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Assessing the global burden of hemorrhage: The global blood supply, deficits, and potential solutions

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Abstract

There is a critical shortage of blood available for transfusion in many low- and middle-income countries. The consequences of this scarcity are dire, resulting in uncounted morbidity and mortality from trauma, obstetric hemorrhage, and pediatric anemias, among numerous other conditions. The process of collecting blood from a donor to administering it to a patient involves many facets from donor availability to blood processing to blood delivery. Each step faces particular challenges in low- and middle-income countries. Optimizing existing strategies and introducing new approaches will be imperative to ensure a safe and sufficient blood supply worldwide.

Keywords

Global blood availability, blood transfusion, global surgery, walking blood banks, unbanked directed blood transfusion

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Introduction

Hundreds of millions of people experience traumatic injury, obstetric bleeding, and pediatric anemias each year and require immediate access to blood transfusion.[1,2] Hemorrhage is responsible for the majority of deaths of trauma patients who do not reach the hospital, and up to 40% of deaths of those who do.[3,4] Postpartum hemorrhage (PPH) is the most common cause of maternal mortality, responsible for up to 35% of maternal deaths.[5] Some estimates suggest that up to 6% of all pregnant women will experience some amount of PPH.[5] In addition, anemias in the pediatric and adult populations from malaria, sickle cell trait, and cancer frequently require blood for treatment.[6,7]

For clinicians in some high-income countries (HICs), administering a blood transfusion to a bleeding patient is relatively straightforward: an order is placed and the blood bank sends blood. For the majority of clinicians and patients in low- and middle-income countries (LMICs), however, obtaining blood for transfusion is not a guarantee. Blood collection rates vary dramatically worldwide;[8] 117 million units of blood are collected annually, but half of this volume comes from just four regions, which account for just 20% of the world's population: the United States (US), Canada, Europe, and Australia.[9] This leaves LMICs with an unmet need totaling over 100 million units each year. A total of 61%

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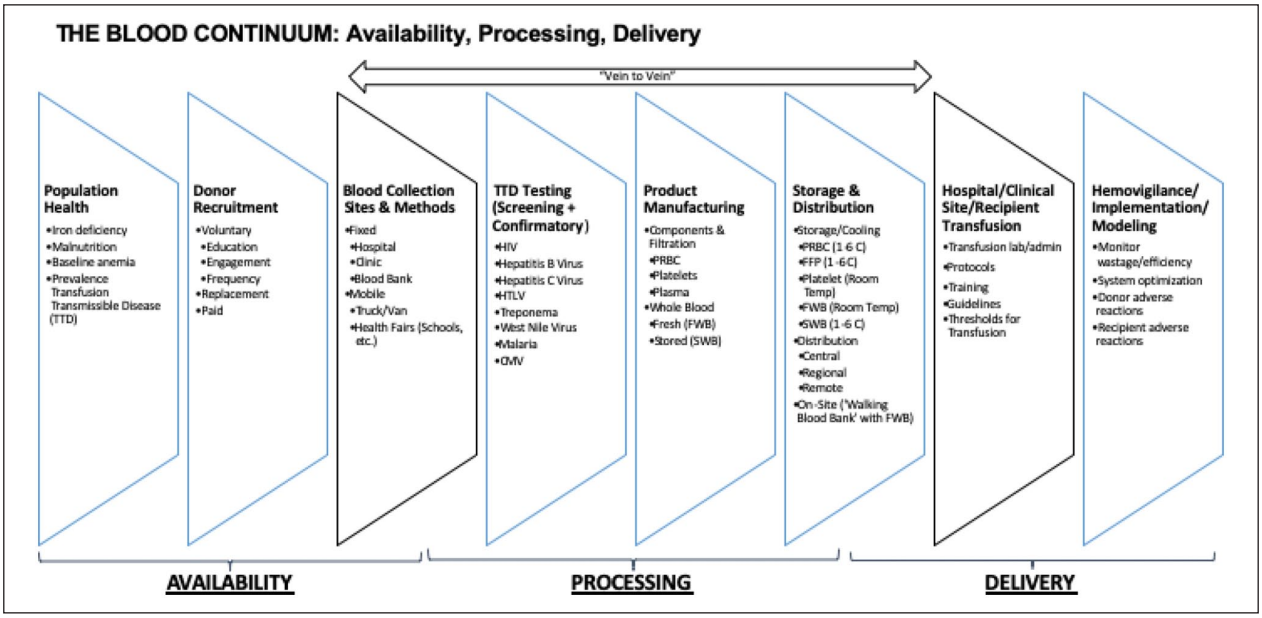

