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ORIGINAL ARTICLE

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Management of blood transfusion services in low-resource countries

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Abstract

Background and Objectives: Enabling universal access to safe blood components should be a key component of every country's national healthcare strategy. This study aimed to assess the current status of infrastructure and resources of blood transfusion services (BTS) in low- and middle-income countries.

Materials and Methods: A cross-sectional survey was designed to gather information on blood donations, components, redistribution, testing resources and quality management systems (QMSs). The survey was distributed to the International Society of Blood Transfusion members between October 2021 and November 2021.

Results: A total of 54 respondents from 20 countries responded to the survey. This included hospital-based BTS/blood centres (46%), national blood centres (11%)and national and regional blood services (11%). Voluntary non-remunerated, replacement and paid donors accounted for 94.2%, 84.6% and 21.1% of donations, respectively. Apheresis donation was available in 59.6% of institutions. National/regional criteria for redistribution of blood components were reported by 75.9% of respondents. Blood components incurred payment charges in 81.5% of respondents' institutions, and payments were borne by patients in 50% of them. Testing methods, such as

manual (83%), semi-automated (68%) or fully automated (36.2%), were used either alone or in combination. QMSs were reported in 17 institutions, while accreditation and haemovigilance were reported in 12 and 8 countries, respectively.

Conclusion: QMS was implemented in most of the countries despite the common use of paid donations and the lack of advanced testing. Efforts to overcome persistent challenges and wider implementation of patient blood management programmes are required.

Keywords

accreditation, blood transfusion services, low- and middle-income countries, quality management systems

Highlights

- In a survey among blood centres located in low- and medium-income countries, two thirds of the 20 respondents had blood redistribution programmes in use and 17 had quality management systems implemented
- Paid donations were reported by 21% of respondents but achieving 100% voluntary blood donation remains a top priority.
- More than half of the respondents use slide technology for blood grouping and cross-matching and rapid testing for transfusion-transmitted infections (alone or in conjunction with advanced testing). Most respondents report a lack of patient and donor haemovigilance programmes.

INTRODUCTION

The World Health Organization (WHO) reported 118.5 million blood donations worldwide in 2018, ranging from 31.5/1000 people in high-income countries (HICs) to fewer than 5/1000 in low- and middle-income countries (LMICs) [1]. Blood transfusion services (BTS) in LMICs have reportedly been inadequate in terms of blood availability, basic testing methods, clinical transfusion guidelines and quality management services [2, 3]. Reported reasons included ineffective regulatory and professional oversight, lack of appropriate legislation and policies and their implementation, insufficient quality and safety programmes for donor screening, testing, monitoring (haemovigilance) and inadequate quality improvement systems (e.g., accreditation, quality assurance) [4, 5]. Cost and availability of critical equipment, reagents and consumables, as well as structural constraints, such as limited space and irregular electricity supply, are additional challenges [6]. Furthermore, the cost of blood and blood components, as well as inadequate government funding, are likely to have impeded the provision of adequate transfusion care [7]. Becauseof the lack of transportation, resources for continuous temperature monitoring and tough geographic conditions, redistribution of blood components is challenging and requires the implementation of enabling policies at the ground level [8]. The WHO recommends strengthening national BTS to ensure a safe blood supply [9]. In 2018, almost a quarter of countries had no national blood policy, and 61% of LMICs had no specific legislation covering the safety and quality of blood transfusion [1].

Despite the numerous obstacles that LMICs face, significant progress has been made in the field of transfusion medicine, with several initiatives in hospital-based blood banks, blood establishments (BEs) and transfusion services. This study aimed to assess the current status of infrastructure and resources in BEs and BTS in LMICs and to explore their challenges and future plans for improvement.

MATERIALS AND METHODS

A cross-sectional survey was conducted using a self-administered questionnaire designed by a multidisciplinary group of the International Society of Blood Transfusion (ISBT) (Data S1). The survey questions were captured electronically using the Survey Monkey® software and were piloted among the group members for content validity and identification of any ambiguity. Forty-five survey questions covered five main sections namely: (1) respondents' demographics ($n = 8$), (2) donation and components manufacturing ($n = 12$), (3) transfusion services ($n = 13$), (4) management systems ($n = 10$) and (5) future plans for improvement ($n = 2$). The donor and components section (second) aimed to address the type of donors and donations, existing component manufacturing facilities and donor recruitment strategies. The transfusion services section (third) explored existing facilities for testing, component storage and redistribution and the cost of blood components. The management system section (fourth) covered documentation, accreditation and quality and existing patient blood management (PBM) and haemovigilance programmes. Finally, the fifth section, sought plans for improvements. The survey was then disseminated by the ISBT office to 1136 ISBT members from all WHO regions. Participation was voluntary, and consent was obtained by completing the survey. The

