Literature Review: Improving Management of Postpartum Hemorrhage with Blood Innovations
Acknowledgments

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The authors gratefully acknowledge the support and contributions of Hans Vemer and Deepti Tanuku of the Accelovate program at Jhpiego; Daniel Freilich of the Veterans Affairs Medical Center, White River Junction, VT; Colin F. Mackenzie of the University of Maryland School of Medicine; Luke Mullany of the Johns Hopkins Bloomberg School of Public Health; and Mohan Pahari of Z-Medica Corporation.

Accelovate—a Partnership in Accelerated Global Health Innovation

Accelovate is a global program dedicated to increasing the availability and use of lifesaving innovations for low-resource settings. Led by Jhpiego, the Accelovate program began in 2011 as a five-year, United States Agency for International Development (USAID)-funded program under the Technologies for Health (T4H) grant.

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- **Excel Tools** present raw data that implementers may develop for programming and advocacy purposes
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This report is made possible by the generous support of the American people through USAID, under the terms of the Technologies for Health award AID-OAA-A-11-00050. The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government.

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This Solution Landscape was developed in 2012 and does not survey later innovations in the field of postpartum hemorrhage management.


Published by:
Jhpiego
Brown's Wharf
1615 Thames Street
Baltimore, Maryland 21231-3492, USA
www.jhpiego.org

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## List of Abbreviations

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<tr>
<td>AMTSL</td>
<td>Active management of the third stage of labor</td>
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<td>CEmOC</td>
<td>Comprehensive emergency obstetric care</td>
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<td>DARPA</td>
<td>Defense Advanced Research Projects Agency</td>
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<td>FWB</td>
<td>Fresh whole blood</td>
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<tr>
<td>HBOC</td>
<td>Hemoglobin-based oxygen carrier</td>
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<tr>
<td>LMIC</td>
<td>Low- and middle-income country</td>
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<td>MHW</td>
<td>Mobile maternal health worker</td>
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<td>MOM</td>
<td>Obstetric Health Workers project in eastern Myanmar</td>
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<tr>
<td>PFBOC</td>
<td>Perfluorocarbon-based oxygen carrier</td>
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<td>PPH</td>
<td>Postpartum hemorrhage</td>
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<tr>
<td>TTI</td>
<td>Transfusion-transmissible infection</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Abstract

Background
Postpartum hemorrhage (PPH) is the leading direct cause of maternal death, but scaling up safe blood services requires long-term broad health systems strengthening. We investigated whether other low-cost, blood-related innovations exist that, with further research, could be brought to scale in the shorter term to manage PPH in low-resource settings.

Methods
Literature review of peer-reviewed and gray literature in English, published in the last 10 years, and consultation with experts.

Results
Artificial blood products have useful characteristics—universal blood matching and long shelf lives—but very few are licensed for use and in only several countries. Long-term clinical research on the effectiveness of artificial blood products is still needed, making this option unavailable as a management tool for PPH in a short timeframe. Several hemostatic agents, or clotting promoters, are used to limit injury-related bleeding that could be studied immediately for PPH management. The “walking blood bank,” where community members donate blood, is already underway in some settings and is another promising PPH management innovation for larger scale evaluation.

Conclusion
Little information has been reported about blood-related innovations for PPH in low- and middle-income countries, but there are promising innovations in which to invest, while more time-intensive blood transfusion banks and services are scaled up.
For most cases of postpartum hemorrhage, in global practice, obtaining a blood transfusion, even from a ready donor, necessitates rapid referral and transport from the delivery site.

Introduction

Postpartum hemorrhage (PPH) has been defined by the World Health Organization (WHO) as blood loss greater than or equal to 500 mL within 24 hours after birth; severe PPH is blood loss greater than or equal to 1,000 mL within 24 hours [1]. Estimates vary, but the WHO suggests that PPH occurs in 10.5% of postpartum women, which equates to nearly 14 million women annually [2,3]. PPH accounts for one-third of all maternal deaths, with 99% of these deaths occurring in low- and middle-income countries (LMICs) in women who give birth outside of a hospital setting [2-4].