Figure 1. Safe transfusion of blood depends on a system of interconnected steps from population health to adverse reaction monitoring, each relying on infrastructure, logistics, human resources, and financial capital.

of countries—including *every* country in sub-Saharan Africa, South Asia, and Oceana—have blood shortages.

In this narrative review, we outline the complex process of blood transfusion and draw attention to the unique challenges to this process in the world's poorest settings. We then highlight some approaches to improve blood availability. We use the term "LMIC" and "low-resource setting" synonymously for the purpose of this review, though we recognize that low-resource settings are not restricted to LMICs, just as adequate resources are not restricted to HICs.

The blood transfusion continuum

Safe transfusion of blood depends on a system of interconnected steps, from population health to adverse event monitoring, each relying on infrastructure, logistics, human resources, and financial capital. This continuum of blood transfusion can be broadly grouped into blood availability, processing, and delivery (Figure 1).

Blood availability

The blood transfusion process starts with collecting blood from suitable donors. Collection organizations advertise to recruit new and repeat blood donors through direct contact, community organizations, and social media.[10] Most organizations collect through clinics and hospitals as well as mobile donation drives and camps. It is important that blood collection organizations collect adequate quantities of blood from healthy donors with low risk of harboring transfusion transmissible illness (TTI). Donor screening questionnaires are employed to identify those with major risk factors.[10] Ideally, the donor voluntarily provides blood without financial reward, also known as voluntary, non-remunerated blood donation (VNRD).[11]

Blood processing

Collected blood is tested for blood type (A, B, AB, O) and for TTIs based on local disease prevalence and international consensus standards. In the US, for example, blood is routinely tested for hepatitis B virus (HBV), human immunodeficiency virus (HIV), human T-leukemia virus, and hepatitis C virus (HCV).[12] Testing for malaria is based largely on travel history. Additional testing for Babesia, Chikungunya, dengue, Zika virus, West Nile virus, and hepatitis E virus is based on specific risk factors and seasonal and regional prevalence.[13–15] In much of South and Central America, testing for Trypanosoma cruzi (Chagas disease) is standard, and many sub-Saharan African and South Asian centers test for malaria.

Most blood banks split whole blood into its components: specifically red blood cells, plasma, and platelets. While there is renewed interest in whole blood transfusion in many high-resource settings for the management of acute bleeding, componentization of blood can improve efficiency by allowing targeted transfusion of necessary blood components, avoiding volume overload with smaller volume transfusions, and improving shelf life and ease of storage of some components. Platelets, for example, can remain at room temperature, while packed red blood cells, plasma, and stored whole blood are refrigerated at 1°C–6°C.[10]

Table 1. Common challenges to the blood transfusion continuum in LMICs across the domains of availability, testing and processing, and delivery.

Blood availability	Blood testing and processing	Blood delivery
• High baseline anemia • High rates of HBV, HCV, HIV, and malaria • High donor deferral and poor follow-up • Distrust of blood donation • Paid and replacement donation predominate	• High rates of transfusion, transmissible infection, and transmission Inconsistent testing • Variability in blood testing strategies • Poor availability of tests with high sensitivity and specificity	• High rates of wastage due to logistical and transport issues • Rare hospital-level transfusion policies and quality improvement programs • Inappropriate use of available blood

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

Blood delivery

Depending on the regional arrangements, blood can either be collected and transfused to patients locally or collected centrally and then distributed to peripheral hospitals and clinics that lack blood banks. Prior to transfusion, the recipient's blood is tested for ABO and Rh types and screened for significant non-ABO antibodies. Patient blood must be additionally crossmatched with the donor blood either physically or with computer algorithms as appropriate. Institutional, regional, and/or national guidelines often guide transfusion processes as well as decisions on whom to transfuse, and how to address and monitor for adverse reactions.[8] Adverse events are carefully tracked and occurrences are reported to the blood bank in a quality assurance process.

