <p>Both infections are recognized as significant public health problems in Latin America and the Caribbean, with an annual incidence of 6,400 children infected by HIV and 164,000 children born with congenital syphilis.</p> <p>In order to achieve its goals of elimination, the regional initiative seeks to ensure that at least 95 percent of pregnant women receive early antenatal care that includes screening for both HIV and syphilis.</p> | <p>Chlamydia is one of the disease control priorities in developing countries. <i>Chlamydia trachomatis</i> is the most common bacterial STI in the world.</p> <p>The current gold standard for detection of chlamydia is NAAT. However, NAAT is expensive and technically demanding. Scientific evidence is in favor of use of POC tests for chlamydia, especially in scenarios where many women will not return for treatment and in populations where the delay in treatment would result in significant STI transmission.</p> | <p>Gonorrhea is one of the disease control priorities in developing countries.</p> <p>The gold standard test for the detection of <i>N. gonorrhoeae</i> is culture, which has high sensitivity and specificity. However, it requires well-trained staff and its performance is affected by specimen transport conditions. In settings where patients are asked to return for laboratory results, some infected patients never receive treatment as they fail to return for their test results. This reduction in treatment, and the possible onward transmission of <i>N. gonorrhoea</i> during any delay in treatment, means that a rapid test of lower sensitivity may be more effective if it results in patients being treated at the initial visit. Even with the low sensitivity of currently available rapid tests (50 percent to 70 percent), modeling shows that they can outperform gold standard tests in populations with high sexual activity and/or low return rates.</p> <p>A barrier for adoption of rapid tests is the cost.</p> |
| Donors/ stakeholders | <p>UNFPA, UNICEF, and WHO support implementation and scale-up of syphilis as well as HIV tests in antenatal care.</p> | <p>Centers for Disease Control and Prevention (CDC); Joint United Nations Programme on HIV/AIDS (UNAIDS); London School of Hygiene and Tropical Medicine; Point-of-Care Technologies Research Network (POCTRN)-Johns Hopkins University ; United Nations Development Programme (UNDP); WHO Special Program for Research and Training in Tropical Diseases (WHO TDR); World Bank.</p> | <p>CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank</p> |
| Pre- and post-sales support | <p>No special pre- or post-sales supports are required.</p> | <p>No special pre- or post-sales supports are required.</p> | <p>No special pre- or post-sales supports are required.</p> |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|---------------------------------|---|---|---|
| | Single Antigen Detection—TABLE 1 | | |
| | Syphilis | Chlamydia | Gonorrhea |
| Need for demand creation | [In Mozambique] Several factors that are key to successful operation within the existing health system (rather than setting up outside narrowly-focused programs) included support for health workers (conduct a short training followed by on-the-job supervision and follow-up on a regular basis) and improved procurement and management systems. | Questions of feasibility, acceptability, costs, cost-effectiveness, cost recovery, sustainability, and the associated policy implications need to be addressed before the widespread use of STI screening programs in developing countries. ¹⁷ | Questions of feasibility, acceptability, costs, cost-effectiveness, cost recovery, sustainability, and the associated policy implications need to be addressed before the widespread use of STI screening programs in developing countries. ¹⁷ |

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|--|---|--|
| | Single Antigen Detection—TABLE 2 | | |
| | Herpes simplex infection | <i>Trichomonas vaginalis</i> | Urine rapid test to detect bacteriuria and UTI |
| Description | The biokit HSV-2 Rapid Test (Biokit USA) is a single-unit, membrane-based immunoassay for the qualitative determination, either in heparinized capillary whole blood taken by finger stick or in serum, of circulating IgG antibodies specific for herpes simplex virus type 2 (HSV-2), which arise as a result of infection with HSV-2. It is intended for in vitro diagnostic use by health professionals in POC testing. Detection of HSV-2 specific antibodies in less than 10 minutes. | Immunoassays intended for qualitative detection of antigens to <i>Trichomonas vaginalis</i> . | A urine dipstick is a colorimetric chemical assay that can be used to determine the pH, specific gravity, protein, glucose, ketone, bilirubin, urobilinogen, blood, leukocyte, and nitrite levels of an individual's urine. It consists of a reagent stick-pad which is immersed in a fresh urine specimen and then withdrawn. The urine dipstick offers an inexpensive and fast method to perform screening urinalyses which help in identifying the presence of various diseases or health problems. |
| Characteristics applicable for low-resource settings | Easy to use and interpret results. Can obtain results in short time. No need for power supply. Can be used by minimally trained personnel. Tests need to be accompanied with appropriate treatment. | Easy to use and interpret results. Can obtain results in short time. Both OSOM® Trichomonas Rapid Test and XenoStrip-Tv™ provide results within 10 minutes. No need for power supply. Can be used by minimally trained personnel. Tests need to be accompanied with appropriate treatment. | No need for power supply. It can be used by unskilled personnel with minimal training. Rapid screening of asymptomatic bacteriuria. Positive women may need confirmation with culture. It can be used in the community and in clinics. |
| Developer and/or manufacturer | Multiple. Example: biokit-HSV-2 (Biokit USA). | Multiple. Examples include: OSOM® Trichomonas Rapid Test (Sekisui Diagnostics). XenoStrip-Tv™ (Xenotope Diagnostics, Inc.) | Multiple. Examples include: UTItest 5V® (QuicklyTest) URISCREEN™ (Savyon Diagnostics) Chemstrip LN (BioDynamics, Division of Boehringer Mannheim Diagnostics) Multistix® SG urine dipstick (Siemens) |
| Status | Commercialized. | Commercialized. Both OSOM® Trichomonas Rapid Test and XenoStrip-Tv™ tests have 510(k) clearance as Class I device. | Commercialized. |
| Efficacy/ effectiveness | For the biokit HSV-2 Rapid Test: Sensitivity: 91% to 100% Specificity: 94% to 98%. However, certain lots of the biokit HSV-2 Rapid Test were recalled in 2010 due to false negatives (source: USFDA website). | For OSOM® Trichomonas Rapid Test: Sensitivity: 94.7% Specificity: 100 % For XenoStrip-Tv™*: Sensitivity: 90% Specificity: 92.5% *Sensitivity: 66.7% and specificity: 100% according to Pillay A., et al. ¹⁸ | The urine dipstick test alone seems to be useful in all populations to exclude the presence of infection if the results of both nitrites and leukocyte-esterase are negative. Sensitivities of the combination of both tests vary between 68% and 88% in different patient groups, but positive test results have to be confirmed. |