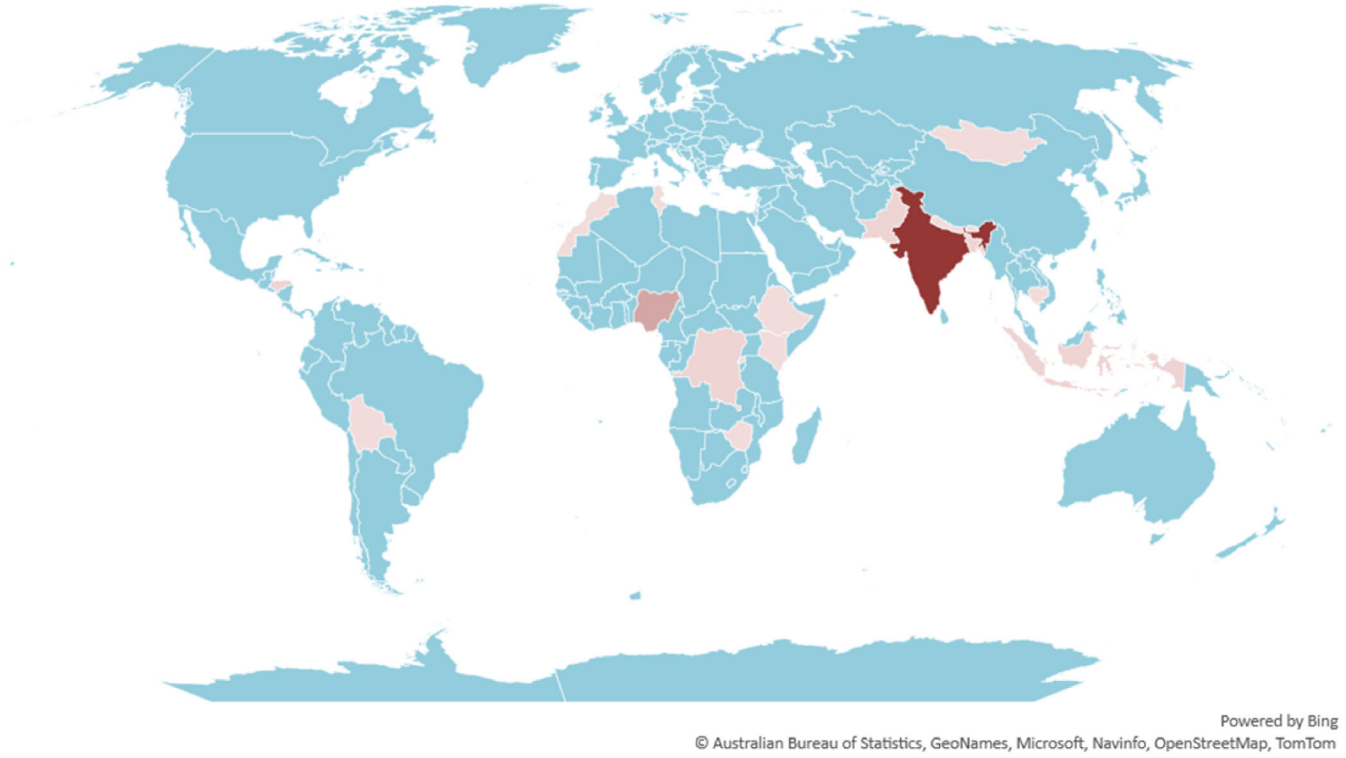

FIGURE 1 Geographic distribution of survey respondents from low- and middle-income countries ($n = 54$)

