Use of whole blood as the routine transfusion product in Africa

Sophie Uyoga1 & Kathryn Maitland1,2

1Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Programme, Kilifi, Kenya
2Department of Medicine, Imperial College London, London, UK

In many countries in sub-Saharan Africa (sSA) whole blood is more commonly available from blood transfusion services than red cell concentrates. Although in recent years, many countries have made significant progress in the implementing component preparation, this has largely been facilitated by external funding support. The large majority of rather than none of the sSA countries are leucocyte-reducing or irradiating blood for transfusion. Systems for the routine detection of adverse consequences of blood transfusions (haemovigilance) only exist where transfusion safety has been identified as a health priority by the government. As a resource, the availability of blood transfusion in these countries is limited since less than 5 units of blood were donated per 1000 population far below the recommended requirement of 20 units/1000 per year. Young children are the main users of blood for transfusion in these sSA regions, largely due severe anaemia secondary to infection and sickle cell anaemia. Outcomes for children with severe anaemia are poor, even in those receiving a transfusion. Although it has been speculated that this may be due to transfusion-related cardiac or pulmonary events, available data from observational studies and clinical trials indicate that these are rare complications of transfusion. Evidence from clinical physiology studies including those examining myocardial functions before and after the receipt of whole blood provide reassuring evidence that volume overload is rare and clinical trials reporting outcomes in children receiving whole blood transfusion, including a Phase II trial examining higher volumes, indicate that there is no evidence of cardiac or pulmonary overload events.

Key words: Africa, children, severe anaemia, whole blood transfusion.

Introduction

The provision of adequate supplies of safe blood for transfusion is an essential undertaking for any health system. A World Health Organization (WHO) resolution in 1975 recognised the importance of blood transfusion services and urged governments to promote and support national blood transfusion services [1]. Yet, more than four decades on the issues of blood safety, adequate supply, equitable access and rational use still remain major challenges throughout the world. The greatest concern is in low-income countries, the majority of which are in sub-Saharan Africa, which have struggled to implement fully the key goals of an integrated strategy of blood availability and safety in the absence of significant external donor funding. This paper focuses upon the unique issues facing sub-Saharan Africa with respect to quality assurance, low donation, high demand, cost-limitations to component preparation and leucocyte-reduction as a background to under why whole blood for transfusion...
remains common. We also report on the the safe use with a specific focus on the paediatric population, the largest user group of blood transfusions in this region [2].

**Blood supply in Africa**

The most recent data with regard to blood supply for the WHO Africa Region, although constrained by under-reporting or no returns by a number of countries, were reported by the Global Database on Blood Safety (GDBS) in 2017 [3]. Data were available from 46 countries in Africa reporting a total of 4.5 million units of blood were donated in the year of 2013. However, important to note that this figure includes nearly one million units from both Mauritius (reporting 39-7 donations/1000 population) and South Africa (18 donations/1000 population), respectively. Outside of these two countries, the vast majority of sub-Saharan African (sSA) countries there were <5 units of blood were donated per 1000 (see figure 3 in [3]), far below the recommended requirement of 20 units/1000 per year. These figures for sSA are very disappointing and not substantially different from the previous survey in 2004 [4], despite substantial support from donor and external funding in the intervening decade [5]. Actual blood requirements are not known but do differ from richer countries where oncology and surgical patients are the biggest users. In Africa, demand is high predominantly because of severe anaemia, infectious diseases in children and haemorrhagic complications of pregnancy [2].

**Progress in improving blood supply in sub-Saharan Africa**

One example of external support, the US President’s Emergency Plan for AIDS Relief (PEPFAR), has provided direct support to a number of sSA countries for the establishment of regional blood collection centres (RBTS) and strengthening of national blood transfusion services. These regional processing centres were introduced to replace hospital-based systems. It has been reported that this has led to an increased number of total blood donations, an increase in the proportion of these from voluntary donors and a decrease in the percentage of donations that were screened as reactive for HIV [6]. However, many of the strategies for increasing voluntary repeat donors focused upon secondary school students. From our experience on the coast of Kenya, we have found that surprisingly few continue to donate once graduating from high school (Uyoga, personal communication). This has been implicated in blood shortages during the school holidays, often coinciding with periods of peak demand. Moreover, the overall cost of this type of ‘Western model’ of national blood transfusion services is more expensive to health services than hospital-based facilities [5]. Involving the establishment of efficient donor recruitment and selection programme, transport costs for distribution from RBTS and support quality-assured laboratory services where cost recovery is unlikely. Hospital-based transfusion facilities used ‘replacement donors’ drawn from the local communities, recruited by families of patients, so therefore the hospitals do not bear the cost of donor recruitment [7]. As external agencies are now indicating long-term withdraw of support, there are concerns about the sustainability of systems in low-income countries which requiring a high level of financial support [8].