Challenges to the blood transfusion process in low-resource settings

The process of safe blood transfusion is logistically complex and resource-intensive. LMICs face multiple challenges with respect to each step in the blood transfusion continuum, from blood availability to processing to delivery (Table 1).

Challenges with blood availability

Poor population health from inadequate nutrition and chronic anemia are pervasive. The World Health Organization (WHO) suggests blood donors should have a minimum hemoglobin of 13 g/dL in men and 12 g/dL in women.[11] Unfortunately, over 40% of all individuals in LMICs are estimated to be anemic, with a staggering predominance in the lower socioeconomic groups.[16] This presents multiple unique challenges to blood collection in LMICs. First, it heightens the need for blood availability should these individuals fall ill, while simultaneously disqualifying much of the population from blood donation. Second, anemia itself may *predispose* women to more bleeding complications. Baseline anemia may be associated with up to a 30% increased risk of PPH.[17]

High rates of TTIs such as HBV, HCV, and HIV in many LMICs further erode an already diminished donor pool.[18] While not reflective of nationwide rates of infection, certain regions of Tanzania, Kenya, Pakistan, and Nigeria have previously demonstrated seroprevalence rates as high as 37% for HBV, 40% for HCV, 30% for HIV, and 50% for malaria.[19,20]

An added consequence of widespread anemia and infection is a high rate of blood donors deferred from donation.[21] A center in Nigeria reported turning away over 30% of volunteers due to poor health, nearly three times rates in some HICs.[22] Donor deferrals impose a cost burden on blood collection efforts and serve as significant negative motivators for volunteers. Importantly, 75% of deferred donors do not return for blood donation, even if they would be eligible at a later time.[23,24]

Distrust of the blood collection system among potential blood donors further lowers collections. In some parts of sub-Saharan Africa, concerns persist due to a shameful history of forced blood donation of Africans for colonist benefit.[25] Concerns about the health risks of blood donation, some justified while others stem from misinformation, also serve as potent disincentives.[26,27]

While the ideal blood donor is an adult acting voluntarily and without financial motivation, as the size of the eligible donor pool narrows, blood banks in LMICs frequently depend on paid or replacement donations, or particular donor populations. Paid donors are monetarily compensated for donation, while replacement donors are typically family members or friends who donate in order to "replace" blood units to a blood bank that has provided blood to the patient. This presents unique logistical and ethical challenges, as oftentimes the patient is denied transfusion until a family member has donated blood, and family members are also often anemic and unfit for blood donation.[28] Paid donation has been associated with safety risks from over-donation under expanded criteria. Avoiding both paid and replacement donors, many blood collection organizations rely on school-aged children to form the majority of the donor pool.[29] In addition to ethical challenges, this leads to dramatic blood shortages when school is out of session.

Challenges with blood processing

The risk of infectious disease transmission through blood transfusion is small in HICs, but remains a threat in

Table 2. Potential solutions to the blood transfusion continuum in LMICs across the domains of availability, testing & processing, and delivery.

Blood availability	Blood testing and processing	Blood delivery
• Nutritional and iron supplementation • Active, coordinated community engagement through public service announcements, use of traditional media and social media, celebrities, community, and religious organizations • Mobile blood donation drives to reduce geographic barriers • Judicious use of non-financial incentives, including blood credits • Investment in professionalized blood donor recruitment services	• Improved donor screening questionnaires • Standardization of high-quality RDT kits • Enhance availability of ELISA and NAT for dual-stage testing • Consider pathogen inactivating technologies • Carefully evaluate local needs and costs/benefits of componentization vs whole blood	• Adopt and implement accreditation standards for blood banks • Policies to govern and promote appropriate use of blood and quality improvement • Consider novel techniques including drone carriers and autotransfusion • Consider UDBT

RDT: rapid diagnostic testing; ELISA: enzyme-linked immunosorbent assay; NAT: nucleic acid tests; UDBT: unbanked directed blood transfusion.

lower-resourced blood systems. The risks of harboring HIV, HBV, or HCV in a unit of blood in the US are 1 unit in 1–2 million.[30,31] Conversely, one study estimated that 1 million units of blood in LMICs harbored 1000 units containing HIV, 4300 units with HBV, and 2500 with HCV.[32] Accounting for the rates of transfusion, the authors estimated the combined number of new HIV, HBV, and HCV infections in 2010 from blood transfusions in LMICs to be 51,870 per year.