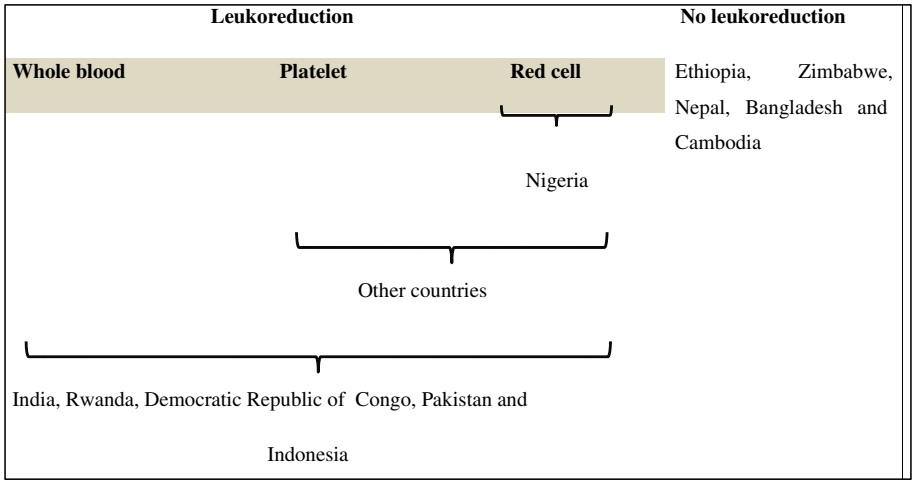

FIGURE 2 Component leukoreduction in respondent's institutions

survey was opened between 14 October 2021 and11 November 2021. Respondents were asked to address both the institution and the country's blood transfusion and management service where possible. Descriptive statistics were applied, and the reported variables were expressed in numbers and percentages.

RESULTS

A total of 54 respondents from 20 LMICs countries completed the survey (response rate 5%). The largest number of respondents were from India (42%), followed by Nigeria (15%). (Figure 1 and Table S1) The majority of respondents worked in hospital-based BTS ($n = 25$, 46.3%). The rest worked in national blood centres ($n = 6$, 11.2%), national BTS ($n = 5$, 9.3%), regional BTS ($n = 1$, 1.8%), regional blood centres ($n = 8$, 14.8%), hospital-based BEs ($n = 1$, 1.8%) and others ($n = 8$, 14.8%), such as thalassemia centres.

BTS in the respondent's countries were broadly categorized into centralized services in national blood centres (9%, $n = 5/54$), decentralized services (50%, $n = 27/54$) and a hybrid of both (40.7%, $n = 22/54$). Ethiopia, Bolivia and Rwanda have centralized

TABLE 1 Donor recruitment and types of incentives/remunerations given to voluntary blood donors ($n = 52$)

		n	%
Recruitment strategies	Motivational speeches in schools, colleges, universities and organizations	43	82.7
	Distribution of motivational and educational leaflets	41	78.8
	Phone calls to blood donors	40	76.9
	Radio/television announcements	36	69.2
	Social media motivational posts	35	67.3
	Campaigns by community leaders, celebrities and/or influencers	33	63.5
	Mass text messages to blood donors	27	51.9
	Emails to blood donors	15	28.8
	Other[a]	4	7.7
Types of incentives/remunerations	Token of appreciation or gifts <25 USD in value	20	38.5
	Day-off from work	16	30.8
	None	15	28.8
	Other (please specify)	14	26.9
	Free transportation passes	6	11.5
	Gift's worth >25 USD in value	3	5.8
	Money/cash	3	5.8

[a]Recognition by Minister, State Governors or National Blood Service, recognition on World Blood Donor Day, or snacks and refreshments.

BTS, while India, Bhutan, Bangladesh and Pakistan have decentralized BTS.

Blood donors and blood donation

The majority of the respondents' institutions performed collection of blood 96.3% ($n = 52/54$) and from different donor sources within the same institution. Voluntary non-remunerated, replacement (family or non-family) and paid donors accounted for 94.2% ($n = 49$), 84.6% ($n = 44$) and 21.2% ($n = 11$), respectively. Exclusive voluntary donations were reported in Ethiopia, Mongolia and Zimbabwe (5.8%), while the rest of the respondent institutions collected blood from both voluntary and replacement donors. Directed and autologous donations were offered in 59.6% ($n = 31$) and 51.9% ($n = 27$) of the respondents' institutions.