**Component preparation and safe use of whole blood**

Availability of funding from external sources has increased attention and provided support for the provision of ‘safe’ blood for blood transfusion services (BTS). The focus for blood safety has been to centralise collection and screening for the various pathogens (largely viruses) in large RBTS and to advocate for ‘component’ preparation. In the 2004, the donor blood safety report for the African region [4] described the use of whole blood from 36 countries. At this time, in only four countries were the proportion of whole blood transfusions <25% of all blood usage. Whole blood for transfusion used was being exclusively used in 6 (17%) countries, in 20 countries (56% of the total) used 75% or more whole blood for transfusion and in 2(6% of the total) used between 51% and 75% whole blood transfusions [4]. In the 2016 report, although similar figures are not as easily teased out; data indicate that median percentage [interquartile range] of whole blood use for transfusion (of all transfusion) in low-income countries (the majority being in sub-Saharan Africa) was 85% (36.9–98.7%) (Table 19 and Figure 20 of the report)[3].

Previously, all transfusions issued in the sub-Saharan African region were whole blood, but an increasing number of transfusions issued are now packed cells or semisettled cells (by gravity) [9]. Important to note that currently none of the sSA countries are leucocyte-reducing or irradiating blood for transfusion. Systems for the routine detection of adverse consequences of blood transfusions (haemovigilance) only exist where transfusion safety has been identified as a health priority by the government [10]. In low-income countries, the frequency of non-infectious adverse events related to blood transfusion is largely unknown as haemovigilance activities are very limited [11]. The FEAST trial conducted in three countries in East Africa, in which 1422 children received a transfusion, reassuringly only 0-4% were considered to have had
a ‘probable’ blood transfusion reaction, and most were mild and self-limiting [12]. Conversely, the only other published study indicated that 40% of transfusions (26,973 units) in given in Yaoundé, Cameroon were associated with fever [13]. However, it is unclear whether fever was present before the transfusion, as was the case in the FEAST trial (enrolling children with severe febrile illness).

Outcomes from children hospitalised with severe anaemia

Although severe anaemia is a common cause of paediatric admission and outcomes remain poor in terms of high in-hospital (8–17%) [14–16]; post-discharge 6-month mortality (12–6%) with long-term follow-up indicating a high frequency of relapse and re-admission (with some but not all receiving a blood transfusion) [17,18]. One question is whether the adverse outcomes of these children are experiencing both in-hospital in the months following admission could be related to the receipt of non-leucocyte reduced whole blood transfusions.

It is well recognised that various constituents present in donor blood could play a significant role in the development of transfusion reactions and post-discharge morbidity [19,20]. In most resource-rich countries, leucocyte-reduction of transfusion products has decreased the risk of immunogenecity and cytokine release and significantly reduced the number of febrile non-haemolytic transfusion reactions (FNHTR) [21,22], post-transfusion purpura and transfusion-associated graft-versus-host disease [23]. Although extensively studied in cancer patients and animal models, it is evident that allogeneic blood transfusions are associated with transfusion-related immunomodulation (TRIM). In sSA, where severe anaemia patients present with co-infections [24] and remain at risk for infectious diseases [18] TRIM would put the patients at greater risk for poor immediate and long-term outcomes as well as the increased risk of malaria and bacterial infection. In addition to TRIM, leucocyte rich blood transfusions also carry the risk of bacterial contamination from phagocytosed pathogens that may be liberated by dying leucocytes during storage. Endotoxins released by these pathogens could result in septic complications in the patient [25]. Transfusion in sub-Saharan Africa has been shown to be at higher risk of pathogen contamination, which has been speculated (although not proven) to be linked to poor immediate outcomes [26]. In Kenya, bacterial contamination, predominantly by environmental organisms, was present in 9% of paediatric transfusions [27]. A study conducted in northern Ghana investigating whole donor blood packs identified a contamination rate of 17-5%; the majority of contaminants in this case were thought to originate from the skin of the donor [28]. These data are similar to 13% bacterial contamination rate of whole blood reported in southern Ghana [29].