A closer look at the testing process provides some explanation for higher rates of transmission. Most HIC blood systems employ a coordinated testing strategy with testing sensitivities for HIV, HBV, and HCV in the range of 95%–99%.[33] A study at six major African blood centers demonstrated heavy reliance on early generation rapid diagnostic testing (RDT) kits, some of which have a sensitivity of under 50% for the hepatitis viruses.[34,35] Not all RDTs performed poorly, however, and the overall testing quality across centers was relatively high. In areas with high disease prevalence, though, even tests with high sensitivities will miss infection. As such, the WHO recommends a dual-stage minimum testing process, combining RDT kits with an enzyme-linked immunosorbent assay (ELISA) or nucleic acid test.[36] In a survey of blood centers in seven African countries, researchers found that only two employed dual-stage testing.[37] Newer generation RDTs can be highly sensitive and specific – rivaling ELISA—but availability and usage is variable.

Challenges with blood delivery

After successful collection and testing of blood, administration of blood to the recipient depends on adequate human resources powered by appropriate infrastructure and organized logistics. National and regional governmental policies can promote organization by coordinating testing strategies and adherence, centralizing resources, and developing mechanisms for donor tracking, engagement, and infection follow-up. According to a 2009 WHO report and a 2013 Pan American Health Organization report, the prevalence of national policies governing blood transfusion systems ranged from 54% (Central and South Americas) to 77% (Europe).[15,38]

At the blood collection stage, the absence of coordination between blood banking organizations can lead to aggressive competition for the same pool of donors—multiple organizations attempting to collect from the same local college, for example—instead of a systematic effort to expand the donor pool. In the testing and delivery phases, absence of harmonization promotes inconsistent refrigeration and challenges with blood storage, difficulties in processing and transportation to and from remote blood centers, data entry errors, and high rates of expiration and wastage.[39–41] A survey of sub-Saharan African blood bank systems found few personnel with training in transfusion medicine, and few had transfusion committees overseeing blood transfusion across the system.[37]

In the absence of standardized transfusion policies and oversight, scarce available blood is often inappropriately over- or under-utilized. Transfusion hemoglobin targets of 10 g/dL persist in some settings, despite high-quality scientific evidence that a target of 7 g/dL is sufficient for most patients.[42,43] In a multi-institution analysis in Tanzania, researchers found an "inappropriate" transfusion rate of 17%–32% within one health system.[44] In addition to poor adherence to guidelines driving inappropriate transfusion, clinician tactics to circumvent chronic shortages such as ordering blood in greater quantities than necessary for fear of it running out, also contributes to wastage.[43]

Addressing the global blood deficit

Strengthening blood systems will require a coordinated, multifaceted approach that both optimizes time-tested recommendations and explores techniques that are both disruptive and innovative, appropriate for local contexts (Table 2).