The most common cause of primary PPH is uterine atony, the failure of the uterus to contract after delivery of the placenta [1,5]. Other causes of PPH include genital tract trauma, uterine rupture, retained placental tissue, and maternal bleeding disorders [1]. Hemorrhage is preventable in many cases with prenatal, labor and delivery, and postnatal interventions. Active management of the third stage of labor (AMTSL) is a multi-step procedure that has recently gained acceptance and global policies support its scale-up. In addition to other interventions, AMTSL includes administering a uterotonic after the delivery of the baby and before the delivery of the placenta to increase contraction of the uterus and prevent hemorrhage. The uterotonic oxytocin reduces PPH by more than 60% [1]. If hemorrhage occurs either in the absence of AMTSL, or despite it, uterotonics can also be used to reduce the need for blood transfusions. However, blood transfusions may still be necessary management to save the lives of as many as 3% of cases of women with severe PPH [6,7].

Transfusions are widely recognized as an effective intervention to manage PPH, particularly those attributed to the most frequent cause—uterine atony [1,5-8]. In common global practice, blood transfusions are viewed as “best delivered” in well-equipped and well-staffed facilities [6]. For most cases of PPH, then, which frequently occur at some distance from a health facility, obtaining a blood transfusion, even from a ready donor, necessitates rapid referral and transport from the delivery site [5]. Blood transfusions are part of the package of comprehensive emergency obstetric care (CEmOC) interventions that the United Nations recommends in at least one facility for every 500,000 people. Although the
current CEmOC facilities theoretically meet recommended levels, these facilities are not always equitably distributed within countries [9,10]. Moreover, some designated CEmOC facilities have been found to be missing the required blood transfusion capabilities [11]. Blood safety is also a widespread concern among the facilities in low-resource settings that offer blood transfusions [6]. Rapid tests exist for blood typing and for the most common transfusion-transmissible infections (TTIs), but the use of such tests is still relatively new to low-resource settings [12]. Addressing the health systems challenges to ensure widespread availability of safe blood for transfusion, including the facilities, trained staff, cold chain, and transport for women in need, should be part of a long-term health systems development plan. However, solutions are needed more immediately to prevent women from dying of PPH. Because of these limitations, a seemingly obvious solution for PPH¾restoring lost blood at the very site of the emergency¾is not always a first-line response. In fact, the WHO makes only “assess(ing) the need for blood transfusion,” not the transfusion itself, part of its recommended PPH care pathway [1].

An analysis was conducted in 2004 on “new or underutilized technologies” to manage PPH in LMICs, including those relating to blood replacement. Although it heralded red blood cell substitutes as the most promising new technology at the time, it dismissed all other blood-related interventions as too complex to consider [7]. The present analysis delves deeper into specific blood supply innovations to inform promising areas for further research that could be brought to scale to manage PPH in low-resource settings.
Methods

Search Strategy

A systematic literature search was applied to PubMed’s Medline (1946-present). The search was adapted for Embase (1974-Present) and Scopus (1966-present). We used a combination of controlled vocabulary and key word terms for blood, artificial blood products, cost, technology, and policy (Table 1). Search results were checked to determine the inclusion of a known set of expected citations; the research team then reviewed the results and refined the strategy iteratively. Limits were placed on the results to retrieve references related to humans and published in English during the years 2004-2014. All titles relevant to our study were retrieved and reviewed independently by at least one of two authors (RPM and RG), from which abstracts and full-text articles were selected for further review. References from selected studies and review articles were manually evaluated to identify any possible relevant study for analysis. The literature search and data analysis were performed between February and March 2014.

Based on the objectives of the analysis and the sharing of the review between two primary reviewers, we used two separate search concepts, one for blood alone and one for artificial blood products. To each of these concepts, we added secondary concepts for cost and technology, to find results most closely related to innovations research and recommendations. For the blood concept, we also added a secondary concept for policy to obtain information on blood-related policies and regulations and a secondary concept for PPH to generate results that associated PPH and blood accessibility. Finally, to the blood concept, we added a tertiary concept for LMICs to limit our results to low-resource settings; we did not do the same for artificial blood products because we discovered in exploratory searches that little had been written about their use in such settings. The six search concept strings are shown in Table 1 and in detail in Appendix A.
<table>
<thead>
<tr>
<th>Concept 1</th>
<th>String 1</th>
<th>String 2</th>
<th>String 3</th>
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<tr>
<td></td>
<td>Artificial blood products</td>
<td>Artificial blood products</td>
<td>Blood</td>
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<td>Concept 2</td>
<td>Cost</td>
<td>Technology</td>
<td>Cost</td>
<td>Technology</td>
<td>Policy</td>
<td>PPH</td>
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<td>Concept 3</td>
<td>—</td>
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<td>LMICs</td>
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**Study Eligibility**

Inclusion criteria were as follows: methods for tracking blood supply and evaluations of their adoption; blood transfusion practices; and development, use, cost, and licensing of oxygen carriers, hemoglobin-based oxygen carriers, blood substitutes, and perfluorocarbon-based oxygen carriers.