Quality of blood

Quality-assurance practices are a legal requirement for blood transfusion services (BTS) in high-income countries in order to minimise patient risk. Yet, even within this context the prolonged storage of donor blood remains [30,31] and transfusions given to critically ill patients have resulted in unintended (adverse) consequences [30–32]. In Africa, demand for transfusion is high, with most given as emergency interventions, yet little research has been conducted to inform us about the quality and safety of donor blood or its effect on outcome. Quality control and audit of transfusion services are advocated, yet little research is currently being undertaken, data that would be very valuable to improving BTS and transfusion practices.

Until recently, most of the work on donor blood quality is from studies conducted in developed countries that have efficient blood bank systems and where red-blood cells (RBCs) are leuco-reduced pre-storage. Efficient transfusion practices in sSA would help reduce the burden on BTS by reducing the need for repeat transfusions. There is an urgent need to validate the safety of blood in terms of quality of RBCs and not just the absence of viral infection, which is the current focus of screening practice. In addition to the pathogenic safety, the quality of the red-blood cells (RBCs) received by the patient is likely key to determining the recovery of the patient from severe anaemia.

An audit of the haematological quality of donor blood used in the recently concluded Transfusion and Treatment of African Children with Severe Anaemia trial (TRACT), described three pack types produced by local BTS were supplied for use in the trial: (1) whole blood, collected from donors and stored without any preparation; (2) packed cells, produced by centrifugation, to removal platelets and plasma, followed by the addition of sodium, adenine, glucose and mannitol (SAGM) solution. In the trial, whole blood, red cell concentrates and packed cells were transfused in 40-7%, 36-8% and 22-4%, respectively [9]. Furthermore, the audit reported on the age of donor blood in use was also heterogenous with a median storage age of 12 days (IQR 6, 19), 18-2% of the packs had a storage age of over 21 days. Despite being a recommended product, the preparation of packed cells by centrifugation is costly and time-consuming and this could explain the low usage of the pack type. The audit also highlighted how improved communication between the clinical and hospital transfusion teams resulted in better labelling and clear identification of blood packs in use [9].
Who needs blood?

Although the magnitude of the shortage of blood for transfusion in sub-Saharan Africa is not certain, the patient groups who suffer the greatest impact are easier to identify. Children under 5 years of age have a high demand for blood with the prevalence of severe anaemia (defined as haemoglobin <5 g/dl) in hospital ranging from 8 to 29% [33]. In malaria-endemic areas, Plasmodium falciparum malaria as well as other infections and nutritional deficiencies have also been associated with severe anaemia in children [15,24,34]. Sickle Cell Disease (SCD) is also a common cause of children being hospitalised with severe anaemia. In case-control study conducted in Kenya, where all children were retrospectively genotyped for SCD and where cases were children with SCD and controls were all other hospital admissions 178/579 (31%) of SCD cases had severe anaemia versus 1470/18297 (8%) in controls [35]. Although they composed of only 3% (576/18 873) of hospital admission they accounted for 9-2% (165/1788) of all transfusions given [35]. In some hospitals, 50% of all children admitted are transfused, thus in some malaria-endemic African countries, children account for ~70% of all transfusions prescribed [14,36,37]. Previous studies have revealed that severe anaemia secondary to malaria without any other complications leads to about 1% mortality; however, this rises to 16% when complicated with respiratory distress (severe, symptomatic anaemia) and over 30% when both respiratory distress and coma also present [38]. Women of reproductive age are also major users of blood transfusions in Africa. Nineteen of the 20 countries worldwide with the highest maternal death rates are in sub-Saharan Africa where the risk of maternal death is 1 in 16, compared with 1 in 2800 in rich countries. The most common cause of maternal death is severe bleeding, contributing to over 40% of maternal deaths, and it has been estimated that a quarter of these women die because of blood shortages [39].

Paediatric treatment guidelines

Worldwide consensus transfusion guidelines for stable children on intensive care units, based on the multicentre non-inferiority TRIPICU trial [40], recommend transfusion with haemoglobin <7 g/dl [41] but explicitly highlight the need for further trials, particularly with 5–7 g/dl. In African given the major burden of paediatric severe anaemia on health services, coupled with scarce resources of donated blood, WHO guidelines encourage restrictive transfusion approaches. The decision whether or not to prescribe a blood transfusion is meant to be based upon an assessment of the clinical condition and haemoglobin levels (See Table 1) and is covered in the Pocket book for hospital care [42]. Specifically, under the WHO rationale use of blood the transfusion guidelines recommend not to transfuse stable children with haemoglobin 4–6 g/dl [42].