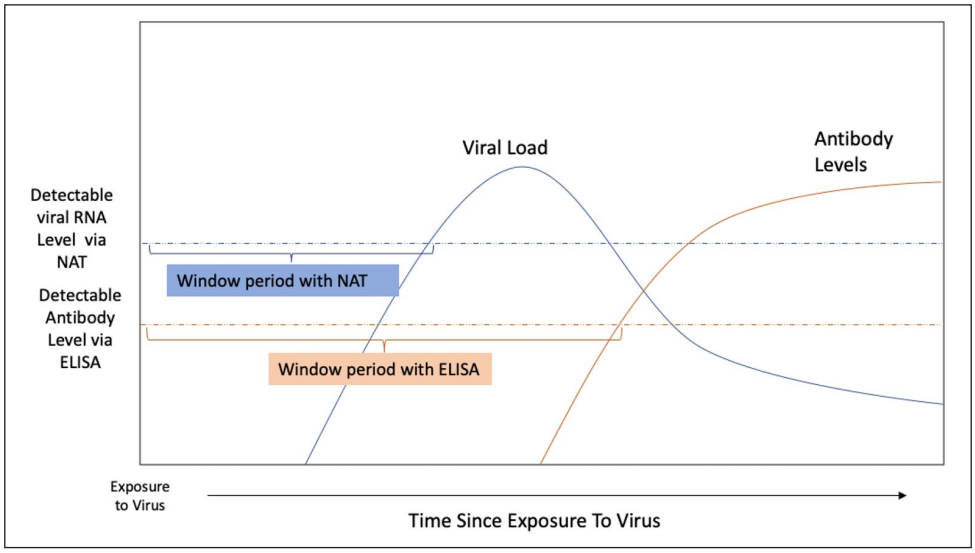

Figure 2. There is a lag before viral infection can be detected using diagnostic tests known as the "window period." Newer diagnostics such as nucleic acid tests (NAT) use polymerase chain reaction to identify viral genetic material sooner than techniques like enzyme-linked immunosorbent assays (ELISA) and rapid diagnostic tests (RDT), which rely on detecting antigens and antibodies that take longer to appear in the bloodstream. Donor screening questionnaires can be used to identify individuals at high risk of harboring infection during the window period.

Increase donor availability

Increasing the number of potential donors starts with improving the baseline population health. Nutritional supplementation and iron replacement regimens have been shown to decrease rates of anemia. Context-specific innovation is required to specifically combat reasons for non-adherence to regimens such as unavailability of supplements, poor provider training on explaining need for supplementation, and misconceptions of side effects.[45,46]

Potential donors can be actively recruited through aggressive public service advertising, community health worker outreach, and blood donation drives. While there are many reasons individuals do not donate, in many instances the most common reason is "nobody asked."[27,47] Television advertisements and programs, including public service announcements with celebrities, are effective in encouraging donation. More recently, social media and innovative mobile health applications have emerged as high-value tools to raise awareness and mobilize donors.[48,49]

Even in settings where healthcare facilities are easy to access, few will make a trip to donate blood.[50] Mobile donation sites in high-traffic areas and through outreach efforts not only reduce geographic barriers to donation but can also serve to educate the public about blood donation and have a record of success across high-income settings.[51]

Purposeful engagement of communities and religious organizations can be effective. Religious altruism is an important motivator of blood donation in some HICs, and in New Delhi and its surrounding areas in northern India over 70% of voluntary donation comes from members of religious organizations.[52,53]

Judicious use of non-financial incentives that drive replacement donation in low-resource settings may also help to augment the donor pool. In one study, half of the potential donors reported increased likelihood to donate blood for future assurance of blood for themselves or their direct family members.[26,54] Blood credits, where individuals who donate are assured future access to transfusion at reduced cost, have shown promise, especially when focusing on groups with higher-than-average blood needs such as taxi drivers or pregnant women. Blood credit programs, however, can be logistically challenging to implement and evaluations of formal, large-scale programs featuring blood credits are lacking.[55]

Regardless of the specific method used, research shows that interventions are most effective when they target social awareness, exploit altruistic motivations, and involve direct, in-person contact.[56] Active engagement through follow-up phone calls is more effective than passive modalities, including email and free gifts.[55,57] This includes efforts to encourage repeat donation, also critical to maintaining the donor pool. While time- and resource-intensive to maintain, donor registries have had success in tracking high-value, low-risk, repeat donors and encouraging donation.[58]

Improve blood processing

Improved blood safety starts with improved donor screening questionnaires. Donor screening questionnaires are a key modality through which to identify donors at high risk for harboring TTIs—those exposed to high risk activities—that may escape detection in the "window period" due to recent infection by yielding a false negative from the screening test (Figure 2). What constitutes a "high-risk" activity, however,

is not the same in all parts of the world. Developing context-appropriate donor screening questionnaires may be a low-cost intervention with high impact. A 2017 study in Cameroon found many local risk factors for HIV such as polygamy or street-vendor treatment for dental procedures that could replace questions, often adapted from HIC questionnaires with little local relevance.[59] Research is imperative to develop adequate, relevant, and culturally appropriate screening questionnaires.