We excluded studies with: references pre-2003 (more than 10 years); non-English language; all pharmacological, surgical, behavioral, etc. methods that were not directly related to the blood supply, e.g., AMTSL, uterotonics, intravenous or prophylactic iron, tranexamic acid, external aortic compression device, anti-shock garment, air-inflated balloon, activated recombinant factor VII; all interventions not related to PPH or excessive blood loss, e.g., postpartum hemolytic uremic syndrome or other postpartum blood transfusion needs not related to PPH; excessive hemorrhage associated with cesarean section; results of artificial blood products before animal testing phases.

A secondary method used to conduct this analysis was consultation with experts in PPH and the fields of trauma and transfusion medicine. Experts provided search term guidance, opinions on current development of products and/or programs, and led us to unpublished sources.
Results

Artificial Blood Products

Artificial blood products serve to carry oxygen to tissues: the two main categories are hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon-based oxygen carriers (PFBOCs) [13]. They differ in their mechanism of oxygen transport. For HBOCs, oxygen is covalently bound to hemoglobin, and for PFBOCs, oxygen is physically dissolved in perfluorocarbons [14].

Two artificial blood products were identified that are approved for human use: Hemopure and Perftoran. They are available in only a few countries (Russia, Kazakhstan, Ukraine, Kirghiz Republic, Mexico and South Africa).

HBOCs are derived from either human or bovine hemoglobin. The developer of Hemopure has unsuccessfully attempted to gain approval from the U.S. Food and Drug Administration (FDA), and recently submitted an application to test Hemopure for anemia treatment [15]. MP4OX is another drug in development and completed Phase IIb. Clinical trials were to be conducted in 56 centers around the world and led by The Royal London Hospital, but results have not been published [16].

PFBOCs are fully manmade emulsions that capitalize on the high solubility of respiratory gases in perfluorocarbons [17]. Perftoran and Fluosol are first generation PFBOCs [17]. Perftoran was first approved for use in Russia in 1996 for hemorrhagic shock and perfusion of human organs [18]. It has also been approved in the Republic of Kazakhstan (2008), Ukraine (2005), Kirghiz Republic (2006), and Mexico (2005) [19]. Perftoran can be stored frozen for three years or under refrigeration for two weeks [18]. Fluosol is the only blood substitute to be approved for human use in the U.S. in 1989, but was later withdrawn in 1994 [17,20]. Production stopped in 1992 after commercial failure because of several problems including: labor-intensive management, long half-life in organs, poor efficacy as an oxygen carrier, and side effects [21]. Oxycyte, a second-generation PFBOC, is undergoing...

1 Artificial blood products have been called “blood substitutes,” but many caution against use of such terminology because these products do not replicate all functions of blood. Instead, some of the following terms are used: hemoglobin substitutes, artificial oxygen carriers, red blood cell substitutes, and O₂ therapeutics.
The efficacy of artificial blood products in resource-poor settings has not been tested, and all trials have been in hospital settings.

Table 2 includes selected artificial blood products and information that could be found regarding their development.