The majority of the blood collecting institutions ($n = 52$) applied national criteria for donor acceptance (80.8%, $n = 42$), followed by WHO (42.3%, $n = 22$) and institutional (36.5%, $n = 19$) criteria. Majority of the 52 institutions with blood collection facilities applied a combination of donor selection criteria, that is, national, WHO and institutional criteria (41, 78.6%). Seven institutions utilized national criteria solely (13.5%), while one used it in combination with WHO criteria. Institutional criteria were applied in two institutions in combination with WHO criteria in one of them. National donor eligibility criteria were applied in institutions in India, Zimbabwe, Mongolia, Bhutan, Nepal, Moroccoand the Lao People's Revolutionary Party (Lao PDR).

Different measures were utilized for donor recruitment. Donor incentives were in use in 71% ($n = 37/52$) of the participant institutions (Table 1). Respondents from Ethiopia, Nepal, Bangladesh, Cambodia and Morocco reported no incentives for the donors.

Blood component processing

Most respondents' institutions had whole blood (100%) and apheresis donation services 59.6% ($n = 31/52$), including plateletpheresis, plasmapheresis, red cell apheresis and leukapheresis. The lack of apheresis facilities was reported by institutions in Bhutan, Cambodia and Lao PDR.

Component separation facilities were available in 94.2% ($n = 49/52$) of the institutions. The percentages of whole blood inventory kept on the shelf for clinical use were variable (Table S2). Whole blood inventory accounted for up to 80% of the total inventory in respondent institutions in Nigeria, Cambodia, Honduras and Indonesia. Leukoreduced blood components were available in 51.9% ($n = 27/52$). According to 67.3% of the respondents, leukoreduced blood components were available in other institutions in their country, and 19.2% reported a lack of leukoreduction resources (Figure 2).

Out of all 54 institutions, blood component storage facilities were available in all the institutions except Zimbabwe, where a few blood centres did not have adequate storage facilities. Adequate storage facilities for red cells were reported by 96.3% ($n = 52/54$), while sufficient storage for platelet and plasma components was reported by 90.7% ($n = 49/54$) of respondents.

BLOOD REDISTRIBUTION PROGRAMME

National/regional guidelines for the redistribution of blood and blood components were reported to be available by 90.7% of the respondents ($n = 49/54$). These were, however, reported unavailable by

respondents from Zimbabwe, Bhutan, Cambodia, Morocco and Tunisia.

Continuous temperature monitoring during transportation was performed using manual methods, temperature charts (25.9%, $n = 14/54$), data loggers (7.4%, $n = 4/54$) or a combination of both (20.4%, $n = 11/54$). However, 24.1% ($n = 13/54$) of respondents reported a lack of temperature monitoring. Other methods of temperature monitoring were reported by 22.2% ($n = 12/54$), including the use of vaccine carriers with in-built thermometers or checking the temperature at the time of shipment and receipt of blood products. The most frequent transportation distance and time between blood centres were 5–25 km (44.4%, $n = 24/54$) and 1–4 h (42.6%, $n = 23/54$), respectively (Figure S1).

While the most frequent means of blood transportation reported were car (75.9%, $n = 41/54$), or dedicated transport ambulance (57.4%, $n = 31/54$), 33.3% also reported the use of public transportation, for example, buses and motorbikes. Air transportation was reported to be available by 22.2% ($n = 12/54$), and drone use was reported by respondents from Mongolia and Rwanda.

Cost of blood and blood components

A majority of respondent institutions (81.5%, $n = 44/54$) reportedly charged user fees for blood components, with responsibility for payment residing with either the patient (50%, $n = 22/44$) or the government for specific patients' categories, such as thalassemia or haemato-oncology patients (38.6%, $n = 17/44$). Respondents from Ethiopia, Bhutan, Cambodia, Bolivia and Kenya indicated that blood components were provided free of charge in their countries.

Participants from India, Lao PDR and Honduras reported that the government paid for treatment in public hospitals while patients used private insurance funds to access treatment in private hospitals. In Honduras, patients made payments through social security accounts. In countries where patients paid user fees for blood components, the charges ranged from 3 to 40 euros for whole blood and 6 to 30 euros for red blood cells. For platelet concentrates and fresh frozen plasma, the charges ranged from 1 to 50 euros. For plateletpheresis procedures, the charges ranged from 14 to 678 euros.

Testing facilities

Basic testing on blood donor units, including ABO and Rh blood grouping, and testing for transfusion-transmitted infections (TTIs), was reported by 47 respondents (Table S3). Reagents for antibody screening and identification on donor units were reported to be available by 57.4% of respondents ($n = 27/47$), while bacterial screening on platelet units before being issued was reported to be available by 10.6% ($n = 5/47$) of respondents only.

