Transfusion in limited infrastructure locations – where to go decades after safe blood initiative by World Health Organization?

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Transfusion demand in sub-Saharan Africa is increasing. Establishment of large national blood services seems to be challenging. Hospital blood services maintain the basic supply. However, they lack effective communication networks. Cell phones/internet provides the infrastructure for establishing such networks and could help in establishing haemovigilance systems. Voluntary non-remunerated donors are the minority of donors (<20%). It seems more appropriate to develop strategies to increase the safety of replacement donor blood instead of insisting on copying Western-world models. Red cell serology is usually restricted to ABO/Rh-D and at best Coombs crossmatch. Introduction of antibody differentiation and additional typing for C,c,E,e and K would prevent 60–70% of delayed haemolytic transfusion reactions. One of the most frequent indications for blood transfusion is major haemorrhage. Why is component therapy still recommended for resource-limited regions, while whole blood is reintroduced in Europe/US for exactly the same indications? Plasma thawed due to electricity failures is usually discarded anyway. Leuco-depleted products would be beneficial (multitransfused sickle-cell patients/neonates/AIDS). An ideal blood product could be whole blood, in-line leuco reduced by gravity filtration, treated by user-friendly pathogen-reduction not requiring irradiation/illumination. The transfusion medicine community should form an alliance to develop an affordable, pathogen-reduced blood product, to train regional auditors and to bring in external expertise to aid knowledge transfer. However, standards to be reached should be defined by the respective national experts who understand the culture and needs of their country. In respectful collaboration, we could learn from each other to finally improve transfusion in resource-limited regions.

Key words: component therapy, pathogen-reduction, sub-Saharan Africa, transfusion, whole blood.

Introduction

Transfusion medicine research currently highlights in vitro production of platelets [1] and red cells [2], and genetically engineered T-lymphocytes are introduced as new forms of cancer treatment as CAR-T cells [3]. In contrast, in many parts of the world with limited resources there is not even enough blood [4] to save women’s lives with severe postpartum haemorrhage [5,6], to treat
children with malaria infection-induced severe anaemia [7–9] or to reduce the burden of sickle cell disease and other haemoglobinopathies [10,11]. While over-transfusion is an important topic in high resource countries in Europe, North America and Australasia and currently addressed by the patient blood management initiative, in many regions in Asia but especially in sub-Saharan Africa under-transfusion is a major risk for patients [4].

In all parts of the world, transfusion safety and especially transmission of pathogens by blood products are major concerns for patients and physicians. Major progress has been made to make transfusion-transmitted infections (TTIs) rare events in areas of the world, which can afford donor screening by highly sensitive tests and donor selection based on rigid exclusion criteria. But in resource-limited countries sensitive screening assays for hepatitis B, hepatitis C and HIV are often not available. The use of point-of-care screening devices, which often have insufficient sensitivity, is the main practice [12–17]. Of similar importance are transfusion transmissible diseases, which are present in tropical countries such as, Epstein Barr Virus, Toxoplasmosis, Babesia microti, Leishmania species, filaria and trypanosomas. For these pathogens, no routine screening tests are available, because there is no market in high resource countries. New, more user-friendly, pathogen inactivation methods are currently developed and are getting applicable for red cells and whole blood [18,19]. This development could and should have a major impact on transfusion practice and safety in low resource countries. It should be a humanitarian obligation of the international community to make these technologies available at affordable costs.

Here, we review the available literature on the practices of blood transfusion in countries with limited resources. We used the following search strings in pubmed and used English language articles published 2013–2019: (((transfusion) AND (blood availability)) AND ((low resource countries) OR (sub sahara) OR (africa) OR (asia)) AND (english))); search string 2:((((transfusion safety) AND (pathogen inactivation)) AND ((low resource countries) OR (sub sahara) OR (africa) OR (asia)) AND (english))).

We focus primarily on sub-Saharan Africa and refer especially to Nigeria, as this is the region several of the authors have first-hand experience. In addition, we include our opinions on potential developments in improving transfusion under (very) limited resources.

