**Title:** Detection of Adverse Events of Transfusion in a Teaching Hospital in Ghana.

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**Running head:** Adverse events of Transfusion in Ghana

**Abstract**

**Background and objectives:** Monitoring the whole chain of events from the blood donors to recipients, documenting any undesirable or untoward effects and introducing measures to prevent their recurrence if possible, are components of haemovigilance systems. Only few sub-Saharan African countries have haemovigilance systems and there **are** very little data on adverse events of transfusion. Adverse events monitoring is an integral part of a haemovigilance system. Our study aimed to establish the incidence and types of adverse events of transfusions in Ghana and to identify interventions to improve effectiveness.

**Materials and method:** This prospective observational 1-year study enrolled 372 recipients of 432 transfusions in a Ghanaian teaching hospital. Vital signs were monitored at 15 and 30 minutes, and 60-minute intervals during the transfusion, then 8 hourly until 24 hours post-transfusion. Three investigators independently classified any new signs and symptoms according to Serious Hazards of Transfusion definitions.

**Results:** **The** adverse events incidence was 21.3% (92/432), predominantly mild acute transfusion reactions (84%). Twenty transfusions (4.6%) were stopped before completion, 60% of them for mild febrile reactions, which could have been managed with transfusion in-situ

**Conclusion:** This prospective study indicates a high incidence of adverse events of transfusion in Kumasi Ghana. The significant numbers of discontinued transfusions, suggest that guidelines on how to manage transfusion reactions would help preserve scarce blood stocks. Gradual implementation of a haemovigilance system, starting with monitoring adverse transfusion events is a pragmatic approach in resource-limited settings.

**Keywords:** Haemovigilance, Adverse events,Blood transfusion, transfusion reactions, Haemoglobin, Allergy, Anaemia

**Introduction**

Blood transfusions are indispensable in sub-Saharan Africa as they play a key role in the correction of anaemia and the prevention of deaths especially in pregnant women and children. Blood shortages are unfortunately a frequent occurrence in Africa with devastating effects ([Lund *et al*. 2013](#_ENREF_8)). Severe anaemia results in one million deaths each year in children less than 5 years old ([Murphy & Breman, 2001](#_ENREF_12)) and 26% of maternal haemorrhage deaths in hospital are due to lack of blood ([Bates *et al*. 2008](#_ENREF_3)).

Haemovigilance is a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow up of its recipients. The purpose of a haemovigilance system is to increase the safety, efficacy and efficiency of blood transfusion by collecting and assessing information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence ([Faber, 2004](#_ENREF_6)).

Haemovigilance has been an effective tool for improving transfusion practice since its emergence in the 1990s ([de Vries *et al.* 2011](#_ENREF_5)). Findings from the UK haemovigilance system, Serious Hazards of Transfusion (SHOT) programme, triggered changes in transfusion practice to reduce complications such as bacterial infections and transfusion-related acute lung injury. The SHOT evidence of wrong transfusions and other mistakes resulted in several national initiatives to improve training and safety ([Bolton-Maggs & Cohen, 2013](#_ENREF_4)).

Subsequently many developed countries such as the US and Canada, and in the European Union, have incorporated haemovigilance programs into legislation. However, almost all sub-Saharan African countries do not have an effective haemovigilance system ([Tagny *et al.* 2008](#_ENREF_15)). This may be due largely to unavailability of resources and appropriate structures to support such systems. Financial support to maintain such systems when established can also be a challenge. South Africa is one of the few countries in Africa with an on-going haemovigilance programme, ([Faber. 2004](#_ENREF_6)) and recently Namibia has also established a haemovigilance programme ([Basavaraju *et al.* 2013](#_ENREF_2)).

Reporting of adverse events of transfusion is a component within a haemovigilance system. An adverse event of transfusion occurs when a person receiving blood or blood component experiences an undesirable and unintended reaction before, during or after the transfusion which may be related to the administration of the blood or component ([Garozzo *et al*. 2010](#_ENREF_7)). Besides seeking to recruit donors to increase blood supply, judicious use of available blood and putting in place measures to reduce wastage, such as avoiding unnecessary termination of transfusions, or preventing adverse events of transfusion, will ultimately make more effective use of the scarce blood resources.