Methods used for blood grouping and cross-match testing were manual with tube and slide technology (83%, $n = 39/47$), semi-automated testing with column agglutination technology (68%, $n = 32/47$), and fully automated testing with solid-phase red cell adherence assay or erythrocyte-magnetizing technology (36.2%, $n = 17/47$). Full automation was reported to be available in some centres in India, Nigeria, Morocco, Honduras and Pakistan.

TTIs screening testing methods reported to be used in respondent's institutions were enzyme-linked immunosorbent assay (ELISA) (82.9%, $n = 39/47$), rapid tests (68.1%, $n = 32/47$), chemiluminescence testing (61.7%, $n = 29/47$) and nucleic acid amplification testing (NAAT) (36.2%, $n = 17/47$).

Quality management systems

Implementation of the quality management system (QMS) was reported in 17 out of the 20 countries surveyed. Respondents from institutions in Magnolia, Rwanda and Tunisia reported the lack of a well-established QMS. Internal and external quality assurance programmes were reported in most of the respondents' institutions (65.9%, $n = 31/47$), while others had either internal (23.4%) or external (10.6%) QMS (Table 2). BTS records were maintained by manual and electronic systems (76.6%, $n = 36/47$), manual/paper-based systems only (19.1%,

TABLE 2 Quality assurance program and proficiency testing in respondent countries ($n = 47$)

S.no.	Programmes	Types	Countries
1.	Quality assurance programme	Internal ($n = 11$, 23.4%)	Rwanda, Demographic Republic of Congo, Nepal, Morocco and Lao PDR
		External ($n = 5$, 10.6%)	Bhutan
		Both ($n = 31$, 65.9%)	India, Ethiopia, Zimbabwe, Bangladesh, Nigeria, Cambodia, Honduras, Pakistan, Indonesia, Bolivia and Kenya
2.	Proficiency testing samples	Local ($n = 15$, 31.9%)	Demographic Republic of Congo, Nepal, Bangladesh, Morocco, Pakistan and Lao PDR
		External ($n = 25$, 53.2%)	Ethiopia, Zimbabwe, Bhutan, Cambodia, Honduras, Indonesia, Bolivia and Kenya
		Both ($n = 7$, 14.9%)	India and Nigeria

Abbreviation: Lao PDR, Lao People's Revolutionary Party.

TABLE 3 Types of accreditation programme in respondent's institutions ($n = 39$)

S. no.	Type of accreditation programme	Number of respondents
1.	National accreditation programmes	26 (70.3%)
2.	International Organization for Standardization (ISO)	11 (29.7%)
3.	Association for the Advancement of Blood and Biotherapies (AABB)	3 (8.1%)
4.	College of American Pathologists (CAP)	3 (8.1%)
5.	Others (African Society for Blood Transfusion [AfSBT], and College of Physicians accreditation programmes)	8 (21.6%)

Note: Four institutions had multiple accreditation programmes: one had national + ISO + AABB + CAP, one had ISO + AABB + CAP, one had national + ISO + AABB and one had national + ISO.

$n = 9/47$) or digital/electronic systems (4.3%, $n = 2/47$). The accreditation programmes were available in a majority of respondents' institutions (81.3%, $n = 39/48$) in 12 countries (Table 3).

Haemovigilance and PBM

Haemovigilance programmes were available in eight out of the 20 countries surveyed, unavailable in eight countries and respondents from four countries were unaware of the existence of such programmes. The majority of the countries ($n = 6$) with haemovigilance programmes had both patient and donor programmes, while one had only a recipient programme and the other maintained only a donor programme. PBM was reported to be implemented in one third of institutions (34%, $n = 16/47$); in 50%, it was not implemented, and the others were not aware of the same.

Future planningfor improvement

The respondents shared their institutions' improvement plans over the next 5–10 years. The most common plans were strengthening haemovigilance, improving quality assurance and quality managementand the achievement of 100% voluntary blood donation (Table 4).

DISCUSSION

This survey highlights the available resources in BTS of LMICs in terms of donor management, testing facilities, blood cost, redistribution policies, quality management services and future planning for improvement.

Almost 25% of the countries surveyed reported decentralized BTS. Decentralization is associated with many risks in the provision of services. As per the WHO guidance document, centralization of key functions of the BTS, such as testing and processing of blood donations, can overcome shortcomings that often exist in decentralized blood systems [10]. Hosseinifard et al. found that centralized BTS led to reducing the blood shortage and expiry of blood units by 40% and 21%, respectively, and also decreased the average age of issued blood to the patients [11].