Nucleic acid testing (NAT) can best mitigate the risk of infection transmission through the blood supply where TTIs are of highest population prevalence, but it is unlikely to be affordable on a large scale throughout LMICs any time soon. NAT dramatically improves detection of window-period infections and reduces false negatives. NAT can reduce the HIV window period by up to 16 days, HCV by up to 65 days, and HBV up to 36 days.[60,61] In HICs, extremely high costs in the setting of low TTI seroprevalence baselines have led some to question its utility.[33] In LMICs, however, high disease prevalence and first-time donors predominate and the added sensitivity can translate into thousands of cases detected, arguably altering the cost-effectiveness equation.[62–65] A study of blood centers in India suggested that infection detection using NAT would be 29 times higher than that in Japan, an HIC with low TTI disease prevalence whose blood banks routinely employ NAT.[60] And while individual testing can be cost-prohibitive, innovative methods to pool specimens—testing hundreds of patients simultaneously and performing individual testing only if the pooled sample tests positive—may be effective in bringing down costs.[62] More controversially, some countries like South Africa have used the increased yield of plasma to generate additional revenue from plasma fractionation and sale of plasma products, which has in turn offset a significant portion of the cost of adopting NAT.[66,67]

While affordable NAT will continue to be elusive for the near future, testing with ELISA will improve detection of false negatives and false positives from RDT. LMICs and funders must work to incorporate this into the testing rubric as soon as possible. The benefits may extend beyond increased blood safety. One study of early generation RDT performance found that only 20% of initially reactive samples were positive on confirmatory testing, and thus regions that rely heavily on RDT for donor screening likely discard a large number of otherwise appropriate blood units.[68]

Finally, RDT, relatively inexpensive and widely available, will likely remain the de facto testing system in much of the world's poorest settings.[34] Rather than lamenting this reality, decision-makers may seek to optimize this process as newer generation RDTs have enhanced sensitivities and specificities rivaling (and sometimes exceeding) ELISA in the appropriate context. Testing RDTs in LMIC contexts to optimize performance and processes must take priority. Recognizing wide variation in RDT kit performance, government laboratories should verify RDT performance and implement quality assurance and monitoring protocols.[33,69]

Pathogen inactivating technologies (PITs) offer a potential paradigm shift in blood transfusion safety, transitioning from a reactive approach of identifying and avoiding blood units from infected donors to a proactive approach of treating collected blood and rendering the pathogens harmless. PITs comprise a variety of modalities that expose collected blood to chelating agents and/or ultraviolet (UV) energy.[70] These technologies are available for treatment of plasma and platelets and lead to an exponential reduction of multiple pathogens, including HCV, HIV, HBV, malaria, and syphilis.[71] One system, used in Ghana to treat whole blood, succeeded in reducing the incidence of malaria transmission via blood transfusion from 22% to 4%.[72] A recent modeling study in Uganda found that combining RDT with PIT, versus the current local standard of single-stage ELISA, would reduce infectious units of HIV, HBV, HCV, and malaria by 100%, 20%, 98%, and 83%, respectively.[73] While promising, cost concerns, as well as challenges with blood product loss and immunogenicity of treated products, will need to be addressed with continued development and field testing in a variety of settings. Additional research is urgently needed.

Ultimately, regardless of the specific testing strategy used, gains in blood safety obtained by mandating a more expensive test with improved sensitivity and specificity must be weighed against increased testing costs. Maintaining that the highest standards of blood transfusion testing must be applied in every case regardless of cost or context will lead to uncounted morbidity and mortality from existing and exacerbated blood shortages.

Componentization has many benefits, is a hallmark of HIC transfusion systems, and has been widely adopted in countries that rely heavily on external financial support for their blood systems.[74,75] On one hand, componentization can enhance the supply by generating multiple products from a fixed quantity of whole blood. On the other hand, componentization in LMICs can increase processing costs and time and wastage of individual components, particularly plasma. Furthermore, there is growing recognition all over the world that severe hemorrhagic shock is best treated with whole blood as opposed to components.[76,77] Thoughtful standards must arise from careful evaluation of the benefits of componentization along with its drawbacks and an understanding of the local blood needs in each regional context.