Three of the criteria defining complicated SA lack scientific justification (including relevant literature to support their inclusion). These are heart failure, dehydration and hyperparasitaemia. First, heart failure (i.e. ‘biventricular’ failure or ‘overload’) is uncommon even in African children and is best corrected with diuretics and other measures. The clinical signs of severe tachycardia and respiratory distress are very common in children with severe and complicated anaemia and have been previously considered as indicative of heart failure. Indeed, the opposite is true such children are compensating for the severity of anaemia by increasing cardiac output [43–45] and have Kussmauls breathing to compensate for hyperlactaemia or oxygen debt [46]. Second, severe dehydration (loss of intracellular water and electrolytes) should be corrected with crystalloid solutions and not transfusion. Finally, hyperparasitaemia is very frequent among paediatric admissions in malaria-endemic areas and hyperparasitaemia has not been shown to be an independent risk factor for poor outcome. Inclusion of this criteria may result in the substantial overuse of a limited transfusion supplies by a large group with low risk.

The under-pinning evidence-base is weak as it is not been informed by clinical trials, consequently adherence is poor as often clinicians fail to follow these guidelines [47,48] and these are hampered further by inconsistent recommendations with regards to haemoglobin thresholds for transfusion for malaria. (See Table 1). Current transfusion guidelines are conservative not only in terms of criteria applied for administering a transfusion at all, but also in terms of the volume of blood transfused. One size fits all policy is advocated for all children with a haemoglobin <6 g/dl. This recommends a standard 20 ml/kg of whole blood (or 10 ml/kg packed cells) [49]. Nevertheless, applying standard formulae to calculate volume required to correct the haemoglobin to levels >6 g/dl (deficit correction) [50] indicates, specifically for children with a haemoglobin <4 g/dl (profound anaemia) thus undertreats by 30% and thus may not be suffice to correct anaemia [14]. A prospective study of 128 Malawian children aged 3–60 months, transfused according to WHO guidelines, examined transfusion failure (defined as a Hb ≤ 6 g/dl >24 h post-transfusion). Only 104 (81%) received the prescribed volume; of these, 24 (23%) were classified as transfusion failures and 83% of these had a subsequent Hb < 4 g/dl [51]. Lackritz and collegues reported mean volumes of 26 ml/kg whole blood [15] and others following WHO guidelines have shown a modest Hb rise of 2.5–3.3 g/dl
Clinical outcome with whole blood for transfusion

Over the years’ reports have varied on the outcome of children with severe anaemia with some speculation that the use of whole blood may contribute to the poor outcomes. Overall mortality in children with profound anaemia (Hb < 4 g/dl) or severe anaemia with life-threatening complications is 15% [17]. Clinical studies in Kenya [14,15] have shown that profound anaemia (Hb < 4 g/dl) is independently associated with death (Odds Ratio (OR) 2.5; 95% confidence intervals (CI) 1.4–4.5), as is SA (defined in this study as Hb < 5 g/dl) complicated by reduced consciousness (OR 7.4 95% CI 4.2–13.1) or respiratory distress (OR 4.1; 95% CI 2.2–7.4) [14]. Many deaths occur within 48 h of admission [54,55], with 25–50% occurring within 6 hours, largely in children who die awaiting an urgent transfusion [14,47]. In Kenyan, children whole blood transfusion appeared to be important in preventing death in children with severe symptomatic malaria anaemia. However, it was not associated with a faster or a superior haemoglobin recovery (~1-month post-admission). Mean haemoglobin at discharge (approximately 3–4 days) being similar in transfused 6–4 g/dl [SD: 1–5] and non-transfused 6–8 g/dl [SD: 1–6] and remaining similar at follow-up (28–35 days) in the transfused (10–2 g/dl) and non-transfused (10–0 g/dl) groups (P = 0.25) [56]. The major factor affecting mean haemoglobin concentration at follow-up was concurrent *Plasmodium falciparum* malaria (8.8 g/dl compared with a mean of 10.5 g/dl in those without malaria parasitaemia, P < 0.001) [56]. Both young age (<24 months) and the type of antimalarial treatment also influenced