Our survey showed that blood donation remains a major challenge in LMICs healthcare systems, with high reliance on replacement blood donations. This is in concordance with other reported literature [9, 12]. We also showed the use of paid donors and incentives in some of these countries. According to WHO, paid donations account for more than half of the blood supply in 72 countries, 64 of which are LMICs. Previous studies suggested the role of non-cash incentives, such as tokens of appreciation (medals and certificates), goods and gifts (T-shirts, mugs, food or vouchers to stores or restaurants) as a possible means of navigating between the two established theoretical frameworks for donation—altruism and payment [13, 14]. Our survey also showed variations in the application of donor eligibility criteria. One institution surveyed did not use national or WHO donor selection criteria, possibly due to a lack of national guidelines, inability to access or a lack of awareness of international/WHO resource materials.

We also found variability in access to component manufacturing, leukoreduction, apheresis and supportive services of component redistribution. According to WHO reports, approximately 25% of LMICs do not have facilities for manufacturing banked blood into components [15]. Leukoreduction helps in the prevention of febrile non-haemolytic transfusion reactions, alloimmunization and leucocytes virus transmission [16]. Therefore, recipients of blood in such environments are more at risk of adverse events and infection. Blood component redistribution helps reduce pressure on inventory levels by decreasing overall discard rates through the transfer of near-expiry blood units to needy blood centres [17]. In LMICs, geographical constraints and resource scarcity are major challenges to the effective implementation of redistribution policies.

In this survey, around 85% of respondents reported that transfusion was payable by patients. Divkolaye et al. reported in a 2019 survey that in LMICs, the total or partial costs of blood were mostly recovered directly from the patients [7]. Testing of blood components accounts for the majority of the charges. According to WHO, 32% of countries had specific governmental budgets for BTS, 16% had a cost recovery system, and 33% reported having both, while the remaining 11% reported neither a specific budget nor a cost recovery system [9].

More than 80% of the responding institutions used manual testing methods for blood grouping and cross-matching. Non-availability of screening equipment and reagents might be one of the major reasons for the lack of advanced testing. In addition, almost more than 40% of respondents reported a lack of antibody investigation tests. The lack of availability of advanced testing may result in adverse transfusion reactions, such as haemolytic transfusion reactions due to alloantibodies or septic transfusion reactions due to bacterial contamination of platelet components [18]. Limited supply or access to test

TABLE 4 Future improvement plans reported by respondents in their institutions and countries

S. no.	Country	Future planning
1.	India	• Centralization of BTS • Universalization of guidelines, leukoreduction, NAAT, accreditation, PBM, and pricing of blood and blood components • Molecular blood grouping • Electronic cross-matching • Pathogen inactivation • Cellular and gene therapy • Rare blood donor registry • Radio-frequency identification system
2.	Bhutan	• National strategies for consolidation of blood donation and TTI testing • Hospital transfusion committee • Accreditation • Centralized blood transfusion information system • Universal component separation • Apheresis services
3.	Nepal	• Qualified person to run the BTS • Development of antibody screening and identification programme
4.	Bangladesh	• Implementation of automated services in blood centres
5.	Indonesia	• Build a new building for blood transfusion centre
6.	Pakistan	• Improve utilization of blood components • Introduction of NAAT
7.	Morocco	• Involvement of an autonomous public establishment in blood banking services • PBM • Apheresis cell therapy • NAAT and chemiluminescence testing for TTI
8.	Tunisia	• Implement electronic record maintenances
9.	Ethiopia	• Improve necessary infrastructure • Resource mobilization • Accreditation • Plasma fractionation • Tissue banking • Organ transplantation
10.	Zimbabwe	• Improve testing of blood donor samples by implementation of NAAT
11.	Democratic Republic of Congo	• Development of national blood transfusion centres with advanced equipment • Easy availability and accessibility of blood to all
12.	Nigeria	• Increase national availability and accessibility of safe blood, regionalization of BTS • Improved collaboration with regional centres • Universal component separation • Leukoreduction • Automated blood grouping • Automated cross-matching • Electronic record maintenances • Universal antibody screening of blood donors and patients • Reference laboratories • Rare blood donor registry • PBM, • Accreditation programme • Hospital transfusion committee
13.	Kenya	• To initiation of antibody screening and molecular testing
14.	Honduras	• Planning of better legislation and regulations for BTS • Standardizations of blood donor acceptance criteria and blood bank protocols • Centralization of testing and NAAT testing
15.	Bolivia	• Easy availability of high-quality blood components
16.	Cambodia	• Development of centre of excellence in accreditation programme
17.	Lao PDR	• Increase plasma collection and decrease the burdens to thalassemia patients