<table>
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<th>Drug (Corporation)</th>
<th>Status</th>
<th>Description</th>
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<tr>
<td><strong>Hemoglobin-Based Oxygen Carriers (HBOCs)</strong></td>
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<tr>
<td>Hemopure/HBOC-201 (OPK Biotech)</td>
<td>Approved for use in South Africa (2001) and Russia (2011). Has failed to gain U.S. FDA approval, but currently recruiting study participants [15,23,24].</td>
<td>Bovine derived and shelf life of 3 years, does not require blood typing. OPK Biotech also produces Oxyglobin (HBOC-301) for veterinary use, which is approved in the U.S. and European Union. [23].</td>
</tr>
<tr>
<td>MP4OX/ formerly Hemospan (Sangart, Inc.)</td>
<td>Completed phase IIb trials [15].</td>
<td>Oxygenated pegylated hemoglobin-based colloid, made from expired blood stocks, designed to improve the perfusion and oxygenation of ischemic tissues [25].</td>
</tr>
<tr>
<td>rHb2 (Baxter)</td>
<td>Program discontinued in 2003 [29].</td>
<td>Recombinant-hemoglobin solution [29].</td>
</tr>
<tr>
<td>HemAssist/DCLHb (Baxter)</td>
<td>Discontinued before 2000 [27,29].</td>
<td>Cross-linked hemoglobin [29].</td>
</tr>
<tr>
<td><strong>Perfluorocarbon-Based Oxygen Carriers (PFBOCs)</strong></td>
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<tr>
<td>Perftoran (Russian Academy of Sciences and the Perftoran Company)</td>
<td>Approved for use in Russia (1996), Kazakhstan, Ukraine, Kirghiz Republic, and Mexico [18,19].</td>
<td>First-generation PFBOC. Shelf life of 3 years (-4°C -- -18°C) and 2 weeks at 4°C [18].</td>
</tr>
<tr>
<td>Oxycyte (Oxygen Biotherapeutics, Inc.)</td>
<td>Phase IIb clinical trials in Switzerland and Israel for use in traumatic brain injury. U.S. phase II trial is currently recruiting participants [15,22].</td>
<td>This second-generation PFBOC may be stored for at least 12 months when refrigerated [30].</td>
</tr>
<tr>
<td>Fluosol (Sanguine Corp. and Green Cross Corp.)</td>
<td>Only oxygen carrier approved by U.S. FDA (1989), then withdrawn in 1994 [17].</td>
<td>First-generation PFBOC. Withdrawn due to limited success, complexity of use, and side effects [20].</td>
</tr>
<tr>
<td>Oxygen (Alliance Pharmaceuticals)</td>
<td>No current trials [15,31].</td>
<td></td>
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<tr>
<td>Oxyfluor</td>
<td>No current trials [15].</td>
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Hemostatic Agents

Several hemostatic agents, or clotting promoters, are currently on the market that could potentially play a role in the reduction of PPH. One of these products is QuikClot, a hemostatic gauze containing a mineral called kaolin to promote blood clotting [32]. Similar products are HemCon/ChitoFlex, CELOX, Chitosan, and fibrin sealant dressing. Several of these have been effectively used by a wide range of providers in the field and hospitals to control hemorrhage [32]. QuikClot is currently marketed for external use only, but intracorporeal use by military and civilian surgeons has been documented [33]. A recent study specifically looked at using one of these products, CELOX, to treat PPH and concluded that the use of “chitosan-covered gauze is a viable option in the treatment of (severe) PPH”[34]. Additional uses have been documented; one case of vaginal hemorrhage from a transobturator sling that was controlled with QuikClot Combat Gauze was found [35]. Another report documents a woman avoiding a “seemingly inevitable hysterectomy” when CELOX was used to successfully control bleeding that persisted several hours after a cesarean delivery [36].

QuikClot’s manufacturer, Z-Medica Corporation (Wallingford, CT), has documented interest in pursuing the use of hemostatic bandages to treat PPH, and applied for a 2011 Saving Lives at Birth Grand Challenge grant to develop a hemostatic agent specifically designed for the treatment of PPH. The application made it to the final round of finalists (80 applicants), but was not selected for the final 20 that received funding. No current trials or further research on clotting promoters for PPH management were found. Reports noted that while intracorporeal use has been lifesaving, it should be used only as a last resort lifesaving maneuver with full understanding and vigilance for its complications [37]. This caution is similar to those for blood transfusions.

Another product with potential application is being developed by Arsenal Medical, Inc.; a foam technology to control intra-abdominal hemorrhage that could potentially be used to control PPH [38]. Few specifics are currently available, but treatment consists of an injection of two liquid polymers that react upon combining to create foam that expands rapidly to compress the injury and control bleeding. The product is designed to control bleeding until the patient can reach medical care, and it has to be
surgically removed [38]. The company announced in December 2012 that it had been awarded an additional $15.5M contract to continue work from the Defense Advanced Research Projects Agency (DARPA) [39]. Current development is focused on treatment of soldiers injured on the battlefield. The company claims the product is durable, lightweight, and easily carried, facilitating battlefield use. Potential use to control PPH has not been documented [39].