Table 1 Recommendation for Transfusion

| Current WHO guidelines | Supportive Care: Management of anaemia (page 276–281) | Give a blood transfusion as soon as possible to: |
|------------------------|--------------------------------------------------------|-------------------------------------------------|
| all children with a haematocrit of ≤12% or Hb of ≤4 g/dl | less severely anaemic children (haematocrit 13–18%; Hb 4–6 g/dl) with any of the following clinical features (complications): |
| clinically detectable dehydration | shock |
| impaired consciousness | heart failure |
| deep and laboured breathing | very high malaria parasitaemia (≥10% of red cells with parasites) |

Guidelines for transfusing severe malarial anaemia

Fever chapter: Part 6.2 Malaria (pages 142–143) | Give a blood transfusion as soon as possible to: |
|------------------------------------------------|-------------------------------------------------|
| all children with a haematocrit of ≤12% or Hb of ≤4 g/dl | less severely anaemic children (haematocrit 12–15%; Hb 4–5 g/dl) with any of the above complications |

[14,15,52] following initial transfusion with ~25% remaining severely anaemic (~5 g/dl) [14]. Anecdotal evidence suggests that multiple, low volume (20 ml/kg) transfusions are frequently given, which is wasteful, inefficient and exposes children to additional risks (e.g. reaction and infection). In a sub-analysis of the FEAST trial data [53] involving 1422 (45%) children who received a blood transfusion, 322 (23%) of those transfused received 2 or more transfusions, the proportion being greater (212/612, 35%) in those with profound anaemia (Hb < 4 g/dl) at trial enrolment.

Fig. 1 Comparing 30 ml/kg versus 20 ml/kg in the correction of severe anaemia [58]
outcome ($P = 0.03$) [56]. The major limitations with all these studies for informing best practice are that they are observational and are not based on clinical trials [57].

The limited published data that are available indicate a higher rates of post-discharge mortality, recurrence of anaemia and re-hospitalisation in Malawian children with SA compared with non-SA hospital or community controls [18]. In this case–control study, in-hospital and 6-month post-discharge mortalities were greater in the cases (6% and 8% respectively) than in either the hospital (0% and 1-6%, respectively) or community controls (0% 6-month mortality). In addition, 17% of cases were readmitted within 6 months of discharge versus re-admission rates of 9–10% and <0.5%, respectively in the hospital and community control groups.

**Blood volume for deficit correction**

As the standard volumes recommended for transfusion (20 ml/kg of whole blood or 10 ml/kg of red cell concentrate equivalent) have been shown to undertreat children with severe anaemia a pilot study, conducted in two sites in Uganda (Oct 2011–Dec 2012) evaluated the safety of a higher volume of whole blood transfusion (30 ml/kg: 80 children) compared with the standard volume (20 ml/kg: 80 children) (ClinicalTrials.gov NCT01461590). The study was designed to provide comparative data on safety, and qualitative data on feasibility and operational components of implementation of the study protocol with special reference to the transfusion service. All blood transfusions given in the trial were whole blood. Median haemoglobin at trial entry was 4.2 g/dl (IQR 3.1–4.9) in both trial arms. Adherence to randomisation arm (transfusion volume) was excellent (97%). Correction of severe anaemia was superior in the 30 ml/kg than the 20 ml/kg (Fig. 1). Severe adverse events (SAEs) were reported in 7 of the 160 children enrolled. Six of the SAEs were deaths, most occurring within <5 h of admission. All deaths were in the 20 ml/kg group. None were reported to be due to volume overload, there was no use of diuretics in the trial. One non-fatal transfusion reaction was reported (in the 30 ml/kg arm): the child was reported to have developed generalised body itching and an urticarial rash shortly after starting the transfusion.

Nevertheless, this was a small pilot trial: whilst it is encouraging that our hypothesis that a larger initial volume would result in a greater increase in haemoglobin was supported, the small sample size means that it cannot conclusively demonstrate that this leads to improvements in mortality and other long-term benefits. This one of the principal questions under investigation in a large Phase III trial: Transfusion and Treatment of African Children with Severe Anaemia trial (TRACT) [57].

Since all blood transfusions given in this Phase II trial were whole blood, it demonstrated that this was safe with regard to not leading to fluid overload–related events and few transfusion-related adverse events, it appears there is a case for maintaining whole blood in the blood transfusion services. As indicated previously, component preparation is both costly and time-consuming and the evidence to support exclusive component preparation is very poor. Most plasma is discarded, and only few centres across Africa prepare platelets and cryoprecipitates. In terms of resource funding would be better directed towards increasing donation rather than a focus on component preparation. The long-term outcome of children receiving whole blood (approximately 50% of the TRACT trial) [9] is currently being investigated [57].