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|---|---|---|
| | Single Antigen Detection—TABLE 2 | | |
| | Herpes simplex infection | <i>Trichomonas vaginalis</i> | Urine rapid test to detect bacteriuria and UTI |
| Manufacturing quality and capacity | Manufactured by BioKit USA in the United States. Regulatory mechanisms to evaluate quality of diagnostic tests are generally weak in developing countries. Proper quality control mechanisms are needed. Also, individuals who are involved in procurement at the country level should identify high-quality tests. | The OSOM® Trichomonas Rapid Test is manufactured by Sekisui Diagnostics, a large international company in the United States. Regulatory mechanisms to evaluate quality of diagnostic tests are generally weak in developing countries. Proper quality control mechanisms are needed. Also, individuals who are involved in procurement at the country level should identify high-quality tests. | Multiple manufacturers. |
| Intellectual property ownership | Patents related to ICS tests in developed countries are predominantly owned by two companies: (1) Becton Dickinson and (2) Inverness (now Alere). Abbott’s lateral flow business was acquired by Inverness in 2007, and Quidel licenses its lateral flow technology from Inverness. | Patents related to ICS tests in developed countries are predominantly owned by two companies: (1) Becton Dickinson and (2) Inverness (now Alere). Abbott’s lateral flow business was acquired by Inverness in 2007, and Quidel licenses its lateral flow technology from Inverness. | No data available. |
| Cost and cost drivers | biokit HSV-2 Rapid Test: US\$448 for 20 tests. ¹⁹ | The OSOM® Trichomonas Rapid Test is available online at US\$209 per kit (25 tests). | UTItest 5V® is available online at £16.63 (including VAT) for 100 strips. The UNICEF Supply Catalog lists urinary test strips at US\$3.28 (100 strips). The strips are also included in a midwifery kit and an obstetric surgical kit. Please note that this urinary test strip is only to detect presence of glucose and protein. Using a decision analysis, screening for and treatment of asymptomatic bacteriuria to prevent pyelonephritis has shown to be cost-effective over a wide range of estimates. |
| Delivery/procurement channels | Except for syphilis and HIV tests, POC diagnostic tests are not listed in UNICEF Supply Catalog for procurement by public sector organizations. Buyers need to purchase the tests from manufacturers or commercial distributors directly. | Except for syphilis and HIV tests, POC diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations. Buyers need to purchase the tests from manufacturers or commercial distributors directly. | Urinary test strips listed in UNICEF Supply Catalog are only to detect glucose and protein. Urinary test strips to detect bacteriuria and UTI could be listed in UNICEF Supply Catalog for purchase by public-sector procurers. |
| Sustainable business models | POC tests for STIs can be used in STI clinics, antenatal care programs or surveillance programs in both the public and private sectors. There are also social franchise clinics that provide testing and treatment for STIs. | POC tests for STIs can be used in STI clinics, antenatal care programs or surveillance programs in both the public and private sectors. There are also social franchise clinics that provide testing and treatment for STIs. | A low profit margin is expected by selling the strip to the public sector and will need to be compensated by higher sales volumes. |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|--------------------------------------|--|---|---|
| | Single Antigen Detection—TABLE 2 | | |
| | Herpes simplex infection | <i>Trichomonas vaginalis</i> | Urine rapid test to detect bacteriuria and UTI |
| Existing and potential demand | <p>The market size will be driven by the number of women who receive antenatal care services as the priority market segment.</p> <p>STI clinics and surveillance programs will also be buyers/users for the tests.</p> <p>Each country's STI prevention/control strategy and prevalence of STIs and HIV are likely to affect implementation of STI screening. This in turn will affect the demand for STI tests.</p> | <p>The market size will be driven by the number of women who receive antenatal care services as the priority market segment.</p> <p>STI clinics and surveillance programs will also be buyers/users for the tests.</p> <p>Each country's STI prevention/control strategy and prevalence of STIs and HIV are likely to affect implementation of STI screening. This in turn will affect the demand for STI tests.</p> | <p>Urinary test strips can be used at any referral hospitals, clinics, and in communities. Use of the test strips is also not limited to women, although the primary target is expected to be pregnant women.</p> |
| Attractiveness | <p>Data on acceptability of specific POC tests to detect HSV are not available. However, based on acceptability data from other POC tests used in other STI diagnostics, it may be reasonable to extrapolate that acceptability for this technology may also be high considering the intrinsic characteristics of a POC tests (easy to use, rapid diagnosis, no need to return for confirmation, confidentiality, etc.).</p> | <p>In a trial in South Africa, adult women were randomized to home testing versus clinic-based testing for STIs. Both groups performed a POC test for trichomoniasis. Acceptability was assessed after testing using four items that measured two subscales: (1) comfort (pain with self-sampling) and (2) confidence (easy to collect the sample, follow test instructions, and read the results). Over 90 percent responded positively to confidence questions, and only 15 percent reported pain with sampling.¹⁵</p> | <p>High acceptability.</p> |
| Price sensitivity | <p>No data available.</p> <p>biokit HSV-2 Rapid Test: US\$448 for 20 tests, or US\$22.4 per test.¹⁹</p> | <p>No data available.</p> <p>As an example, the OSOM® Trichomonas Rapid Test is available online at US\$8.36 per test, which could be a reference price.</p> | <p>Urinary test strips are already available.</p> <p>UTitest 5V® is available online at £16.63 (including VAT) for 100 strips.</p> |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|------------------------------------|---|--|---|
| | Single Antigen Detection—TABLE 2 | | |
| | Herpes simplex infection | <i>Trichomonas vaginalis</i> | Urine rapid test to detect bacteriuria and UTI |
| Policy environment | <p>The definitive diagnosis of genital herpes relies on demonstrating the presence of HSV in the genital area, either by virus isolation or detection of antigen.</p> <p>Rapid tests are useful in obtaining an immediate determination. However, in most developing countries diagnosis is made clinically.</p> <p>Although the prevalence of HSV infections is high and HSV infection can increase the risk of acquiring HIV, it is not clear that using a single antigen detection panel to detect HSV will be considered as a priority.</p> | <p>Culture remains the gold standard for the diagnosis of trichomoniasis, but this method requires a laboratory and specialized equipment for growing and identifying <i>T. vaginalis</i>. It is not a practical diagnostic method in STD clinics, adult health centers, and physicians' offices, where there is a rapid turnaround of patients.</p> | <p>The gold standard test for asymptomatic bacteriuria is urine culture, but it can also be detected with a dipstick test for nitrite.</p> <p>Screening for and treatment of asymptomatic bacteriuria in pregnancy has become a standard of obstetric care, and most antenatal guidelines include routine screening for asymptomatic bacteriuria.</p> |
| Donors/ stakeholders | <p>CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank</p> | <p>CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank</p> | <p>UNICEF WHO</p> |
| Pre- and post-sales support | No special pre- or post-sales supports are required. | No special pre- or post-sales supports are required. | No special pre- and post-sales supports are required. |
| Need for demand creation | <p>Questions of feasibility, acceptability, costs, cost-effectiveness, cost recovery, sustainability, and the associated policy implications need to be addressed before the widespread use of STI screening programs in developing countries.¹⁷</p> | <p>Questions of feasibility, acceptability, costs, cost-effectiveness, cost recovery, sustainability, and the associated policy implications need to be addressed before the widespread use of STI screening programs in developing countries.¹⁷</p> | <p>Might require clear differentiation between urinary test strips to detect protein and strips to detect bacteriuria/UTI to avoid confusion by procurers and users.</p> |

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|---|--|---|
| | Multiplex Technologies | | |
| | Molecular diagnostics for detection of chlamydia and gonorrhea | Molecular diagnostic for detection of four common STIs | Molecular diagnostic for detection of ten different STIs |
| Description | PATH and Ustar Biotechnologies (Hangzhou) Ltd. are developing a multiplex, POC chlamydia/gonorrhea test using Ustar's platform which combines their proprietary isothermal amplification technology, cross-priming amplification, with a robust and potentially low-cost lateral flow-based detection system. | PATH and Biocartis are developing a multiplex specimen-in, read-out molecular diagnostic for common STIs that harm men and women throughout the world. Biocartis developed a platform and cartridge-based disposable system that integrates specimen preparation and DNA extraction, polymerase chain reaction (PCR) or isothermal amplification, and fluorescent multi-channel detection. This project, with funds from the National Institutes of Health, will create an all-in-one cartridge that will allow rapid (within 2 hours) detection of <i>Neisseria gonorrhoeae</i> (GC), <i>Chlamydia trachomatis</i> (CT), <i>Trichomonas vaginalis</i> , and bacterial vaginosis. | The FilmArray [®] STI Panel (Idaho Technology, Inc.) is an investigational POC molecular diagnostic device that features minimal sample handling, integrated sample preparation, and a multiplexed PCR output. This fully automated system is capable of detecting many PCR targets from a single specimen in less than one hour. The panel for the FilmArray [®] STI Panel detects the following organisms: CT, GC, <i>Treponema pallidum</i> (syphilis), <i>Trichomonas vaginalis</i> , <i>Mycoplasma genitalium</i> , <i>Ureaplasma urealyticum</i> , <i>Ureaplasma parvum</i> , <i>Haemophilus ducreyji</i> , and herpes simplex viruses (HSV-1 and 2). |
| Characteristics applicable for low-resource settings | Unlike rapid tests for chlamydia and gonorrhea that are currently available in the market, this multiplex POC test will be accurate and simple to use. The readout of the test will be visual, and the amplification products are fully contained to avoid potential cross-contamination. | This technology is fully integrated and requires no user interface or actions after the specimen is inserted into the cartridge and the cartridge is inserted into the instrument. Thus, we can extend molecular testing and more importantly multiplex molecular testing to settings and users that are not typically equipped or trained to carry out DNA- or RNA-based testing. | The test requires electricity and well-trained laboratory technicians. Could be used at referral facilities depending on the price of the test. |
| Developer and/or manufacturer | Ustar Biotechnologies (Hangzhou) Ltd. (China) | Biocartis NV (Belgium)/PATH | FilmArray [®] STI Panel (Idaho Technology, Inc), DIATHERIX Laboratories |
| Status | Under development. | Under development. The technology is in alpha prototype stage. PATH and Biocartis are evaluating and optimizing the system with approximately 1,000 specimens collected in Seattle, WA and Mombasa, Kenya. It is expected that a beta prototype stage where specifications are locked down will be reached by the first quarter of 2013. Further data and information is required in order to assess supply- and demand-side issues for this test which is still under development. | Under development. Further data/information is required in order to assess supply- and demand-side issues for this test which is still under development. |