The need for blood in sub-Saharan Africa

There is paucity of data on the number of units that are needed to meet up with the transfusion demand, but what is glaring is that blood banks do not have enough units to transfuse [8,20]. Blood need in most hospitals in sub-Saharan Africa exceeds the blood supply [21,22]. There is an increasing number of donors but the need for blood is even greater [23]. This results from a combination of two effects. The first is the rapidly growing population. The second is paradoxically the positive developments of the healthcare systems. Medical care has improved considerably and surgical as well as medical treatment options are becoming increasingly available (at least to those who can afford). However, these interventions often require transfusion support, which creates a rapidly increasing demand for supportive transfusion during critical situations. Topmost on the list of indications for blood is severe anaemia from malaria [7,8,23] as seen mainly among paediatric age group, patients with sickle cell anaemia, severe sepsis, blood-borne infections, parasitic infections, but also support of cancer patients [8]. The obstetrics indications for blood transfusion are also high due to the large number of patients who do not have access to standard ante- and perinatal care resulting in pre- and post-partum haemorrhages [24]. These figures are also high due to a high prevalence of iron deficiency anaemia, child marriages that are rampant in most places in Africa, and multiparity. This is further aggravated by the use of traditional birth attendants who are unskilled in giving optimal obstetrics care to the women while pregnant and during labour and delivery. Nigeria has currently a peripartal maternal death rate of 814/100 000 deliveries, most of them caused by fatal bleeding (this is 100–200 fold higher than the peripartal maternal death rate in the countries of the European Union; 4–8/100 000 deliveries) [25]. Many of these young women could be saved with the availability of blood components for emergency transfusion.

As the circumstances leading to a high transfusion demand are likely to remain unchanged in the near future and will rather aggravate, transfusion medicine has an important role in saving lives in resource-limited settings.

National blood services vs. hospital-based blood services

Blood transfusion in many African countries is hospital based [26,27]. Coordinated efforts to achieve a centralized blood transfusion service were introduced in several countries, often following the model of organization of centralized blood services in Europe. As an example, in Nigeria, the National Blood Transfusion Service (NBTS) was inaugurated more than 10 years ago [28]. Its mission is to promote sustainable safe blood availability to individuals that need them. The NBTS should recruit blood donors, screen for TTIs using ELISA-based technique and distribute the units to the public and private hospitals. The expectation is that the NBTS could perform above
the level of hospital-based transfusion centres, assisting in sourcing of ‘rare’ blood groups such as Rh D negative donors and conducting extended red cell phenotyping. Each geopolitical zone in Nigeria has a centre where blood should be collected and screened for TTIs and then transported to hospitals that have needs. Presently, we have observed that only a few of these centres operate at their maximum capacity possibly due to low turnout of blood donors [29]. Due to dearth of available blood donors and increased prevalence of TTIs [30] coupled with lack of political will by government also several other National Blood Centres in sub-Saharan Africa do not function optimally. In Ivory Coast, NBTS failed to meet up with its mission because they lack blood collection equipments and due to poor donor turn out [31]. This same setback is also seen in Mali [32] and also in Nigeria [33] where the lack of infrastructure, trained personnel and poor funding undermine the production of safe blood from the facilities. Other likely contributory factors are long distances between centralized services and hospitals, failures of infrastructure such as constant electricity supply and, lack of political support. Together, this makes it difficult to sustain a coordinated blood service delivery on the national level. It is beyond the scope of this review to analyse the reasons why these national blood services failed to achieve their goals in detail.

Currently, in Nigeria, the blood supply is primarily maintained by hospital-based transfusion services run by a great number of private and public hospitals [26,27]. In this scenario, the individual hospitals source for their own blood donors, screen them for TTIs and then bank the units for clinical use. In hospital-based transfusion services, blood units are often reserved for intending recipients [34] who may eventually not require those blood units until the end of their shelf life. This practice increases both, the scarcity of blood products and the number of wasted blood products. Another major setback of decentralized hospital-based transfusion services is the tendency to have ‘mal-distribution’ of blood units; in one hospital there may be excess with a tendency for wastage due to expiration, while in a nearby hospital there may be gross scarcity.

Summary and opinion of the authors

The establishment and sustainability of large national blood service organizations seem to be highly challenging in sub-Saharan African countries, while decentralized blood services maintain a basic supply of blood for transfusion. However, they currently lack an effective communication network between each other. In this regard, the wide availability of cell phones and internet already provides the technical infrastructure needed for establishing communication networks between local blood services. This could be used to establish a virtual regional common blood bank, which allows hospitals to share blood products and thereby reducing wastage and shortages. Such a ‘blood communication network’ will help hospitals to optimize patient care at affordable costs.

Taboos and superstitious beliefs surrounding blood donation in Africa

Blood donation is not a culture in most African societies. Ehimen et al. [35] noted that 91-5% of respondents in their study had never donated blood. Blood donation is believed by many to be fraught with myths, religious beliefs and perceived dangers such as fear of imminent death, contracting infections from the process, loss of sexual libido, infertility and high blood pressure [28,36,37]. Many would prefer to ‘purchase’ blood products to donating blood themselves. Baig et al. [36] also included fear of not having enough blood, apprehension of the donation process, permanent weakness and anaemia as other reasons behind refusal to donate blood. All these factors lead to the dearth of blood donors in Africa.