Improve blood delivery

A systematic and coordinated policy approach can positively impact all stages of the blood continuum. Protocols and professionalized blood banking staff are critical components. Multiple transnational organizations, such as the Pan American Health Organization and the Africa Society for Blood Transfusion, offer training and guidance to blood bank staff on all aspects of the blood continuum.[78,79]

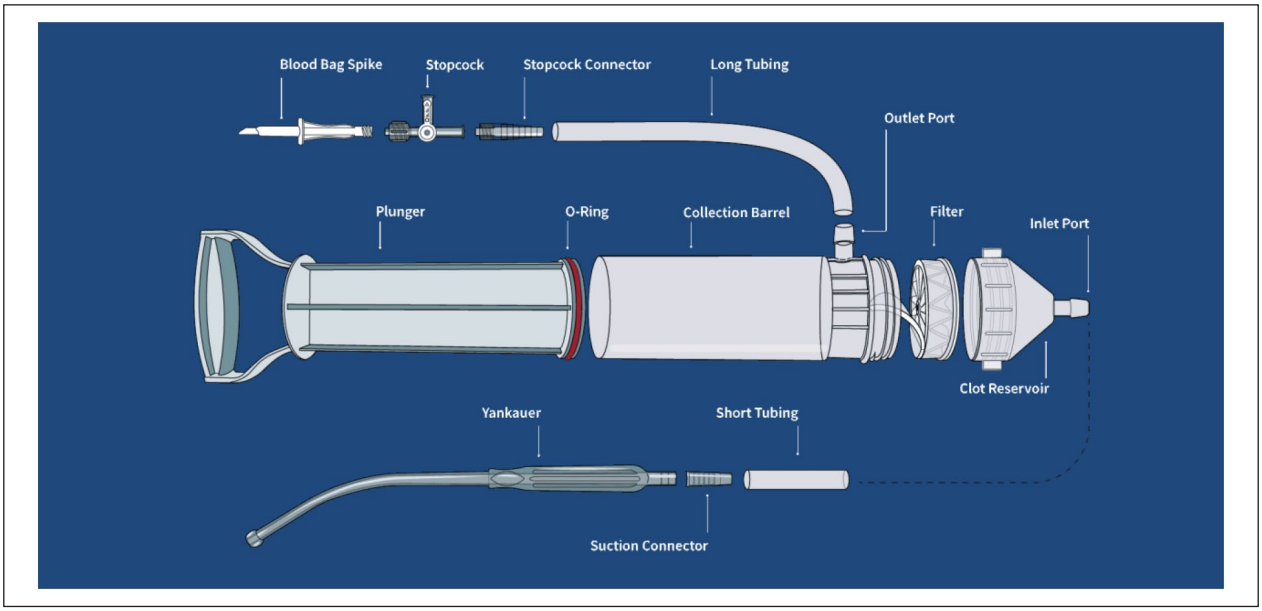

Figure 3. Hemafuse is a mechanically operated autotranfusion device currently undergoing clinical trials in sub-Saharan Africa. Photo from https://sisuglobal.health/hemafuse.

Ultimately, the ability to take tested and processed blood from a blood bank and administer it to the right patient at the right time, while taken for granted in many high-income health systems, requires the coordinated function of multiple individuals from blood banking staff to nurses, physicians, quality improvement/process monitoring personnel, and patients and their family members. A 2019 article by Pirabán et al.[80] provides a comprehensive review of the proposed models and methods for decision making and modeling blood distribution systems (also referred to as *blood supply chains*). The article presents a taxonomy for categorizing current literature (2005–2019) in blood supply chains and also presents gaps and overlaps in modeling.