Abbreviations: BTS, blood transfusion services; Lao PDR, Lao People's Revolutionary Party; NAAT, nucleic acid amplification testing; PBM, patient blood management; TTI, transfusion-transmitted infection.

kits, as well as basic training of the laboratory technicians, were common barriers [19].

We also found that 70% of respondent institutions performed rapid testing exclusively or in conjunction with ELISA, chemiluminescence and NAAT facilities. Only 18% of these used rapid testing and ELISA testing in combination, while the rest used rapid testing with all the tests, such as ELISA, chemiluminescence and NAAT. In 2008, as many as 39 countries were unable to screen all donated blood for one or more of the infections: HIV, hepatitis B, hepatitis C and syphilis [20]. This difference leads to an enormous gap in residual risks of TTIs between developed and developing countries [20].

Safe and good-quality blood requires an established QMS. In our study, we found that 17 out of 20 respondent countries had QMS in use, of which 11 countries had both internal and external quality assurance programmes. As per WHO, external quality assessment monitoring is reportedly available in only 34% LMICs compared to 81% of HICs [8]. This was in keeping with our report. In 2016, up to 5 million deaths in LMICs were ascribed to poor-quality health services [21]. Safe, quality BTS are a vital component of quality health systems.

In our study, we found that more than 70% of respondent institutions implemented national accreditation programmes, while the rest implemented international accreditation programmes. Many LMICs have developed national accreditation programmes for hospitals, but the lack of financial resources remains a key constraint to the success of accreditation and its sustainability [22–24]. For example, in 2009, the 'Yellow Star' accreditation programme in Uganda was suspended by the government after development partner funding from the United States Agency for International Development was cut [25]. In Zambia, the programme was stopped [26].

We discovered that only eight respondent countries had implemented haemovigilance programmes, with only six having both donor and recipient programmes. Haemovigilance programmes play a major role in quality improvement in BTS. In a recent study of 10 sub-Saharan African countries, it was found that a lack of a comprehensive legal framework, a lack of clear understanding, distinction of the function of the blood service and a lack of human resources were major constraints to the implementation and performance of haemovigilance systems [27].

This survey revealed that only one third of the respondents' institutions have fully implemented PBM. Ironically, PBM is especially relevant for countries such as LMICs that do not have enough blood supply [28].The application of PBM helps to establish restrictive blood transfusion policies and utilizes pharmacological alternatives for allogeneic blood transfusion. Insufficient training on transfusion medicine, the lack of available clinical transfusion guidelines or the ineffective implementation of any existing guidelines could be the reasons behind its limited utilization in LMICs [29, 30].

Over the next 5–10 years, nearly all the respondents plan to achieve 100% voluntary blood donations, improve quality assurance and QMSs and strengthen their haemovigilance programmes. Within blood banking and transfusion medicine, gaps are known in LMICs with respect to competent training programmes and leadership development [31]. Universal guidelines and implementation of advanced techniques, along with improvements in basic infrastructure and manpower, are key potential areas for improvement of any BTS.

To the best of our knowledge, this is the first study that highlighted the current state of BTS/BEs in LMICs with future plans for improvement in their institution or country. Our study had some limitations, one of which was its reliance on email as the method of distribution, which made generalization difficult. Individual participant responses could not be extrapolated to represent uniform practices across any given country. We also observed diversity within a country with more than one response. There was a wide range of respondents (1–24) from different countries. Many respondents did not answer the entire questions, which led to different denominators in different response calculations. Some phrases, such as 'adequate storage facilities,' were not defined in the survey to shorten the length of the survey, which may have resulted in subjective bias. Selection, recall and desirability bias may have also influenced the responses.

In conclusion, despite the numerous challenges, the majority of LMICs had well-established QMSs and accreditation programmes. The implementation of quality systems was identified as essential for blood and transfusion safety, but without regulatory oversight, it is unlikely to be achieved.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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