| Supply Information | TECHNOLOGY/SOLUTION | | |
|---|--|---|--|
| | Multiplex Technologies | | |
| | Molecular diagnostics for detection of chlamydia and gonorrhea | Molecular diagnostic for detection of four common STIs | Molecular diagnostic for detection of ten different STIs |
| Efficacy/ effectiveness | No data available. | No data available. | No data available. |
| Manufacturing quality and capacity | Further analysis is necessary to evaluate the most optimal manufacturing scenarios. | Further analysis is necessary to evaluate the most optimal manufacturing scenarios. | The product is still under development. |
| Intellectual property ownership | Ustar's core technology is protected by patent. PATH and Ustar plan to develop a global access strategy for the technology. | No data available. | The product is still under development. Need further investigation. |
| Cost and cost drivers | No data available. | No data available | The product is still under development. Need further investigation. |
| Delivery/ procurement channels | This work will be carried out by PATH once additional funding has been secured. Except for syphilis and HIV tests, STI diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations. Buyers need to purchase the tests from manufacturers or commercial distributors directly. | This work will be carried out by PATH once additional funding has been secured. Except for syphilis and HIV tests, STI diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations. Buyers need to purchase the tests from manufacturers or commercial distributors directly. | No data available. Except for syphilis and HIV tests, STI diagnostic tests are not listed in the UNICEF Supply Catalog for procurement by public-sector organizations. Buyers need to purchase the tests from manufacturers or commercial distributors directly. |
| Sustainable business models | This work will be carried out by PATH once additional funding has been secured. This POC tests can be used in STI clinics, antenatal care programs, or surveillance programs provided in both public and private sector. There are social franchise clinics that provide testing and treatment for STIs. Since prevalence of gonorrhea is low and chlamydia is not included in case reporting in China, demand generation outside China will be critical. | No data available. | The product is still under development, and needs further investigation. |

| Demand Information | TECHNOLOGY/SOLUTION | | |
|------------------------------------|---|---|--|
| | Multiplex Technologies | | |
| | Molecular diagnostics for detection of chlamydia and gonorrhea | Molecular diagnostic for detection of four common STIs | Molecular diagnostic for detection of ten different STIs |
| Existing demand | The target market for this technology is adult women and men living in low-resource settings. The test could be used at STI clinics and/or incorporated into antenatal care. | The target market for this technology is adult women and men living in low-resource settings. | The product is still under development. No further data are available. |
| Attractiveness | No data available. The product is still under development. | No data available. The product is still under development. | No data available. The product is still under development. |
| Price sensitivity | No data available. The product is still under development. | No data available.. The product is still under development. | No data available. The product is still under development. |
| Policy environment | Diagnosis of these two conditions which is difficult to diagnose syndromically addresses the most important causes of maternal infection during pregnancy and the postpartum period. | Diagnosis of these conditions addresses the most important causes of maternal infection during pregnancy and the postpartum period. | No data available. Although diagnosing ten STIs might be useful in developing countries, it is necessary to evaluate the value propositions for this test. |
| Donors/ stakeholders | CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank | CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank | CDC London School of Hygiene and Tropical Medicine POCTRN-Johns Hopkins University UNAIDS UNDP WHO TDR World Bank |
| Pre- and post-sales support | Some level of pre- and post-sales support are likely to be necessary. However, since this POC test is easy to use, requirements for such support are expected to be low. | Some level of pre- and post-sales support are likely to be necessary. | The product is still under development. No data available. |
| Need for demand creation | Need further investigation. Evidence from field evaluation and demonstration studies are necessary for demand generation. Laboratory technicians at lower level of health care systems might appreciate this POC test since it will provide additional capability to them. | Need further investigation. Evidence from field evaluation and demonstration studies are necessary for demand generation. | Need further investigation. Although this test might be useful for developing countries, cost and resource requirements to introduce and implement this test might outweigh the benefit of the test. |

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Temperature Monitoring to Diagnose Postpartum Infections

Many women who give birth in facilities are frequently discharged within a couple of hours or days following childbirth. The short period of observation may not afford enough time to exclude evidence of infection prior to discharge from the hospital. In one study, 94 percent of postpartum infection cases were diagnosed after discharge from the hospital.¹ In many situations, women are sent home without indications on where to obtain further care or support.²

Postpartum infections are one of the most devastating complications of the postpartum period. They comprise a wide range of entities that can occur after vaginal and cesarean delivery or during breastfeeding. In addition to trauma sustained during the birth process or cesarean procedure, physiologic changes during pregnancy contribute to the development of postpartum infections.¹

Diagnosis of maternal infection is primarily based on clinical signs and symptoms and characterized by fever and other physical symptoms depending on the type of infection. Early diagnosis of any infection can help lead to successful treatment, prevention of septic shock and its long term effects, as well as death. Postpartum fever is defined as a temperature greater than 38°C on any two of the first ten days following delivery exclusive of the first 24 hours. The presence of postpartum fever is generally accepted among clinicians as a sign of infection that must be determined and managed.¹

It is important to recognize that low-grade temperature elevations are also very common in the early postpartum period, particularly in the first 24 hours. Causes of such fevers include dehydration, tissue trauma, and breast engorgement. Although fever occurring in the first 24 hours after delivery has generally been regarded as unrelated to infection, a temperature of 38°C or higher within the first 24 hours should alert the midwife to the possibility of puerperal sepsis.²

The World Health Organization (WHO) recommends that women go to a hospital or health center immediately, day or night, without waiting, if fever presents after the woman is sent home and in the period of time following six weeks after childbirth. Postpartum care for the mother has conventionally focused on routine observation and examination of vaginal blood loss, uterine involution, blood pressure, and body temperature.²

In broader context, most care in the postpartum and postnatal period takes place at home, where the woman is caring for herself and her baby, supported by her family. One objective of postpartum and postnatal care delivered through the health system is to encourage mothers and

families to adopt evidenced-based practices at home and to build sustaining community support for these practices. Increased access to temperature monitoring at home is one tool that could assist providers as well as pregnant women/new mothers in determining if an infection may be present and treatment is needed.

Mercury thermometers are one of the most commonly used devices to monitor temperature in developing countries. However, these devices are not especially durable and are harmful to the environment and people.³ In addition, in remote areas where literacy level is low, women may not be able to read or interpret the results. Following a WHO initiative to promote the substitution of mercury-based medical devices (including thermometers) with safe, affordable, accurate alternatives around the world, a number of other temperature monitoring technologies have been developed that are user friendly, mercury free, and low cost. Disposable temperature devices are one example of those alternative technologies.

Positive field experience with disposable thermometers in low-income countries exists. These devices have been used to monitor temperature—in particular hypothermia—of neonates in the postnatal period.⁴ These studies have also shown high acceptability and usability by mothers. Considering these initial results in neonates, the use of these devices can be extrapolated to women during the postpartum period. Since women in developing countries may not have access to postpartum care, there is a need for easy to use and inexpensive devices to register temperature. These low-cost temperature monitoring technologies are key tools that could be integrated into birthing kits and could also be something that is sent home with new mothers that present higher risk of infection (cesarean section, urinary tract infections, sexually transmitted infections, etc.) after delivery.

The technologies and solutions included in the tables below are tools with potential to increase access to temperature monitoring to diagnose postpartum infections.