Donor recruitment

Although it has been an ongoing argument about whether the centralized western model of blood donation fits the sub-Saharan African setting [38], World Health Organization has stated the need to have voluntary non-remunerated donors (VNRD) because they are the safest group of donors. This practice is seen in most developed parts of the world. To increase the number of VNRDs, hospital transfusion services organize donor recruitment drives to various institutions in the vicinity of the hospitals. The use of incentives such as T-shirts, face caps or food has been shown to increase the number of donors per donor drive [39]. A promising development is the engagement of young voluntary non-remunerated donors, for example the ‘club 25’ approach, especially at tertiary institutions. Student bodies for instance the medical students, form clubs and associations of blood donors to aid in procuring blood for the hospital-based blood banks. These blood donor associations may have the capacity to form the nucleus for an increasing voluntary donor population.

However, despite all these activities in sub-Saharan Africa, VNRD makes up less than 12–25% of blood donors in Nigeria [26,40]. The large majority of blood donors are family replacement donors according to Addai-Mensah et al. in Ghana, Ugwu et al. and Aneke et al. in Nigeria and the rest are paid donors [28,41,42]. Despite the obstacles of taboos and misconceptions about
blood donation, family replacement donors are more likely to donate blood at the hospitals where their relatives are admitted [26]. Total rejection of replacement donors would lead to an immediate collapse of the blood supply chain in resource-limited settings like Nigeria.

**Opinion of the authors**

Given these numbers, it might be more appropriate to think about how to develop a model which could increase the safety of using blood from replacement donors, instead of insisting on copying the models which work in the Western world.

**Adequate screening for red cell antibodies, TTIs, haemovigilance and quality assurance**

Transfusion safety not only requires sufficient amounts of blood to fulfil the transfusion need, it also requires adequate testing to avoid immunological and infectious disease-related complications. However, the laboratories in hospital-based transfusion services in the large majority of hospitals are rather rudimentary. Red cell serology is usually restricted to ABO and Rh-D blood groups. In some regions, pre-transfusion Coombs crossmatch is rather widely established, while in other places a tile crossmatch is performed, which will detect ABO incompatibility only. Performing extended red cell phenotyping is beyond the capacity of most hospital-based transfusion services in sub-Saharan Africa due to lack of reagents to carry out these tests and also due to lack of technical skills. This is especially problematic considering the high number of multiply transfused Sickle Cell patients who have developed alloantibodies [43,44]. More than 70% of these antibodies are directed against antigens of the rhesus- or the Kell-systems. Introduction of antibody differentiation and typing for C,e,C,E,e and K in addition to ABO and Rhesus-D would help to prevent the large majority of delayed haemolytic transfusion reactions [45].

Similarly, the screening tests for TTIs are often of low sensitivity with little if any quality management system established, resulting in a high prevalence of transfusion transmissible infections [46,47]. A prevalence of 10.9% for HIV, Hepatitis B and C and syphilis in blood donors was recorded by Shittu et al. [46] in Nigeria, comparable to Kenya (9.4%), [48] while a total seroprevalence of these TTIs was 6-6% in Ethiopia [49]. Methods of screening for TTIs include NAT, ELISA and lateral flow test strips. While ELISA methods, as recommended by the WHO [50] is the practice in some blood banks in sub-Saharan Africa, most hospital blood banks use single rapid tests [51,52] due to lack of funding and technical capacity to use standard methods of testing, especially since PEPFAR funding has declined. Sensitivity of the rapid tests is rather low, and they have a large diagnostic window. The only countries in Africa where nucleic acid testing is done to assess blood products are Ghana, Egypt, Namibia and South Africa [53].

Unlike in many developed countries where both internal and external quality assurance systems exist, in most sub-Saharan Africa countries technical staff responsible for conducting screening for TTIs are not properly trained [54]. Where there is training there is usually no record of retraining and conducting proficiency testing. Control samples are often not available or not routinely used. Consequently, errors are bound to occur. All these factors together result in a high risk of transmitting TTIs. Due to lack of established haemovigilance systems these errors are not properly documented and corrective measures cannot be put in place. It is therefore desirable to establish haemovigilance systems in transfusion medicine, especially in regions with limited resources to identify the most important measures for which the restricted resources should be used. Adequate documentation and regular review, however, require adequate nursing staffing on patient wards.

**Whole blood fractionation and component therapy**

Blood fractionation is a routine process carried out in most developed countries. In contrast, the commonest blood product used in sub-Saharan Africa is fresh whole blood [32,55,56]. Okoye et al. [55] noted that only 43.4% of centres in Nigeria had a cold centrifuge for component preparation. These centres offer on-demand processing of blood into its components as a result of cost and low donor turn out.

