Blood Screening

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
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Summary

Blood transfusion is often essential to manage life-threatening blood loss and anemia. There are a range of blood screening methods that ensure that available and/or donated blood is safe for transfusion. But women die because blood is not available in many low-resource health care facilities. Where blood is available, it is often unsafe.

Statement of Need

While most pregnancies and births are uneventful, all pregnancies are at risk. Around 15% of all pregnant women develop a potentially life-threatening complication that calls for skilled care, and some will require a major obstetrical intervention to survive.¹ About 1,000 women die from pregnancy- or childbirth-related complications around the world every day; of these, 99% occur in low-resource countries.² Improving maternal health is one of the eight Millennium Development Goals (MDGs) adopted by the international community in 2000. The fifth MDG is to achieve a 75% reduction in maternal mortality between 1990 and 2015. Emergency obstetric care (EmOC), access to family planning, and skilled attendance at birth are three key interventions that have been implemented globally to reduce maternal mortality.

EmOC is a package of medical interventions that has been developed to treat the five direct obstetric complications (see Table 1) — obstetric hemorrhage, obstructed labor, septicemia, hypertensive disorders in pregnancy, and unsafe abortion — that cause 75% of maternal deaths.

Table 1. Signal functions for basic and comprehensive EmOC³*

<table>
<thead>
<tr>
<th>Basic EmOC Functions Performed in a health center without the need for an operating theater</th>
<th>Comprehensive EmOC Functions Requires an operating theater and is usually performed in district hospitals</th>
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<tbody>
<tr>
<td>Intravenous (IV) / Intramuscular (IM) antibiotics</td>
<td>All six Basic EmOC functions PLUS:</td>
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<tr>
<td>IV/IM oxytoxics</td>
<td>Cesarean operation</td>
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<td>IV/IM anticonvulsants</td>
<td>Blood transfusion</td>
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<td>Manual removal of placenta</td>
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<td>Assisted vaginal delivery</td>
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<td>Removal of retained products</td>
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The World Health Organization (WHO) recommends there should be four basic EmOC facilities and at least one comprehensive EmOC facility per every 500,000 population.² A recent analysis of 24 national

* For a facility to meet these standards, all six or eight functions must be performed regularly and assessed every three to six months.
or near-national needs assessments showed that all but two countries met the minimum acceptable level of one comprehensive EmOC facility per 500,000 population, and in countries with high maternal mortality ratios the number of basic facilities was insufficient.\(^2\)

Of all the causes of maternal mortality, obstetric hemorrhage is responsible for around 25% of maternal mortality worldwide.\(^4\) Any obstetric hemorrhage can also be a cause of short- and long-term severe morbidity, and approximately 12% of women who survive postpartum hemorrhage will have severe anemia.\(^5\) Severe anemia can also result from other pregnancy-related complications, multiple pregnancies with poor birth spacing, malaria, worm infestations, malnutrition, and sickle-cell disease. Blood transfusion is frequently central to the management of life-threatening blood loss and anemia, but many women die because safe blood is not available, even in some urban health care facilities.

In many cases, blood is not available because effective systems for collection and/or storage do not exist. Where blood is available, it is often unsafe. Of the 164 countries that provided WHO data for screening, 40 countries collect less than 25% of their blood supplies from voluntary unpaid blood donors; 39 countries are still not routinely testing blood donations for transfusion-transmissible infections (TTIs) including HIV, hepatitis B, hepatitis C, and syphilis; and 47% of donations in low-income countries are tested in laboratories without quality assurance.\(^6\) The result is that of all patients who are able to receive a blood transfusion of the proper type, around 10% will later die of viral disease infection from the donor blood.\(^6\) In particular, the risk of HIV infection through unsafe blood and blood products is exceptionally high (95%–100%) compared to other common routes of HIV exposure such as 11% to 32% for mother-to-child transmission and 0.1% to 10% for sexual contact.\(^7\)

Deaths from hemorrhage or anemia and serious side effects from unsafe blood transfusions could be prevented if reliable and rapid screening systems were made available when blood transfusion is required. The following minimal requirements for blood screening tests are necessary to meet the demands of blood screening:

- Rapid.
- Simple to use with minimum chance of user errors.
- Affordable.
- Should not require large electricity-dependent instruments to perform the test.
- Have a high rate of inter-reader agreement.
- Minimum evaluated sensitivity and specificity levels of all assays as high as possible and preferably not less than 99.5%.\(^7\)

**Technology Solutions Landscape**
Blood transfusion is frequently central to the management of life-threatening blood loss and anemia, and readily available safe blood is essential to the survival of these women. There are three strategies to ensure blood safety:

1. Collection of blood from well-selected, voluntary non-remunerated blood donors from low-risk populations, particularly those who donate regularly.
2. Screening potential donors with a standardized questionnaire.
3. Screening blood for TTIs to exclude blood donations at risk of transmitting infection from donors to recipients, testing donated blood for ABO† and Rh(D)‡ grouping and red cell antibody screening, and cross matching to avoid immunological transfusion reactions.

**Collection of blood from well-selected, voluntary non-remunerated blood donors**
The safest blood donors are voluntary non-remunerated blood donors from low-risk populations. The prevalence of TTIs in voluntary non-remunerated blood donors is generally much lower than among family/replacement and paid donors. Despite this, family/replacement and paid donors—which are associated with a significantly higher prevalence of TTIs including HIV, hepatitis B, hepatitis C, syphilis, and Chagas disease—still provide more than 50% of the blood collected in developing countries. WHO advocates and recommends to its member states to develop national blood transfusion services (BTSs) based on voluntary non-remunerated regular blood donation in accordance with World Health Assembly Resolution No.28.72, which was adopted in 1975. Implementing these recommendations would require each country to establish voluntary blood donor programs which provide donor information and education and develop stringent national criteria for blood donor selection and deferral to exclude prospective donors at risk of TTIs.

Unfortunately, many countries have not yet been able to establish a system for collecting blood from voluntary non-remunerated blood donors due to a variety of constraints. At the national level, the main challenges are often ineffective policies, lack of national standards or screening strategies, and limited resources for implementing the national blood-screening program. At the operational level, the major TTIs constraints may be a lack of equipment to adequately store blood or a lack of rapid tests that allow screening blood without laboratory equipment or trained staff.

**Screening potential donors with a standardized questionnaire**
Screening potential donors using a standardized questionnaire before donating blood could potentially reduce time and money spent on blood donation and subsequent screening, reduce the discard of contaminated donated blood, and improve efficiency and use of resources. Criteria for deferment would

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† There are four major blood groups determined by the presence or absence of two antigens (A and B) on the surface of red blood cells:
- Group A has only the A antigen on red cells (and B antibody in the plasma).
- Group B has only the B antigen on red cells (and A antibody in the plasma).
- Group AB has both A and B antigens on red cells (but neither A nor B antibody in the plasma).
- Group O has neither A nor B antigens on red cells (but both A and B antibody are in the plasma).

‡ In addition to the A and B antigens, there is a third antigen called the Rh(D) factor, which can be either present (+) or absent (-).
have to be set nationally but could include potential donors over age 65, presence of specified chronic diseases, risk of having a sexually transmitted infection, or refusal for donation in the past. Other reasons for temporary exclusion could include the presence of a pathologic condition at the moment of donation, the presence of another condition not compatible with donation (pregnancy, medication, recent vaccination, or surgery), or the presence of a physical or laboratory contraindication (presence of an infectious disease, anemia, malnutrition).

In a study in Mozambique, 9.5% of potential blood donors were deferred by means of the screening questionnaire, and the seroprevalence of hepatitis B surface antigen (HBsAg) was significantly higher among those deferred than those that were accepted based on the questionnaire.

Developing the questionnaire requires knowledge about the national prevalence of TTIs. In addition, the questions should have high sensitivity and specificity to avoid turning away potentially “clean” donors and reliably deferring those with TTIs. A questionnaire that lacks sensitivity and specificity could potentially damage efforts to recruit donors if too many are turned away. Completing the questionnaire accurately requires additional time up front and may also be threatening to some potential donors.