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|--------------------|--|---|---|---|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Description | <p>A single-use, disposable clinical thermometer that can measure oral, rectal, or axillary body temperature. Available in Fahrenheit or Celsius, the thermometers are sterile and individually wrapped.</p> <p>3M™ Tempa-DOT™ thermometers are accurate, convenient, versatile, and economical body temperature measuring devices. Clinically accurate oral body temperature can be obtained in 60 seconds and axillary temperatures in three minutes.</p> <p>Tempa-DOT™ thermometers use a dot sensor matrix consisting of temperature-sensitive indicating dots. Each dot changes color from tan to blue at a specific temperature relative to the melting point of the specific chemical mixture of the dot. Each dot changes color at a temperature of 0.2°F or 0.1°C higher than the preceding dot. Body temperature is read from a numerical temperature scale</p> <p>Measures body temperature in Celsius range of 35.5°C to 40.4°C.</p> | <p>A simple way for mothers to check their newborn babies are not cold. When put under a newborn's armpit, the black disk turns green and a smiling face appears as long as the infant's temperature is over 35.5°C. If the baby's temperature drops, the smile disappears and the spot turns black. The device can stay in place for up to ten days.</p> <p>Discussions with the manufacturer suggest the technology could be modified to measure fever in mothers as well as hypothermia.</p> | <p>Core adjusted temperature. Can measure 33°C to 41°C. Feverscan Forehead Thermometer Strips have liquid crystals that change color to indicate temperature. These strips use thermo chromic liquid crystal technology for the measurement of clinical temperature trends in the health care environment. Liquid crystals are chemical compounds and mixtures that exhibit the mechanical properties of liquids and the optical characteristics of solids. Feverscan Forehead Thermometer Strips are composed of a series of discrete temperature events; each event shows a green color as the indicated temperature is attained. Fast, simple temperature monitoring system based on proprietary color change technology. Feverscan Forehead Thermometer Strips have self-adhesive on the back which peels for easy application to the forehead. It is available as a disposable type for hospital use and reusable type for home use.</p> <p>The product offers a continuous display of forehead temperature readings. Possible applications include monitoring during transport, watching for hypothermia or hyperthermia, and pre- and post-operation surveillance.</p> | <p>ionX™ Body Temperature Alert Patch, is a disposable body core temperature indicator that warns the wearer if and when there is a danger of overheating. When body temperature increases to a level associated with an elevated risk of heat exhaustion or heat stroke, the patch changes to a highly noticeable color to alert the individual to take measures to reduce his or her body temperature. Once the individual has cooled to a non-risk temperature, the patch will return to the original color.</p> <p>In order to accurately measure core temperature, the ionX™ Body Temperature Alert Patch must be placed on an area with blood vessels close to the surface of the skin. These areas include:</p> <ul style="list-style-type: none"> • Neck artery. • Bicep just before the inner elbow. • Inner forearm just before inner elbow. • Wrist just before the hand. <p>The product minimizes false positives with a thin coating that blocks the sun's rays.</p> |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|---|---|---|---|---|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Characteristics applicable for low-resource settings | Depending on where the thermometer is placed, measurement time is different, which might require clear instructions. Cannot measure body temperature <35.5°C. | Low cost, easy to use, disposable. | Easy to use, disposable. | Currently designed for use in developed-world athletic markets. Manufacturer has expressed interest in opportunities to collaborate for use in low-resource settings. |
| Developer and/or manufacturer | Tempa-DOT™ thermometers are manufactured by 3M. ⁵ | ThermoSpot™ was developed by John Zeal and David Morley. It is manufactured in the United Kingdom is distributed through Maternova ¹¹ and Teaching-aids At Low Cost. ⁶ | Feverscan Forehead Thermometer Strips are manufactured by LCR Hallcrest. ⁷ | ionX™ Body Temperature Alert Patch is manufactured by IonX iDOT International, LLC. ⁸ |
| Status | Commercialized. The thermometer conforms to American Society for Testing and Materials (ASTM) Standard E 825-98 (reapproved 2003), which is the guideline required to meet for phase-change thermometers. | Commercialized. The product has a CE mark indicating the manufacturer ensures that the product conforms with the essential requirements of the applicable European Community directives. | Commercialized. The product has a CE mark indicating the manufacturer ensures that the product conforms with the essential requirements of the applicable European Community directives. | Commercialized. Sold in packages of 10, 30, 100, and 500 through preferred distributors. |
| Efficacy/effectiveness | Tempa-DOT™ thermometers meet ASTM E 825-87 requirements which include accuracy requirements for disposable fever thermometers. In addition, accuracy comparison to other types of thermometers has been proven in published clinical studies, and, 3M™ has data available from an independent test laboratory (Ci-Tech data) supporting the accuracy of Tempa-DOT™ Thermometers. ⁵ | Sensitivity: 19% to 100% Specificity: 97% to 100%. Data show no effect on neonatal mortality when integrated into newborn care package. ⁴ Although all options were comparable to mercury-in-glass thermometers, the author of a study involving 207 patients favored the digital thermometer for general use, the tympanic model for uncooperative patients, and the liquid crystal forehead method for home use. ⁹ | Although all options were comparable to mercury-in-glass thermometers, the author of a study involving 207 patients favored the digital thermometer for general use, the tympanic model for uncooperative patients, and the liquid crystal forehead method for home use. ⁹ | Data not available. |
| Manufacturing quality and capacity | 3M is a large manufacturer with very large capacity to produce thermometers. | Manufactured in the United Kingdom, currently small capacity. | Multiple manufactures globally with various capacities depending on devices, this includes multiple manufacturers in China. | Ionx iDOT International LLC (headquartered in Lexington, Kentucky) manufactures the patch. Manufacturing capacity unknown. |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|--|---|---|---|---|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Intellectual property ownership | Tempa-DOT™ thermometer is a trademark of 3M™. Covered by US patent numbers 4189942, 4232552, 4345470, 4397570, 4339207, and 4362645. ¹⁰ | ThermoSpot™ is trademarked and uses a liquid crystal technology. Liquid crystal technology is already an established technology. It is unlikely that this thermometer is protected by patent. | Adhesive thermometers use liquid crystal technology. Liquid crystal technology is already an established technology. It is unlikely that this thermometer is protected by patent. | The patch is based on patented nano-polymer technology. |
| Cost and cost drivers | US\$15.98 for a pack of 100 by Amazon.com. No hidden costs to use the product associated with cleaning, disinfection, maintenance, battery or recharging time, probe or ear cover costs, or theft associated with electronic and tympanic thermometers. | US\$6.00 for 25 disks (US\$0.24 per disk) through Maternova. ¹¹ No hidden costs to use the product associated with cleaning, disinfection, maintenance, battery or recharging time, probe or ear cover costs, or theft associated with electronic and tympanic thermometers. | US\$0.20 to US\$0.50. No hidden costs to use the product associated with cleaning, disinfection, maintenance, battery or recharging time, probe or ear cover costs, or theft associated with electronic and tympanic thermometers. | Wholesale price is 34 cents per dot, and the company also sells them in packs of 10 for US\$9.95 and 500 for US\$229.95. No hidden costs to use the product associated with cleaning, disinfection, maintenance, battery or recharging time, probe or ear cover costs, or theft associated with electronic and tympanic thermometers. |
| Delivery/ procurement channels | The thermometer could be provided to mothers who had babies at facilities when they are discharged. Also, midwives could provide mothers with thermometers as part of a clean delivery kit (CDK). United Nations Children’s Fund (UNICEF) Supply Catalogue includes a battery-operated digital thermometer at US\$0.89. The disposable thermometers listed in this table could be included in the UNICEF Supply Catalogue for bulk procurements. | The thermometer could be provided to mothers who had babies at facilities when they are discharged. Also, midwives could provide mothers with thermometers as part of a CDK. UNICEF Supply Catalogue includes a battery-operated digital thermometer at US\$0.89. The disposable thermometers listed in this table could be included in the UNICEF Supply Catalogue for bulk procurements. | The thermometer could be provided to mothers who had babies at facilities when they are discharged. Also, midwives could provide mothers with thermometers as part of a CDK. UNICEF Supply Catalogue includes a battery-operated digital thermometer at US\$0.89. The disposable thermometers listed in this table could be included in the UNICEF Supply Catalogue for bulk procurements. | The thermometer could be provided to mothers who had babies at facilities when they are discharged. Also, midwives could provide mothers with thermometers as part of a CDK. UNICEF Supply Catalogue includes a battery-operated digital thermometer at \$US0.89. The disposable thermometers listed in this table could be included in the UNICEF Supply Catalogue for bulk procurements. |