In conclusion, the use of whole blood is still the main source for transfusion in many parts of sub-Saharan Africa. Although component preparation has been introduced into many countries, which is more costly and time-consuming, there is some evidence in children presenting to hospital with severe anaemia that whole blood can be safely used without leading to fluid overload events. More research needs to be conducted in other patient populations in Africa, for example bleeding from pregnancy-related complications or trauma to examine whether these observations can be extended to these indications.

**Conflicts of interest**

Both authors declare no conflicts of interests.

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**References**

1 World Health Organization: Utilization and supply of human blood and blood products. In: Official Records of the World Health Organization No. 226 Twenty –Eighth World Health Assembly, Geneva, Switzerland, 13–30 May 1975, Resolution 28.72, Vol. 1, 40p, 1975.

2 Hassell O, Bates I, Maitland K: Blood Transfusion in Resource-Limited Settings, 9th edn. London: Magill - Maguire – Ryan – Solomon; 2012: 162–167.

3 World Health Organization: Global status report on blood safety and availability 2016. Geneva: World Health Organization, 2017.

4 Taponk JB, Sam O, Diarra-Nama AJ: Status of blood safety in the WHO African Region: report of the 2004 survey. In. Brazzaville: WHO Regional Office for Africa; 2007: 1–25.
Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018; 9S(Suppl 1):S98–S113

42 World Health Organization: Pocket book of hospital care for children: second edition Guidelines for the management of common childhood illnesses. Geneva: World Health Organization; 2013.

43 Maitland K, Levin M, English M, et al.: Severe P. falciparum malaria in Kenyan children: evidence for hypovolaemia. QJM 2003; 96(6):427–434

44 Yacoub S, Lang HJ, Shebbe M, et al.: Cardiac function and hemodynamics in Kenyan children with severe malaria. Crit Care Med 2010; 38(3):940–945

45 Kotlyar S, Olupot-Olupot P, Nteziyaremye J, et al.: Assessment of myocardial function and injury by echocardiography and cardiac biomarkers in African children with severe plasmodium falciparum malaria. Pediatr Crit Care Med 2018; 19(3):179–185

46 English M, Muamb B, Mithwani S, et al.: Lactic acidosis and oxygen debt in African children with severe anaemia. QJM 1997; 90(9):563–569

47 Kiguli S, Maitland K, George EC, et al.: Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness. BMC Med 2015; 13(1):21

48 Opoka RO, Ssemata AS, Oyang W, et al.: High rate of inappropriate blood transfusions in the management of children with severe anaemia in Ugandan hospitals. BMC Health Serv Res 2018; 18(1):566

49 World Health Organization. Utilization and supply of human blood and blood products. In: Official Records of the World Health Organization No. 226 Twenty-Eighth World Health Assembly, Geneva, Switzerland, 13–30 May 1975, Resolution 28.72, Vol. 1, 40p, 1975

50 Walker RH: Mathematical calculations in transfusion medicine. Clin Lab Med 1996; 16(4):895–906

51 Esan MO, Phiri KS, Molyneux EM, et al.: High transfusion failure rates in Malawian children with severe anaemia following a standard blood transfusion regimen. Br J Haematol 2011; 154(6):783–785

52 Cheema B, Molyneux EM, Emmanuel JC, et al.: Development and evaluation of a new paediatric blood transfusion protocol for Africa. Transfus Med 2010; 20(3):140–151

53 Maitland K, Kiguli S, Opoka RO, et al.: Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011; 364(26):2483–2495

54 Bojang KA, Van Hensbroek MB, Palmer A, et al.: Predictors of mortality in Gambian children with severe malaria anaemia. Ann Trop Paediatr 1997; 17(4):355–359

55 Ernest SK, Anunobi NE, Adeniyi A: Correlates of emergency response interval and mortality from severe anaemia in childhood. West Afr J Med 2002; 21(3):177–179

56 Akech SO, Hassall O, Pamba A, et al.: Survival and haematological recovery of children with severe malaria transfused in accordance to WHO guidelines in Kilifi, Kenya. Malar J 2008; 7:256

57 Mpoya A, Kiguli S, Olupot-Olupot P, et al.: Transfusion and Treatment of severe anaemia in African children (TRACT): a study protocol for a randomised controlled trial. Trials 2015; 16(1):593

58 Olupot-Olupot P, Engoru C, Thompson J, et al.: Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anaemia. BMC Med 2014; 12(1):67