**Screening blood for TTIs**

WHO recommends mandatory screening of all blood donations for HIV-1 and HIV-2, hepatitis B, hepatitis C, and syphilis (*Treponema pallidum*), with screening for other infections, such as those causing malaria, Chagas disease, human T-cell lymphotropic viruses I/II, and human cytomegalovirus, based on local epidemiological evidence. The donated blood should also be tested for ABO and Rh(D) to ensure the safety and compatibility of the transfusion for the patient.

The US Armed Services and a project working among internally displaced populations in Eastern Burma have used a system whereby prospective donors are recruited from community volunteers, thus maintaining a “walking blood bank.” The US Armed Services prescreen potential donors, and when the need arises for additional blood, donors (i.e., “walking blood banks”) are contacted to give blood. “Walking blood banks” require no refrigeration and can provide a wide variety of blood types; prescreened donors require only a rapid recertification before blood is donated, and blood is infused immediately without need for refrigeration. In Eastern Burma, maternal health workers conducted community education about the need for blood transfusions in advance, recruited prospective donors from community volunteers and tested them for blood type, and, when needed, requested donors with a matching blood type.

Although a “walking blood bank” eliminates the need for refrigeration and blood storage, the testing of blood donors for TTIs before they donate blood (pre-donation testing) is the subject of debate. While it is sometimes considered to be a cost-saving measure, particularly in high-prevalence situations, WHO argues that pre-donation testing of the donor does not ascertain the infectious status of the donation and will need to be followed by tests on the blood sample collected during the blood donation process. Pre-donation testing for potential donors may lead to a waste of resources and increased screening costs.
unless prevalence is extremely high. WHO, therefore, recommends that all screening of blood donations for TTIs be carried out only on samples taken during the donation process and in a quality-controlled environment. In areas without blood banks or inadequate stocks of blood, a compromise could be to test potential donors for ABO and Rh(D) grouping in advance, thus reducing the pool of donors to call if there is the need for an emergency transfusion.

In the past, testing for TTIs was limited to laboratories with sensitive equipment that required electricity and specialized technicians. Recently, heat-stable rapid diagnostic tests to screen blood for malaria, syphilis, hepatitis B and C, and HIV 1/2 have been developed that can be used at lower levels of the health care continuum. These tests make the establishment of “walking blood banks” and provision of either person-to-person or warm blood transfusions a viable alternative to blood banking. There are numerous products currently available for rapid screening of donated blood.

Because performance is similar for many tests and specimen types, countries will need to choose rapid tests based on criteria from the ASSURED model (Affordable, Sensitive, Specific, User-friendly [simple to perform with minimal training], Rapid and Robust, Equipment-free or minimal, and Delivered to those who need it). Additional characteristics that will likely be determining factors for countries when selecting rapid screening tests include local availability, rate of inter-reader agreement, convenience, time to result, shelf life, and storage requirements. Regardless of the accuracy of tests, however, the efficacy of screening depends on their correct use and the presence of well-maintained quality systems.

BTSs routinely screen for TTI markers (HIV antigen-antibody, HBsAg, anti-hepatitis C virus, and syphilis) at the same time, mostly to reduce the time needed for screening so that the blood or blood components, especially labile components such as platelets, can be released in a timely manner. Some laboratories may use sequential screening by initially testing for one or two infection markers. If a reactive result is obtained, no further testing is performed on this donation. The screening strategy for determining the test or tests that are undertaken first will be influenced by the prevalence of infections in the blood donor population. While there is potential for cost savings, these savings would more likely be made at high-volume facilities. In peripheral health care facilities, providers will most likely be dealing with only one blood donation at a time and will be collecting blood for emergency needs. Rapid screening methods take from 5 minutes to 2 hours to process, and sequential testing could seriously delay the transfusion.

Gap Analysis

Screening all donated blood for TTIs in a quality-assured manner requires the following:

- Government commitment and support for implementing a BTS and a national blood screening program.
- A national blood policy and plan.
Countries that are still unable to screen all donated blood for TTIs in a quality-assured manner face a variety of constraints. At the national level, the main challenges are often ineffective policies, lack of national standards or screening strategies, and limited resources for implementing the national blood screening program. At the operational level, the effectiveness of blood screening is often constrained by the fragmentation and lack of coordination of the BTS, inadequate infrastructures, shortages of trained staff, and poor quality systems.5

Implementation of “walking blood banks” at peripheral facilities would require considerable efforts to mobilize the community and promote voluntary donors that could make themselves available when blood is needed. They would also require development of and training in use of a screening questionnaire; selection of rapid tests for the prevalent TTIs; purchase of additional commodities for blood transfusion; and training health care providers on rational use of blood transfusion, screening blood, safely transfusing patients, and counseling and managing donors who test positive for TTIs. Finally, a quality assurance system for managing “walking blood banks” will need to be established.