| Supply Information | TECHNOLOGY/SOLUTION | | | |
|------------------------------------|--|---|--|--|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Sustainable business models | Currently sold to clinics and consumers through commercial channels. For the developing-country markets, the device could be provided through skilled birth attendants and/or public health care facilities. Nongovernmental organizations (NGOs) and clinical social franchise networks could also be additional distribution models. | Currently sold to clinics and consumers in developing-world markets through commercial channels. Distribution through sites like Maternova suggests there is a growing interest among NGOs and clinical social franchise networks. The manufacturer has requested assistance to develop a relevant business plan for those markets. | Currently sold to clinics and consumers through commercial channels. For the developing-country markets, the device could be provided through skilled birth attendants and/or public health care facilities. NGOs and clinical social franchise networks could also be additional distribution models. | Currently sold to clinics and consumers through commercial channels. For the developing-country markets, the device could be provided through skilled birth attendants and/or public health care facilities. NGOs and clinical social franchise networks could also be additional distribution models. |

| Demand Information | TECHNOLOGY/SOLUTION | | | |
|------------------------------------|--|--|--|--|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot™ (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Existing demand | Can be used both for facility-based and home delivery. The market size is therefore driven by the number of births both at facilities and home. The use of the thermometer could be extended to any patients with fever if precise measurement is not required. | Can be used both for facility-based and home delivery. The market size is therefore driven by the number of births both at facilities and home. The use of the thermometer could be extended to any patient with fever if precise measurement is not required. | Can be used both for facility-based and home delivery. The market size is therefore driven by the number of births both at facilities and home. The use of the thermometer could be extended to any patients with fever if precise measurement is not required. | Can be used both for facility-based and home delivery. The market size is therefore driven by the number of births both at facilities and home. The use of the thermometer could be extended to any patients with fever if precise measurement is not required. |
| Attractiveness | Reading temperature requires looking at small dots and understanding which dots changed color. This might be a little more complicated than the other thermometers listed in this table. | Easy to use and safe. | Easy to use and safe. | Easy to use and safe. |
| Price sensitivity | No data available. However, disposable thermometers may be priced lower than that of reusable digital thermometers available for bulk purchase through UNICEF. Qualitative, or semiquantitative, results that disposable thermometers can provide are likely to favorably affect users' preference and their willingness to pay. | No data available. However, disposable thermometers may be priced lower than that of reusable digital thermometers available for bulk purchase through UNICEF. Qualitative, or semiquantitative, results that disposable thermometers can provide are likely to favorably affect users' preference and their willingness to pay. | No data available. However, disposable thermometers may be priced lower than that of reusable digital thermometers available for bulk purchase through UNICEF. Qualitative, or semiquantitative, results that disposable thermometers can provide are likely to favorably affect users' preference and willingness to pay. | No data available. However, disposable thermometers may be priced lower than that of reusable digital thermometers available for bulk purchase through UNICEF. Qualitative, or semiquantitative, results that disposable thermometers can provide are likely to favorably affect users' preference and their willingness to pay. |
| Policy environment | In a 2005 policy paper, WHO called for a phase out of mercury measuring devices from health care. In their technical guidance published in 2011, WHO included several alternatives to mercury-in-glass thermometers. ¹² | In a 2005 policy paper, WHO called for a phase out of mercury measuring devices from health care. In their technical guidance published in 2011, WHO included several alternatives to mercury-in-glass thermometers. ¹² | In a 2005 policy paper, WHO called for a phase out of mercury measuring devices from health care. In their technical guidance published in 2011, WHO included several alternatives to mercury-in-glass thermometers. ¹² | In a 2005 policy paper, WHO called for a phase out of mercury measuring devices from health care. In their technical guidance published in 2011, WHO included several alternatives to mercury-in-glass thermometers. ¹² |
| Donors/ stakeholders | WHO and ministries of health. | WHO and ministries of health. | WHO and ministries of health. | WHO and ministries of health. |
| Pre- and post-sales support | Instruction for use is required to enforce proper use. This thermometer is non-instrumented and does not require calibration by users. | Instruction for use is required to enforce proper use. This thermometer is non-instrumented and does not require calibration by users. | Instruction for use is required to enforce proper use. This thermometer is non-instrumented and does not require calibration by users. | Instruction for use is required to enforce proper use. This thermometer is non-instrumented and does not require calibration by users. |

| Demand Information | TECHNOLOGY/SOLUTION | | | |
|---------------------------------|---|---|---|---|
| | Disposable phase-change thermometers | Adaptation of ThermoSpot™ (liquid crystal thermometer) for fever | Liquid crystal adhesive thermometers | Adaptation of the ionX™ Body Temperature Alert Patch for fever |
| Need for demand creation | <p>Studies to evaluate the impact of home use of thermometers among new mothers (or pregnant women) and the impact on early detection of maternal infection are necessary to generate demand.</p> <p>Cost-effectiveness studies to compare use of digital thermometers with that of disposables ones are likely to affect uptake of disposable thermometers.</p> <p>Training to service providers to use disposable thermometers with new ways of reading temperate is also likely to facilities demand creation.</p> | <p>Studies to evaluate the impact of home use of thermometers among new mothers (or pregnant women) and the impact on early detection of maternal infection are necessary to generate demand.</p> <p>Cost-effectiveness studies to compare use of digital thermometers with that of disposables ones are likely to affect uptake of disposable thermometers.</p> <p>Training to service providers to use disposable thermometers with new ways of reading temperate is also likely to facilities demand creation.</p> | <p>Studies to evaluate the impact of home use of thermometers among new mothers (or pregnant women) and the impact on early detection of maternal infection are necessary to generate demand.</p> <p>Cost-effectiveness studies to compare use of digital thermometers with that of disposables ones are likely to affect uptake of disposable thermometers.</p> <p>Training to service providers to use disposable thermometers with new ways of reading temperate is also likely to facilities demand creation.</p> | <p>Studies to evaluate the impact of home use of thermometers among new mothers (or pregnant women) and the impact on early detection of maternal infection are necessary to generate demand.</p> <p>Cost-effectiveness studies to compare use of digital thermometers with that of disposables ones are likely to affect uptake of disposable thermometers.</p> <p>Training to service providers to use disposable thermometers with new ways of reading temperate is also likely to facilities demand creation.</p> |

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Antibiotic Delivery for Prevention and Treatment of Puerperal Sepsis

Antibiotic prophylaxis for women undergoing cesarean section

Cesarean section, apart from being one of the most common obstetric surgical procedures, is the single most important risk factor for postpartum maternal infection.¹ Women having cesarean section have a 5- to 20-fold greater risk of infection than women having a vaginal delivery. Rates of wound infection and serious infectious complications can be as high as 25 percent.² Post cesarean infections include urinary tract infection, endometritis, wound infection, perineal infection, and sepsis. All of these complications lead to prolonged hospital stays and increased health care cost.

Factors that have been associated with an increased risk of infection among women who have a cesarean delivery include emergency cesarean section, labor and its duration, ruptured membranes and the duration of rupture, the socioeconomic status of the woman, number of prenatal visits, vaginal examinations during labor and internal fetal monitoring, urinary tract infection, anemia, blood loss, obesity, diabetes, general anesthesia, the skill of the operator and the operative technique.^{1,3,4} Labor and ruptured membranes appear to be the most important factors, with obesity particularly important for wound infections. The association of bacterial vaginosis with an increased incidence of endometritis following cesarean delivery has also been reported.⁵

The purpose of antibiotic prophylaxis in surgical procedures is not to sterilize tissues but to reduce the colonization pressure of microorganisms introduced at the time of operation to a level that the patient's immune system is able to overcome.⁶ Without prophylaxis, the incidence of endometritis post cesarean is reported to range from 20 percent to 85 percent; rates of wound infection and serious infectious complications as high as 25 percent have been reported.⁷

Overall, the use of prophylactic antibiotics with cesarean section results in a major, clinically important, and statistically significant reduction in the incidence of episodes of fever, endometritis, wound infection, urinary tract infection, and serious infection after Cesarean section.⁸ The current World Health Organization (WHO) recommendation is to provide antibiotic prophylaxis in all cases of cesarean section.⁹ Despite this recommendation, inconsistent adherence to policies for administering antibiotic prophylaxis are reported.¹⁰ Simple quality improvement methods have been demonstrated to improve adherence with overall and timely administration of prophylaxis and reduced infection rate.¹¹

These antibiotics have been administered intra-operatively after umbilical cord clamping on the basis of two theoretical concerns related to the fetus: (1) antibiotics in neonatal serum may mask newborn positive bacterial culture results, and (2) fetal antibiotic exposure could lead to an increase in newborn colonization or infection with antibiotic-resistant organisms. Recently, several randomized clinical trials investigated the timing of antimicrobial prophylaxis for cesarean delivery. Based on surgical research data, antimicrobial prophylaxis to prevent surgical site infection should ideally begin within 30 minutes, and definitely within 2 hours, of skin incision. For longer surgery, the same dose of antibiotic may need to be given again at intervals of one or two times the half-life of the drug.¹²

There is a need to establish consistency in the recommended regime and time of administration of antibiotics in order to successfully protect women from developing infections after cesarean section.