Blood Accessibility

Blood Donation

The WHO maintains that the key to an adequate and reliable supply of safe blood is a stable base of regular, voluntary, unpaid blood donors [40]. An “adequate” supply of stored blood requires donation from approximately 1–3% of a country’s population [40]. The median blood donation rate is 36.4 donations per 1,000 people in high-income countries, 11.6 in middle-income countries, and 2.8 in low-income countries [40]. In sub-Saharan Africa as a whole, fewer than 3 million units are collected each year for a population of 700 million [41]. Although a number of LMICs have laws or guidelines supporting exclusive donations from voluntary, unpaid donors, 40 countries still obtain more than 75% of their blood from paid or family/replacement donors [40]. Studies of donor motivations in LMICs have concluded that lack of knowledge and access to collection facilities are two of the primary barriers against donation, but cultural beliefs and practices can also affect the willingness to donate, particularly among certain religions and during religious holidays [42-45].

There are many documented strategies to recruit donors to blood banks, but two methods, mobile collection and media outreach, have shown consistent success at recruiting large numbers of volunteer, unpaid donors across a range of LMICs, to contribute to their respective blood supplies. Successful examples of mobile collection were found in Burkina Faso, Chile, Morocco, and Ghana [46-49]. Blood donors have been shown to have significantly higher exposure to print, radio, and television media than non-donors [47,50,51]. A set of radio blood drives in Ghana achieved a high percentage of spontaneous, repeat donations in direct response to the radio appeal [48,52]. Key aspects to increase
the number of voluntary and repeat donors included: collection several times per week (including weekends), diverse locations, inclusion of remote areas, and support by local religious leaders and community associations [46]. Media outreach has been used in many LMICs as a free way to advertise blood collection activities and promote donor education, overcoming two of the main barriers to blood donation.

Walking Blood Banks

For populations that are out of reach of any supply of stored blood, “walking blood banks” provide a way to obtain local blood for fresh whole blood (FWB) transfusion. Walking blood banks typically consist of prearranged lists of community volunteers who have been recruited and typed in advance of a transfusion need and are then recertified for a person-to-person transfusion once a need arises [53]. The concept of a “walking blood bank” is not new, but its recent use has been documented most extensively in the context of U.S. military combat treatment in Iraq and Afghanistan and in obstetric care among mobile medical teams in eastern Myanmar. Data on the numbers of walking blood banks presently in operation, as well as specific operational details such as cost, could not be easily located, but literature suggests that they are relatively common in low-resource settings and can be added on with relatively little additional cost to existing community health services. One potential challenge with walking blood banks is that in certain cultures, gender norms determine who donates and from whom a woman with an obstetric emergency can receive blood [54].

The U.S. military permits the use of FWB or whole blood that is kept at room temperature and transfused within 24 hours of collection when standard blood components are not available for lifesaving therapy [55]. Donors are military personnel or staff at combat hospitals who have been screened for eligibility with a standardized questionnaire; typing and testing to check donor blood do not occur until after the blood is collected, likely because of the military’s entry requirements, as well as the availability of rapid blood tests [55]. Under optimal conditions, the time to transfusion can take as little as 25 minutes [55]. A retrospective study of combat patients’ receiving FWB and traditional stored component therapy revealed significantly higher 24-hour and 30-
day survival rates among those receiving FWB as the component therapy, a finding that might be attributable to the decreased presence of additives and anticoagulants in the FWB [56].