Sound policymaking that addresses the multiple ground-level barriers to safe and efficient transfusion should be based on the committed inquiry of all stakeholders. Hospital-based, regional, and national transfusion committees can adopt this work and establish evidence-based guidelines adapting the best of international standards to local needs.[29]

Outside of the traditional paradigm of the blood banking continuum, new technologies and approaches may provide alternative ways to address blood shortages. Novel transportation technology, for example, may provide ways to expand the distribution radius of a blood bank. Many organizations are actively exploring drones as a means to deliver medications and blood into remote areas with challenging geography.[81] One company has combined drones with a mobile app that allows hospitals and physicians to order blood supplies on-demand, with arrival in as little as 30 min.[82]

Another expanding area of development is autotransfusion, either in the preoperative or intraoperative setting. Preoperative autologous transfusion, where blood is collected from patients before an operation in preparation for potential blood loss, has had success in sub-Saharan Africa for elective surgery.[83] Emergent options for autotransfusion require different strategies.[84] Collecting lost blood, filtering, and administering it back to the patient as a transfusion has been commonplace in HIC operating rooms during cardiac and spinal surgery since the 1980s.[85] In the face of extreme blood scarcity and significant trauma volume, several authors of this article have collected blood from a chest tube collection cannister and provided it as a blood transfusion.[84] Yet, there are differences between makeshift intraoperative autotransfusion and more sophisticated technologies that wash red cells prior to autotransfusion. Again, more research is urgently needed. Several prototypes are being developed. The Hemafuse device, for example, is a low-cost handheld device that uses manual pump suction instead of electricity and is undergoing clinical trials in Ethiopia (Figure 3).[86]

For the time being, a hospital-based replacement donor strategy will likely need to coexist with a volunteer nonremunerated donor base to meet urgent demand.[75] The pursuit of 100% VNRD, a stalwart of WHO and expert consensus for decades, continues to be a major (and elusive) goal of many LMIC blood systems. Replacement donation is cheaper and more available. Studies that previously argued that replacement donors carry a higher rate of TTI compared with VNRDs have been reevaluated and shown to have significant methodologic flaws, including confounding between first-time and repeat donors.[29,87–89] First-time donors do have a higher rate of TTI than recurrent donors, and the studies that showed a higher rate of TTI in replacement donors never controlled for the higher rate of first-time donors in the replacement pool. One ground-up alternative incorporates

elements of both. Unbanked, directed blood transfusion also known as "walking blood banks," works through a network of prescreened donors in the community available for summons in an emergency, with an expedited blood testing process prior to transfusion.[90] The system is designed to function in austere environments in which patients may need blood immediately but with low frequency, or which lack local storage capacity, such as military combat zones.[91] In these military settings, time to fresh whole blood transfusion has been reported to be as little as 18 min.[92] Civilian walking blood banks (cWBBs) have been used informally since at least the 1990s in remote settings in India, though formal study in the civilian sector has yet to be conducted. While seemingly ideal for civilian use in remote settings, significant knowledge gaps exist in the feasibility of establishing reliable WBBs in the civilian context. More data are needed, and governments and academic institutions should actively explore opportunities to perform pilot studies.

This is a narrative literature review. As such, the data included are subject to the biases associated with narrative reviews. Nonetheless, given that the review was designed to highlight a broad range of challenges and solutions across the continuum of blood transfusion, a systematic review would not have been appropriate. The authors have clinical and research experience in low-resource settings and have attempted to balance perspectives represented in the literature accurately.

Conclusion

There is a critical shortage of blood in most LMICs, resulting in increased morbidity and mortality from conditions that include traumatic injury, obstetric hemorrhage, and anemia. Safe transfusion of blood depends on an interconnected system that spans population health to adverse reaction monitoring, each component relying on infrastructure, logistics, human resources, and financial capital. Many blood systems share common challenges in blood availability, processing, and delivery. Addressing the shortage and appropriate stewardship of scarce resources requires a multifaceted approach employing traditional best practices, context-appropriate innovations, and multidisciplinary policymaking through all levels of the delivery chain from hospitals to national governments.

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Author contributions

N.P.R. and K.R. designed and wrote the manuscript. M.K., B.O., N.R., P.O., A.Z., and J.M. provided critical perspectives based on firsthand accounts in LMICs in addition to literature review and writing support. J.M., A.M.V., J.R., B.B., B.Z., and J.C.P. provided literature review and editing. All authors reviewed the manuscript.

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