Antibiotic therapy following pPROM and PROM

Pre-labor rupture of the membranes at or near term (term PROM) and preterm premature rupture of membranes (pPROM) increases the risk of infection for a woman and her baby.

A Cochrane review of antibiotic administration for pPROM reported that antibiotic treatment was associated with a significant reduction in risk of chorioamnionitis (RR 0.57; 95% CI, 0.37–0.86), and longer time to delivery (RR 0.71; 95% CI, 0.58–0.87), as well as major markers of neonatal morbidity, but no statistical differences in perinatal mortality were reported (RR 0.90; 95% CI, 0.74–1).¹³

Antibiotic therapy could improve outcome in two ways. First, they treat the maternal/neonatal infection, thereby reducing infection-related morbidity. Second, by stopping the ascending bacteria, antibiotics may prolong pregnancy, allowing the fetus to further mature. The benefit of antibiotics is greatest following pPROM less than 32 weeks of gestation. Ampicillin, amoxicillin, and erythromycin are all commonly used, either in an intravenous (IV) phase followed by an oral phase, or using an oral phase alone.¹⁴

A Cochrane review of prophylactic antibiotics in cases of pre-labor rupture of membranes (PROM) found no statistically significant differences in perinatal mortality (RR 0.98; 95% CI, 0.14–6.89), 5-minute Apgar score less than 7 (RR 0.98; 95% CI, 0.28–3.34), or chorioamnionitis (RR 0.60; 95% CI, 0.30–1.18). However, risk of endometritis was significantly reduced (RR 0.09; 95% CI, 0.01–0.73).^{15,16}

The routine use of antibiotics for women at the time of term PROM may reduce this risk. However, due to increasing problems with bacterial resistance and the risk of maternal anaphylaxis with antibiotic use, it is important to assess the evidence addressing risks and benefits in order to

ensure judicious use of antibiotics. Thus it is also of critical importance to supply providers with clear guidance on which antibiotic to use in different situations (pPROM and PROM).

The technologies and solutions included in the table below are tools with potential to increase access to antibiotic delivery for prevention and treatment of puerperal sepsis.

| Supply Information | TECHNOLOGY/SOLUTION | | | | | |
|---|--|---|--|---|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Description | Continuous quality improvement strategy to increase use of prophylactic antibiotic prior to cesarean section. | Mobile devices to provide active targeted digital job aides (checklists, decision support, reminders) have been piloted and shown to demonstrate improved efficacy over passive paper-based systems. These systems can leverage a multitude of device form factors from low-cost feature phones receiving text messages, to higher-end smartphones and tablets that provide clinical decision support and integrate with health care systems' health information management systems. | Saline fluid or Ringers lactate/Hartmans with or without antibiotics is infused transcervically through a catheter into the uterine cavity or transabdominally through a narrow-gauge needle, or subcutaneously through an amniotic fluid (AF) replacement port system. This method is used mostly to recover volume from leakage of AF to avoid pulmonary hypoplasia and malformations in the baby. It has also been used to prevent postpartum maternal infections. | See information on magnesium sulfate (MgSO4) data sheet. | | |
| Characteristics applicable for low-resource settings | Prophylactic use of antibiotics (regardless of regimen) in women undergoing cesarean section reduces the risk of infection-related complications and serious infection post operation. Antibiotic prophylaxis should be used in all cases of cesarean section. | Potentially increases access to antibiotic treatment in women who present symptoms of pPROM and PROM by providing community health workers and health workers in communities and clinics with clear guidelines on type of antibiotic needed. This technology needs to be accompanied by recommended antibiotics used in the community and clinics. Clear guidelines on antibiotic use will potentially limit the risk of antibiotic resistance caused by improper use of these medications at the community and clinic level. | Amnioinfusion is an invasive procedure and requires highly specialized providers. Intervention should be carried out in secondary or tertiary care settings where cesarean section can be performed, if needed. Use of ultrasound is required for transabdominal amnioinfusion Complications of amnioinfusion include umbilical cord prolapse, uterine overdistention, fetal bradycardia, and one report of possible AF embolism. | Antibiotic delivery is a critical component in the treatment of puerperal infections. In complicated cases, as in the case of puerperal sepsis, IV infusion of antibiotics is required. In these cases, the use of low-cost infusion pumps has the potential for easing delivery of these medications, decreasing potential medication errors, and increasing patient safety. | | |

| Supply Information | TECHNOLOGY/SOLUTION | | | | | |
|--------------------------------------|--|--|--|--|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Developer and/or manufacturer | Various manufacturers. Ampicillin or first-generation cephalosporins. | Various manufacturers. Multiple small-scale pilot studies ongoing by different research organizations. Technologies are generally off-the-shelf components (phones, tablets, netbooks, etc.) with custom software. No standardization by technology manufacturers specific to health care has occurred and been adopted. | Several interventions: Intracervical, intraabdominal and subcutaneous (subcutaneously implanted AF replacement port system). | Various (see information on MgSO4 data sheet). | | |
| Status | Antibiotics are already marketed both in developed and developing countries. | Under development. Many studies are looking at improved effectiveness of moving to digital guidelines. No known examples are looking at antibiotic usage. | Technique already exists and is well documented. It may be possible to adapt technique to accommodate for lack of expensive catheters in developing countries. Providers may use catheters (nasogastric tubes, pediatric tubes). Transcervical amnioinfusion may be more suited for developing countries. Studies have shown it to be a simple, inexpensive, and feasible technique to improve fetomaternal outcome. Multiple subcutaneous port systems are already commercialized and sold in developed countries. The United States Food and Drug Administration (USFDA) classifies the device as Class II, and manufacturers need to obtain 510(k) clearance. | See information on MgSO4 data sheet. | | |

| Supply Information | TECHNOLOGY/SOLUTION | | | | | |
|---|---|--|--|---|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Efficacy/ effectiveness | The odds of wound infection are likely to be reduced by between about 50% and 70% by giving antibiotics routinely at cesarean section. Routine use of prophylactic antibiotics reduces the risk of post-cesarean fever and infections by over 50% from baseline rates as high as 20% to 50%. Based on systematic reviews of over 80 clinical trials, this benefit applies to both nonelective and elective (scheduled) procedures. Because antibiotic prophylaxis shortens overall length of hospitalization and reduces treatment costs associated with cesarean, it is highly cost-effective. | The researchers have demonstrated that the use of an electronic checklist developed to consistently prompt clinicians to provide comprehensive discharge instructions showed significant improvement from 37 percent to 93 percent ¹⁷ in instruction delivery. No studies have been conducted examining the use of digital guidelines on antibiotic usage. | In various clinical trials, transabdominal amnioinfusion following PPRM resulted in better neonatal outcomes (decreased sepsis, infection, and death) and decreased puerperal sepsis than conventional management. Studies have also shown that amnioinfusion reduces rates of cesarean section. | See information on MgS04 data sheet. | | |
| Manufacturing quality and capacity | Multiple manufacturers' commercialized antibiotics. For example, Cipla Ltd., one large pharmaceutical manufacturer, produces ampicillin. | | Multiple subcutaneous port systems are marketed: Therastick® (Fresenius Kab AG), Bard Access Systems Inc. (Bardport@Implanted Port). | See information on MgS04 data sheet. | | |
| Intellectual property ownership | Data not available. | Various. Some software leverages open source standards such as Open Data Kit (University of Washington/Google). | Not applicable. | See information on MgS04 data sheet. | | |