In the Mobile Obstetric Health Workers (MOM) project in eastern Myanmar, an area of recent intense conflict and instability that precludes access to facility-based care, a cadre of community health workers who had at least four months of basic health training and generally at least two years of fieldwork were further trained for six months (two in the classroom, four in clinic) on blood transfusion and the six basic emergency obstetric procedures. Once in the field, the mobile maternal health workers (MHWs) conduct community education about the need for blood, collect a list of prospective volunteer donors and type them to record their blood types, and then approach these donors at the time of an emergency and perform confidential screening, counseling, testing and, if the blood is safe, transfusion [57]. The testing protocol was adapted from an existing protocol in local clinics, using heat-stable rapid diagnostic tests to screen for malaria, syphilis, hepatitis B and C, and HIV [58]. The testing was done in a sequential manner starting with assessing infection for malaria, followed by syphilis, Hepatitis B and C, and lastly, HIV. If a person tested positive at any point, the testing and donation process ceased, and the person was both informed of the results and treated or referred, whichever was appropriate. The MOM testing sequence is depicted in Figure 1.
Case studies from MOM imply that this method enabled emergency, home-based blood transfusions that would not otherwise have taken place. For example, in a remote area of Karen State, an MHW was able to transfuse and stabilize a woman who suffered three days of vaginal bleeding near her due date using such strategies as mobilizing relatives and screening potential donors for safe blood. In a similar case of vaginal bleeding for three days, in which the MHW induced labor and delivered a stillbirth, the MHW was also able to transfuse blood, and the woman survived [59]. As the MOM project illustrates, walking blood banks created outside of any clinical setting will require the development of a specially trained community health workforce that is capable of performing all blood screening procedures as well as the transfusion itself. Such “task-shifting,” or delegation of care to lower-level providers while maintaining safety and efficacy, has been shown to work well in some settings for other forms of comprehensive emergency obstetric care, including surgical procedures [60].

Adapted from Mullany, 2010 [57].
In situations where there is no possibility of obtaining a homologous blood transfusion, either stored or fresh, or where there are serious concerns with TTIs or immunologic reactions, the practice of autologous blood transfusion or the use of fresh whole blood collected from the recipient herself has become more acceptable but is still controversial [61]. This technique, also known as intraoperative cell salvage, has been described in a low-resource setting as requiring the filtering of collected blood through gauze swabs, aspiration of the blood by siphoning into a standard blood bag containing anticoagulant, and then transfusion to the patient through a filtered giving set [62]. Autologous blood transfusions should not be considered if there is any suspicion of sepsis or contamination of the blood, usually diagnosed by odor [62].

### Blood Storage and Distribution

If blood is not being used immediately, it is typically transported to a blood bank for storage, a procedure that requires a certain temperature range, or cold chain, throughout transportation and storage [63]. The blood cold chain requires equipment with different specifications from the cold chains for other medical supplies, such as vaccines; as a result, the blood cold chain has developed in parallel to and at a different, usually slower, pace than other cold chains [64]. Maintaining the blood cold chain is essential to prevent the misuse or wastage of blood because deviations can affect the viability of the blood constituents [63]. Transport boxes and refrigerators, two key pieces of equipment, are necessary to avoid breaks in the cold chain.

Although there is little published literature about innovations in the blood cold chain, there are countless documented cases of faulty or poorly maintained equipment and expensive equipment that simply becomes obsolete [65,66]. There are also resource limitations, such as a lack of continuous electricity and transportation difficulties, that prevent even working equipment from being used properly.

One success story in Sierra Leone from 1997 describes the revitalization of a donated 10-year-old blood bank refrigerator for blood storage and the use of a kerosene-capable refrigerator from Amsterdam for power outages, especially during the dry season [67]. To address the difficult of keeping stored blood close to
distribution needs for PPH management, India has established blood storage centers at first referral units for emergency obstetric care, funding recurring costs (but not equipment) from its national blood safety division [68]. A related innovation being piloted in Malawi and India for resource-limited settings is the concept of “mini-blood banks.” These would enable collection, processing, testing and storage of blood components in rural areas and use hollow-fiber blood separation technology by gravity and a solar refrigerator [69].

**Blood Safety**

More than 80% of the world’s population has access to only 20% of the world’s safe blood supply [70]. Indeed, more than 40% of donated blood in LMICs is not screened for all relevant TTIs [71]. As a result, unsafe blood accounts for 8–15 million hepatitis B infections, 2.3–4.7 million hepatitis C infections, and 80,000–160,000 HIV infections (5–10% of all new HIV infections) each year [41,70]. The WHO recommends that, at a minimum, blood be screened for HIV, hepatitis B, hepatitis C, and syphilis [39]. Some countries mandate additional screening tests, such as malaria in India and Chagas disease in Chile [47,72]. In some settings, even basic cross-matching between donor and recipient to avoid ABO-incompatible transfusions is not routinely performed [73].