A potential side effect of increasing access to blood is the inappropriate use of blood. Most evidence suggests that a complex intervention is needed, combining development and dissemination of national guidelines on the appropriate clinical use of blood, integrating quality improvement measures (including informed consent) into practice, and conducting ongoing monitoring and review of blood usage and adverse events associated with transfusion.13

Care for donors who screen positive for TTIs will also have to be addressed if a blood screening service is set up. All donors found positive with any screening test will need to be offered specific counseling about the need for further confirmatory workup. Individuals with confirmed serological diagnosis of a TTI will need to be evaluated and managed according to the current standard of care.

**Investment Opportunity**

While implementing a BTS and a national blood screening program is ideal, establishing a quality-assured BTS will not be a reality for many countries in the near future. For countries without an established BTS or in which blood donation is limited to tertiary hospitals, establishing “walking blood banks” at peripheral and level 1 referral facilities with blood that is tested using heat-stable rapid diagnostic tests could serve as an interim solution to improve access to safe blood in resource-constrained settings until a quality-assured BTS is established.
Rapid tests are currently being used effectively for case management of selected infections including HIV, malaria, syphilis, and hepatitis B and C. They have also been used by the US military and a few international nongovernmental organizations for “walking blood banks.” However, to date there is not yet enough clinical and programmatic evidence to provide useful recommendations for implementing “walking blood banks” using rapid tests on a large scale in low-resource countries. Clinical studies and/or operations research could be conducted to document safety, feasibility, and impact of using “walking blood banks” for obstetric emergencies in selected peripheral and level 1 referral facilities that do not currently have blood banks. Critical elements of the intervention would include:

- Development of guidelines for clinical use of blood, screening donors, testing blood for donation (TTIs that are prevalent), administration of blood and blood products, and protocols for screening blood for emergency transfusion.
- Development of a quality-assurance program for “walking blood banks.”
- Contextualization of the screening questionnaire.
- Selection of rapid tests for prevalent TTIs that:
  - Are locally available and affordable.
  - Have sensitivity and specificity levels of not less than 99.5%.
  - Are simple to use with minimum chance of user errors.
  - Have a high rate of inter-reader agreement.
  - Take 20 minutes or less to process.
  - Have shelf lives of at least 12 months at room temperature.
  - Require minimal or no equipment to process.
- Purchase of additional commodities for blood transfusion.
- Training health care providers on rational use of blood transfusion based on national guidelines on the clinical use of blood, screening blood, safely transfusing patients, and counseling and managing donors who test positive for TTIs.
- Constant supply of quality-assured rapid or simple screening tests.
- Rigorous quality control, including ongoing monitoring and review of blood usage and adverse events associated with transfusion.
- Community mobilization and sensitization to increase awareness of the need for blood transfusion and donors.
- Development of a pool of donors with lower risk profile for the “walking blood bank.”

Indicators for the clinical studies/operations research could include:

- Women requiring a transfusion.
- Number of transfusions.
- Percentages of transfusions that were appropriate and inappropriate.
- Cost per transfusion.
- Adverse effects from transfusions.
- Number of acquired TTIs in women who received a transfusion.
- Number of and reasons for missed transfusions.
- Selected indicators for maternal and perinatal outcomes.
- Maternal mortality from severe anemia and obstetric hemorrhage.
- Cost for implementation.
- Savings to the woman and health care system by making blood transfusion available at peripheral and first-referral-level facilities.

Careful documentation of implementation, disruptions, sustainability, lessons learned, and financial and service costs will help inform decisions to scale up and provide valuable guidance for implementation. Finally, feedback will be collected from women, family members, providers, and managers on perceptions of quality of care and impact of the intervention on maternal morbidity and mortality that should also assist with if and how to scale up the use of “walking blood banks.”
References