| Supply Information | TECHNOLOGY/SOLUTION | | | | | |
|---------------------------------------|---|--|---------------------|---|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Cost and cost drivers | Ampicillin 500 mg powder for injection (vial) is listed in the United Nations Children’s Fund (UNICEF) Supply Catalog. The indicative price is US\$3.41 for a box of 25. | Cost of the technology is variable and is driven by the level of sophistication of the tool and the level of integration. Phones can cost between US\$30 to US\$200. Greater costs are in training and changes to existing work flows. | Data not available. | See information on MgS04 data sheet. | | |
| Delivery/ procurement channels | Ampicillin is listed in the WHO Essential Medicines List (EML) and the UNICEF Supply Catalog, and it can be purchased by the public sector. Manufacturers also can supply antibiotics to hospitals through their distribution channels. National regulatory authorities provide approval to manufacturers to produce drugs for commercial purposes. However, in developing countries, systems to monitor drug quality after initial market approval are generally insufficient. | Phones leverage off-the-shelf components that are readily available in country, as well as existing cellular networks. | Data not available. | See information on MgS04 data sheet. | | |
| Sustainable business models | These antibiotics are already produced, marketed, and distributed. No significant cost increase is expected in production and distribution by expanding their use to women undergoing cesarean section. | Sustainable business models are being explored broadly within the category of mHealth, and clear strategies have yet to be determined. | Data not available. | See information on MgS04 data sheet. | | |

| Demand Information | TECHNOLOGY/SOLUTION | | | | | |
|-----------------------------|--|--|--|---|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Existing demand | Antibiotics already exist and have demand. Prophylactic use of antibiotics will expand the current demand, which will be driven by the number of women who have cesarean sections. In a study done in four southeast Asian countries, overall 27 percent of women had a cesarean section, with rates varying from 19 percent to 35 percent between countries. ¹⁸ | Existing segments identified in developing-country settings are community clinics and other frontline health workers. | Clinical guidelines for amnioinfusion need to be developed in order to understand the potential market size, market segmentation, and primary target segments. | See information on MgS04 data sheet. | | |
| Attractiveness | Reduction in wound infection, which is likely to lead to a faster recovery and higher comfort. | Necessary cellular infrastructure, cost of devices (especially replacement), and dramatic changes to work flows are key barriers to use. | Data not available. | See information on MgS04 data sheet. | | |
| Price sensitivity | Needs to be evaluated. Should be equal or less than the current prices. | Data not available. | Data not available. | See information on MgS04 data sheet. | | |
| Policy environment | A global review of the key interventions related to reproductive, maternal, newborn and child health includes prophylactic antibiotic for cesarean section. ¹⁹ | Not currently. USFDA guidelines for digital clinical support are pending and could be adopted outside the United States, raising the regulatory hurdles for adoption and distribution. | Data not available. | See information on MgS04 data sheet. | | |
| Donors/ stakeholders | WHO and obstetrics and gynecology associations such as the International Federation of Gynecology and Obstetrics. | To be evaluated later. | No known stakeholders working in this area. | See information on MgS04 data sheet. | | |

| Demand Information | TECHNOLOGY/SOLUTION | | | | | |
|------------------------------------|---|--|---|---|---|-----------------------------------|
| | Optimizing peri-operative antibiotic prophylaxis for women undergoing cesarean section | mHealth guidelines for antibiotic delivery during pPROM and PROM | Amnioinfusion | Low-cost infusion pumps for drug delivery | | |
| | | | | Syringe infusion pump (IV) | Programmable nonmechanical IV infusion pump | Gravity-fed IV bag and stand (IV) |
| Pre- and post-sales support | Harmonization in clinical guidelines and adherence to protocol are the main challenges. | Development of both pre- and post-sales support is necessary for the maintenance of human and technical resources. No projects have left the pilot stage where local scalable support has been demonstrated. | Data not available. | See information on MgSO4 data sheet. | | |
| Need for demand creation | Harmonization in clinical guidelines is required. | One main benefit of digital guidelines is the ability to support task shifting to lower cadres of health workers. The tool provides global standards and defines clear delineation for what services are appropriate for the health worker to provide and what should be referred. | Harmonization in clinical guidelines is required. | See information on MgSO4 data sheet. | | |

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Postabortion Care

Postabortion care (PAC) consists of a series of interventions designed to manage a woman presenting after spontaneous or induced abortion (with or without complications). PAC is an important component of comprehensive reproductive health services because it saves women's lives and reduces morbidity. The model for PAC supported by the PAC Consortium consists of five elements¹: (1) treatment of incomplete and unsafe abortion and abortion-related complications that are potentially life threatening, (2) counseling to identify and respond to women's emotional and physical health needs and other concerns, (3) contraceptive services and information to help women prevent an unwanted pregnancy or practice birth spacing, (4) reproductive and other health services that are preferably provided on site or via referrals to other accessible facilities in clinicians' networks, and (5) community and service-provider partnerships.

The World Health Organization estimates that 21.6 million unsafe abortions take place every year, with 98 percent of these occurring in developing countries where abortion is either illegal or accessibility to safe, legal abortions is limited.² Unsafe abortion is a major contributor to maternal mortality, accounting for 68,000 maternal deaths worldwide, 5 million hospital admissions, and 1.7 million cases of secondary infertility in developing countries each year.³ Septic abortion is a frequent complication of unsafe abortion and a common cause of the maternal mortality and morbidity associated with unsafe abortion. Septic abortion refers to any abortion (spontaneous or induced) associated with uterine/pelvic infection. It has been reported to be responsible for up to 88 percent of complications from unsafe abortions and is responsible for the majority of deaths due to abortion complications in low- and middle-income countries (LMICs).^{4,5}

Septic abortion is typically preceded by either incomplete abortion resulting in retained products of conception or the introduction of pathogens into the uterus during unsanitary or self-induced abortion. Rates of septic abortion tend to be highest in settings where safe abortion services are restricted by law or otherwise. The incidence of septic abortion has been reported to be from 4.8 percent to 22.6 percent in LMICs, the incidence is difficult to ascertain in developing countries due to under reporting and differing case definitions.

Unfortunately, women with complications from unsafe abortion may delay seeking treatment and be reluctant to admit undergoing abortion procedures, especially where abortion is illegal. In these cases, removal of retained products of conception and early antibiotic treatment may prevent septic abortion. Active management of incomplete abortion, using either vacuum aspiration or medical methods, is highly effective in treating incomplete abortion. Misoprostol, the most common and thoroughly studied medical method for treatment of incomplete abortion, is a newer option to expand PAC services into places where manual vacuum aspiration may not be available. Misoprostol provides a highly effective,

noninvasive treatment for incomplete abortion, enabling women to receive appropriate and effective PAC from nonsurgically trained, mid-level providers.⁶

The technologies and solutions included in the tables below are tools with potential to increase access to improved postabortion care.

| Supply Information | TECHNOLOGY/SOLUTION | |
|---|---|--|
| | Manual vacuum aspiration (MVA) | Misoprostol |
| Description | <p>Manual vacuum aspiration (MVA) is a method of uterine evacuation that involves use of a handheld plastic aspirator providing a vacuum source attached to a cannula (thin tube) and manually activated to suction the uterine contents. Plastic cannulae, which vary from rigid to very flexible, are used with MVA aspirators.</p> <p>MVA is appropriate for treatment of incomplete abortion through the 13th week of pregnancy (including miscarriage, spontaneous abortion, and removal of retained products from an induced abortion), first-trimester abortion (menstrual regulation), and endometrial biopsy.</p> | <p>Misoprostol, a synthetic prostaglandin E1 analogue is effective for labor induction, the treatment of incomplete or missed abortion, the prevention and treatment of postpartum hemorrhage (PPH), and the elective termination of pregnancy.</p> <p>The World Health Organization (WHO) recommends mifepristone combined with misoprostol as the most effective method of medical abortion. Where mifepristone is unavailable, however, misoprostol alone is being used by providers to terminate unwanted pregnancies and by women to self-induce abortion. In most places misoprostol is available for reproductive health care through off-label use only.</p> |
| Characteristics applicable for low-resource settings | Safer, less costly, and as effective as the traditionally used dilation and curettage (D&C). | Reduces the need for surgically trained health providers, is low cost and has few side effects. ⁷ |
| Developer and/or manufacturer | Developed by Ipas; sold by WomanCare Global. ⁸ | Misoprostol was invented and marketed by GD Searle & Company (now Pfizer) under the trade name Cytotec. It is now available as a generic and is produced by numerous manufacturers globally. |
| Status | Commercialized. | Commercialized. |
| Efficacy/effectiveness | <p>Success was high for both MVA and misoprostol groups (100% vs 91%, P=0.002).⁹</p> <p>When compared to D&C, MVA is a safer, more readily accessible, and potentially a less expensive way to offer high-quality service to women.¹⁰</p> <p>Studies demonstrate that the efficacy of MVA is comparable to electric vacuum aspiration and is successful in approximately 99 percent of cases for early-elective abortion and management of early pregnancy loss. Studies show that 98 percent of vacuum aspiration procedures occur without complications, much higher than the alternative D&C method, which may induce incidences of excessive blood loss, pelvic infection, cervical injury, and uterine perforation.¹¹</p> | <p>Varies: 400 ug regimen: 50 percent of misoprostol users require additional surgical care.¹² 800 ug regimen: 60 percent. Studies in which efficacy was assessed later (3 to 15 days): 60 percent to 90 percent depending on regimens.</p> <p>Researchers 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.¹³</p> |