The most important arguments for fractionation of whole blood are the reduced risk of adverse reactions due to anti-A and anti-B if blood is given to patients with other blood groups, and availability of volume reduced blood units in paediatric packs. The gain of platelets from whole blood (instead of apheresis) for the increasing number of haemat-oncologic and platelet type bleeding disorders would be highly relevant, but the 4/5 bag blood systems needed are too expensive.

**Opinion of the authors**

Given that one of the most frequent indications for blood transfusion is major haemorrhage, it should be seriously questioned why component therapy is being pursued by countries with limited infrastructure for preparation and storage, while at the same time whole blood transfusion is reintroduced in the US and Europe for exactly the same
The perspective of pathogen inactivation

Whole blood will most likely remain the most widely used blood product in sub-Saharan Africa for many years to come, and the risk of transmission of pathogens will also remain high. Pathogen reduction of whole blood is becoming technically feasible. It will not substitute testing, but it has the potential to reduce the transmission risk of many micro-organisms including parasites, viruses and bacteria, even when the donor is in the window period. Availability of methods to inactivate cellular blood components and even whole blood has come into reach. The different pathogen reduction methods for whole blood are nicely reviewed by Nkohkwo et al. [60]. Pathogen reduction systems may also have adverse effects like inducing immune responses and unknown long-term effects of the added chemicals [61]. While for regions with very low risks of TTIs the balance between benefit and risk of pathogen reduction is unclear, in most regions with limited resources pathogen reduction may make transfusion safer (Fig. 1). The MIRASOL system has been used in Ghana to treat whole blood and has been shown to reduce transmission of malaria [62]. Another method is developed by CERUS. Their compound S–303 can reduce pathogens in whole blood without the need of additional irradiation/illumination. Glutathione is an antioxidant used to quench reactions of S–303 with other molecules like plasma proteins. Dr. Soraya Amar of the Swiss Red Cross blood service is developing together with CERUS a whole blood pathogen reduction system, which does not require sophisticated equipment and centrifugation of whole blood (personal communication). This approach has features coming close to an easy to apply user-friendly system. However, up to now the preclinical assessment of this technology is only available in abstract form. The costs for pathogen reduction are currently high. They must be rigorously reduced. Otherwise, the majority of hospitals in sub-Saharan Africa will be unable to purchase the technology for use [63].

Perspectives and opinion of the authors

An ideal product for blood transfusion in locations with limited resources would be whole blood, which is leuco-depleted by gravity filtration soon after blood donation and then treated by a pathogen reduction method, which does not require irradiation/illumination by energy-rich light (Fig. 2). Its production would not need a centrifuge, it would have a grossly reduced risk of TTIs, could be produced independent of electricity supply and even stored using a solar panel powered 4°C fridge.

A role model for how transfusion medicine experts in resource-rich countries could support major progress in transfusion safety in regions with limited resources is the supply of clotting factor VIII to treat haemophilia A patients in resource-limited countries organized by the
World Federation of Haemophilia. The transfusion medicine community of physicians, hospitals, blood services and companies should form an alliance to develop an affordable safe blood product for regions with limited resources.

Organization of transfusion services

In regions with limited resources, establishing a quality management system in transfusion medicine is probably the most important task. This will help to reduce wastage and costly errors, which further restrain the available resources. Gallagher et al. [39] propound a hybrid transfusion service which combines a centralized system and a hospital-based service. While the centralized system ensures quality of the blood product, hospital-based blood banks will ensure availability when needed. Such an approach seems to be promising, but needs to be adopted to the requirements and circumstances, which differ between regions.

In the opinion of the authors, the ‘centralized system’ should start as a group of trained auditors who assess regularly the hospital-based blood services, hereby slowly increasing the standards. The technical infrastructure of internet and mobile phones is available everywhere. This should be used to form bottom-up regional networks between hospital transfusion services to facilitate peer driven improvement of quality and logistics of the blood supply.

The international Transfusion Medicine community could strongly continue to support this by training of auditors and bringing in external expertise to aid knowledge transfer by sustaining efforts initiated by, for example PEPFAR and AABB [64]. Regardless of which structure is chosen, definition of the standards that should be reached requires careful considerations of availability of resources. Rather than copying models which work in resource-rich countries. These standards have to be defined by the national experts in transfusion medicine who understand the culture and needs of their country. A system which works in Europe or North America likely will not work in Nigeria and vice versa. But in respectful collaboration, we can learn from each other to develop the appropriate measures for finally improving transfusion in resource-limited regions.

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Conflict of interest

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