In LMICs, screening standards must carefully balance access and safety, given that as many as 50% of patients for whom a transfusion is indicated are at risk of dying immediately if the transfusion is withheld [71]. Highly technical and centralized screening procedures can cause major processing delays: in one study of a major regional blood bank in Uganda, the average duration between blood collection and final labeling for storage was 15.4 days [74]. Finally, most blood testing supplies are costly and imported; therefore, testing kits are a frequently cited supply need [40,71,73].

**Rapid and Sequential Testing for Blood Type and TTIs**

Within the last decade, the use of rapid testing for pre-donation screening in low-resource settings has become much more widely accepted and practiced [12,75]. Rapid blood tests allow for the screening of small numbers of blood samples to be performed...
quickly and locally, requiring minimal training and take only 10 or 15 minutes to perform [71]. Each test requires only a few drops of whole blood, serum, or plasma, followed by appropriate reading of the results, which can be color-coded or visualized as a dot or band appearing on the device strip [71,76]. The most common error in implementing rapid tests is not following instructions and allowing insufficient time before reading results [77]. Because the results are read visually, they are dependent on subjective evaluation, and no permanent record of the results can be retained [77]. Testing products were found to vary widely in their accuracy (i.e., sensitivity and specificity), and the majority of rapid tests are sold in countries with little or no regulatory oversight [71].

One new rapid testing product that has potential for scale-up in low-resource settings is the ABORh Card, which was developed by the U.S. military for rapid blood typing in emergencies [78]. The ABORh Card was approved by the FDA in 2010 and is a registered trademark of Micronics, Inc.; a similar product is sold in bulk by at least one medical supply company for $3.90 per card or in a kit with all supplies required to perform the test (including the card) for $4.55 per kit [78-80]. A review of rapid diagnostic testing for safe blood transfusion in resource-limited settings found that test kits in the WHO bulk procurement scheme had prices ranging from US $0.40 to US $2.00 per test [81]. Sequential testing for relevant TTIs, such as that used in the MOM study, has been shown to be as accurate as and more cost-effective than conventional simultaneous testing because the testing process can be stopped and the donor deferred as soon as there is one positive reaction [82]. Sequential testing using a protocol that prioritizes less expensive tests over more expensive ones is also likely to have less expensive average costs and marginal costs [83].

Pathogen Inactivation

An emerging set of technologies to circumvent blood testing and to reduce blood wastage is the treatment of blood components with biological, chemical, or physical substances, a procedure called “pathogen inactivation” or “pathogen reduction.” These technologies include light treatments, solvent detergent treatments, and the targeting of nucleic acids [84]. Treatment of plasma products with a solvent detergent has been studied for
more than 15 years and has been found to be effective in virtually eliminating all pathogens without reducing quality [84]. However, because the treatment works by breaking down cell membranes, it cannot be used on cellular blood components [84]. All other forms of pathogen inactivation are less well documented or are at earlier stages of development, and all have some adverse effects.

Pathogen-inactivation technologies are unlikely to gain popularity unless they: (i) can inactivate all relevant TTIs, even when titers of the infectious agent are at high levels; (ii) are nontoxic to the recipient, even after multiple transfusions; (iii) and do not impair the clinical efficacy of the blood components or lead to increased amounts of blood components being transfused [85]. The ideal technology would also employ just one procedure for all blood components, providing a single, uniform safety strategy for the entire blood supply [85]. Many questions about the process of pathogen inactivation, such as disposal and neutralization of the treatment, remain unanswered, and the technologies have also not undergone a rigorous costing analysis [86].

The Foldscope

The Foldscope, a “fully functional microscope that can be assembled from folded paper a tiny bead of glass” and a watch battery, can be configured to diagnose blood-borne diseases [87]. Rather than requiring full laboratories to test blood, these can be made for approximately 50 cents and could be used in low-resource settings. Prototyping and field-testing were conducted in Southeast Asia and Africa. There are no mechanical moving parts, it packs in a flat configuration, and is considered “extremely rugged and can be incinerated after use to safely dispose of infectious biological samples” [87]. The Foldscope could be a single-use tool, but field-testing in Uganda found they were typically used for months before it needed to be discarded [87]. As development continues, these should be monitored for their potential application in facilitating safe blood transfusion.