| Supply Information | TECHNOLOGY/SOLUTION | |
|---|--|---|
| | Manual vacuum aspiration (MVA) | Misoprostol |
| Manufacturing quality and capacity | USAID and donor PAC programs have relied upon one manufacturer/distributor of MVA equipment. Although there are other manufacturers in the world (England, India, Mexico, Taiwan), Ministry of Health managers have little or no knowledge of other companies and thus are not pursuing the standard business practice of obtaining three bids for large purchases. ⁷ | Misoprostol is available in more than 80 countries. ⁷ Efforts to improve the quality of misoprostol in developing countries are required. In a study that evaluated misoprostol products in multiple countries and regions, the researchers found problems of content and purity with certain misoprostol finished pharmaceutical products (FPPs). Although misoprostol does not require refrigeration, it requires specific environmental storage conditions to guarantee its quality. Temperature and humidity have significant impact on the active pharmaceutical ingredient and the FPP during the transport and storage of the product. Post-marketing surveillance programs to ensure quality of product may be needed in the long term. |
| Intellectual property ownership | No data available. | Available as a generic. |
| Cost and cost drivers | Use of MVA for management of first-trimester, incomplete abortions reduces costs. Studies in Bolivia, Mexico, and Peru showed that although the cost per patient for inpatient D&C services ranged from US\$66 to US\$151, a change to ambulatory MVA reduced costs to US\$33 to US\$66, a decrease of 56 percent to 72 percent. ¹⁴ | Supplier pricing (International Drug Indicator) Tab 200 ug Median: US\$0.45 Range: US\$0.21 to US\$0.68 The course of treatment is brief and essentially involves two outpatient visits. At the first visit, the incomplete abortion status should be confirmed by history and clinical exam and eligibility for misoprostol assessed. ⁶ |
| Delivery/procurement channels | MVA can be purchased by government and other organizations in bulk and/or through commercial distributors. | Misoprostol is incorporated into 61 percent of essential drug lists. However, lack of a dedicated label for use for PAC is an issue. ¹⁵ In 2009, an additional indication for use—“for management of incomplete abortion and miscarriage, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used”—was included in the WHO Essential Medicines List (EML). As of March 2011, no manufacturers of misoprostol have been prequalified by WHO. |
| Sustainable business models | Multiple funding mechanisms are available for purchases of MVA equipment and the equipment is available through public-sector channels. However, some countries (e.g., Bangladesh and Brazil) have successfully developed commercial distribution channels. | “Although misoprostol’s benefits in obstetrics-gynecology are well established—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. Although many medications are used off label, this status for misoprostol severely limits its application and complicates efforts to document its use.” ¹⁶ In 2009, use of misoprostol for PAC was added in the WHO EML, which is expected to increase the application of misoprostol for postabortion care. |

| Demand Information | TECHNOLOGY/SOLUTION | |
|------------------------------------|--|---|
| | Manual vacuum aspiration (MVA) | Misoprostol |
| Existing demand | <p>The potential total market size will be driven by the number of women who had incomplete abortion. MVA can be generally used at facilities while misoprostol can be offered in the periphery of low-resource countries where surgical services are limited and oxytocin is not available. However, there are some case studies in which MVAs are used by community health workers with proper training.</p> <p>MVA is reusable after disinfection. The number of uses per device should be taken into account when estimating the demand.</p> | <p>The potential total market size will be driven by the number of women who had incomplete abortion. Misoprostol can be offered in the periphery of low-resource countries. MVA can be used at facilities where surgical services are possible.</p> |
| Attractiveness | <p>Safer, less costly, and as effective as the traditionally used D&C.</p> <p>Can be performed with low levels of pain control while D&C is typically performed under general anesthesia; therefore, hospital stay for patients will be reduced.⁷</p> <p>Women in the MVA arm reported fewer side effects but higher pain scores. Women who received misoprostol were significantly more likely to be “very satisfied” with the treatment and willing to choose the method again.⁹</p> <p>Importing and ensuring a sustainable supply of MVA might be a problem in some countries.</p> | <p>Has a reported success rate of 66 percent to 95 percent. Reduces the need for surgically trained health providers and is low cost and has few side effects.⁷</p> <p>Women in the MVA arm reported fewer side effects but higher pain scores. Women who received misoprostol were significantly more likely to be “very satisfied” with the treatment and willing to choose the method again.⁹ (In studies reviewing acceptability, more than 90 percent of women have reported being satisfied or very satisfied with misoprostol for their postabortion treatment.^{17,18,19,20} A feasibility study in Nigeria showed high acceptability to women among a largely Muslim population in the north. The same study showed that participating clinicians (including doctors, midwives, and nurses) also reported a high degree of satisfaction.^{21,22}</p> |
| Price sensitivity | No data available. | No data available. |
| Policy environment | <p>WHO recommends the use of MVA as the preferred method for uterine evacuation before 12 weeks of pregnancy.²³</p> <p>Increasingly, private foundations and donor governments, including Denmark, Finland, the Netherlands, Norway, Sweden, and the United Kingdom, have funded activities to advance access to safe abortion.</p> | <p>Increasingly, private foundations and donor governments, including Denmark, Finland, the Netherlands, Norway, Sweden, and the United Kingdom, have funded activities to advance access to safe abortion.</p> |
| Donors/ stakeholders | <p>David and Lucile Packard Foundation; Department for International Development (DFID); Deutsche Gesellschaft fuer Technische Zusammenarbeit (GTZ); EnengerHealth; FHI 360; Future; Gynuity; Ipas; Jhpeigo; John Snow, Inc (JSI) ; Pathfinder International; Population Council, the Rockefeller Foundation; United Nations Children’s Fund (UNICEF); United Nations Population Fund (UNFPA); WHO.</p> | <p>David and Lucile Packard Foundation; DFID; EnengerHealth; FHI 360; Future; GTZ; Gynuity; Ipas; Jhpeigo; JSI; Pathfinder International; Population Council; Rockefeller Foundation; UNICEF; UNFPA; WHO.</p> |
| Pre- and post-sales support | <p>Information and training are necessary for proper use.</p> <p>Effective treatment should include standard infection prevention precautions, informed consent, appropriate pain management, sensitive physical and verbal patient contact, and follow-up care.</p> | <p>Information and training are necessary for proper use.</p> <p>Effective treatment should include standard infection prevention precautions, informed consent, appropriate pain management, sensitive physical and verbal patient contact, and follow-up care.</p> |

| Demand Information | TECHNOLOGY/SOLUTION | |
|---------------------------------|--|--|
| | Manual vacuum aspiration (MVA) | Misoprostol |
| Need for demand creation | <p>Need to recognize that PAC does not always involve complications, and that complications are not always life threatening but may be in the absence of swift and appropriate medical attention.</p> <p>Social, religious, policy, and legal restrictions on abortion and contraception continue to pose challenges to programs offering PAC. Advocacy will be needed to increase awareness and implementation of PAC in Safe Motherhood, essential emergency obstetric care, and other global health initiatives.²⁴</p> | <p>Social, religious, policy, and legal restrictions on abortion and contraception continue to pose challenges to programs offering PAC. Advocacy will be needed to increase awareness and implementation of PAC in Safe Motherhood, essential emergency obstetric care, and other global health initiatives.²⁴</p> |

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