National Blood Policies

With the exception of some locally adapted and decentralized innovations, such as the MOM walking blood protocol and India’s Blood Supply Centers, both of which notably address PPH,
there is overwhelming agreement in the literature that a more centralized blood supply with standardized blood transfusion guidelines creates a safer and more effective blood supply. Not only can centralization provide better attention to donors and be equipped to break blood down into its component parts, extending the reach of blood donations, but it can reduce the risk of TTIs with better testing and more specialized personnel [88].

A recent application to add blood products and plasma substitutes of human origin to the WHO’s Model List of Essential Medicines was approved [89] and the 18th WHO Essential Medicines List (EML), revised in October 2013, is the first to have added these products. This change could increase pressure on LMICs to secure sustainable funding for the blood supply and establish effective regulatory oversight through mechanisms such as national blood policies [90]. It might, as proponents admit, have the negative consequence of pushing countries off the track toward collecting only from voluntary, unpaid donors [90]. The applicant, AABB, is an international nonprofit representing individuals and institutions in the field of transfusion medicine and cellular therapies, and the application received letters of support from the U.S. FDA and governments of some high-income countries [91,92]. However, a number of letters and expert review findings were filed that requested more time and more extensive investigation, particularly regarding the effects of an approval on low-resource settings.

Upon review of a number of national blood policies for LMICs, the most striking consistency is their lack of depth, containing only the broadest outline of a blood program and leaving further decisions up to a subsidiary entity. None of the policies pointed to legislation that would promote the policies’ implementation and enforcement. However, most of the policies were drafted within the last few years, so it is likely too early to judge their performance or suggest improvements.
Summary of Findings

The WHO’s recent addition of blood to the Essential Medicines List could have broad implications for the global blood supply, but implementation presents more abstract technical and political challenges that are not likely to be solved in the next few years. Our review indicates that artificial blood products might be a worthwhile investment, but development has not resulted in a widely acceptable product to date, with only Perftoran and Hemopure approved for human use in any country. MP4OX (formerly Hemospan) has completed stage IIb trials, including in the U.S., and while it will not be ready for implementation within the next few years, it merits monitoring for possible future employment.

Two other innovations for the low-resource settings in which PPH most frequently occurs, and ones for which meaningful impact data could be developed within the next few years, are artificial clotting products and a more structured form of a walking blood donor program. Clotting substitutes could gain traction for the management of PPH because of their widespread external use in conflict settings and recent trials for intraoperative use. The walking blood donor program in eastern Myanmar has already been implemented with some success, and it provides a procedural innovation that could be further tested and scaled. A walking blood donor program using rapid testing kits would require new community-level training investments to create a transfusion-capable workforce, as well as donations or price reductions of necessary supplies, but such a program negates the need for the costly and complicated logistics and training involved in standard blood banking. This intervention could lead to greater community empowerment through this participatory intervention and improved individual health through increased awareness and treatment of blood-transmitted diseases, and radically alter the possibility of having a ready source of safe, matched blood available for pregnant and postpartum women across the globe in their own communities.
References


91. AABB. Who We Are. Bethesda, MD: AABB.

### Appendix A

**Table 1. Search Concept Strings**

<table>
<thead>
<tr>
<th>Concept 1</th>
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**Artificial Blood Products Terms**


**Cost Terms**


**Technology Terms**


**Blood Terms**

Policy Terms

OR “regulations” [tiab] OR “regulatory” [tiab] OR “procedure” [tiab] OR “procedures” [tiab]
OR “hemovigilance” [tiab] OR “haemovigilance” [tiab]

PPH Terms

“Postpartum Hemorrhage” [Mesh] OR “postpartum hemorrhage” [tiab] OR “postpartum haemorrhage” [tiab]
OR “maternal mortality” [tiab] or “maternal health services” [Mesh] OR “pregnancy complications” [Mesh]
OR “Maternal Health Services/organization and administration” [MAJR] OR “Pregnancy Complications/therapy” [MeSH Terms]

Low and Middle Income Terms—Adapted from Norwegian Cochran Centers Developing Country filter and Johns Hopkins filters. (Both filters based on World Bank LMIC country classification 2013).

“developing country” [tiab] OR “developing countries” [tiab] OR “developing nation” [tiab] OR “developing nations” [tiab]
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