In Africa, there are generally limited data on adverse events of transfusion and haemovigilance. Compared to more wealthy countries, there are only a few studies from Africa that have investigated adverse events of transfusion and the reported incidence of these events has been varied. In a prospective review of patient records in a Cameroonian hospital done in 2001, more than 50% of transfusions were associated with unfavourable outcomes. These reactions were predominantly febrile or urticarial reactions ([Mbanya *et al.* 2001](#_ENREF_10)). A study in 2013 from Zimbabwe determined the incidence of transfusion reactions to be 0.46 per 1000 blood components ([Mafirakureva *et al*. 2014](#_ENREF_9)) and a recent study in Namibia demonstrated significant under-reporting of transfusion reactions ([Meza *et al*. 2014](#_ENREF_11)).

This aim of our study was to establish the incidence and types of adverse events of transfusions in Kumasi, Ghana in order to identify events for which interventions can be quickly put in place to reduce adverse events and make blood transfusions safer. In addition we aimed to identify and prevent inappropriate stoppages of transfusion so that our scarce blood resource can be used more effectively in the hospital.

**Methods**

**Study site and participants:** This study was conducted from January to December 2010 at the Komfo Anokye Teaching Hospital (KATH) in Kumasi Ghana. KATH is a 1200 bed hospital with approximately 17,000 transfusions annually, 80% as whole blood. Seventy percent of the blood is sourced from voluntary donors. Donated blood is neither irradiated or leukoreduced. It is collected in bags with anticoagulant Citrate Phosphate Dextrose Adenine and stored for up to 35 days after which if not used, the blood unit is disposed off.

Hospitalised pregnant women, children, and adults with malignancies, chronic liver and kidney diseases were eligible for the study if they were to be transfused with whole blood or packed red cells. These patients were selected because they comprised the most transfused groups in the hospital and are the most likely to need recurrent transfusions because of their chronic medical conditions. Patients with altered consciousness or who received their transfusion in the operating theatre were excluded from the study because members of our study team could not monitor them. Eligible patients were initially identified at the blood bank when a request for blood was received. Members of the study team interviewed patients and reviewed their clinical records to ensure that patients fulfilled the eligibility study criteria (i.e. belonged to one of the groups listed above, were conscious and not in the operating theatre). Informed consent was subsequently obtained from the study participants prior to the start of their blood transfusion.

**Study design and procedures:** This was a prospective observational study during which patients receiving blood were monitored for the entire duration of the transfusion and for 24 hours after. Temperature, pulse, respirations and blood pressure of patients were recorded immediately they were enrolled into the study. This was about half an hour before they received their blood transfusion. Though recommended, rigorous monitoring of transfusions is not routinely done in many hospitals in Africa including in KATH. To obtain data for this study, study personnel stayed close by patients through the entire transfusion and recorded vital signs at 15 minutes, 30 minutes and hourly until the transfusion was completed. Patients were asked about any new symptoms they experienced during the period of blood transfusion. The monitoring of vital signs and new symptoms continued 8 hourly up to 24 hours post transfusion. Haemoglobin measurements were performed on patients’ samples prior to transfusion and on days 1, 3 and 7 post transfusions. Study personnel did not interfere with the clinical management of the patient or the transfusion. Patients who were discharged before post transfusion evaluation could be done were given follow up appointments with the study physicians.

To investigate and ascertain the cause of any adverse event, the offending blood bag was sent to the blood bank. An immediate post transfusion blood sample from a vein on the non-transfusion arm was also taken. **A** r**epeat blood grouping, repeat compatibility testing of patient’s serum with the cells of the donor and a direct antiglobulin test were immediately done”**. In cases where there was a temperature rise of greater than 2 degrees Celsius, blood culture was performed on both the transfused blood and the patient’s samples. To obtain blood from the patient for culture, a venepuncture site on the opposite arm was cleaned with alcohol and 10 mls of blood taken aseptically. A 10 ml sample from the transfusion bag was also taken aseptically after cleaning the blood bag lines with alcohol.

Based on the recorded signs and symptoms and investigations carried out, the adverse events were categorised according to the revised SHOT classification (Table 1**) (Serious Hazards of Transfusion, 2011)**. Briefly the SHOT categories are a standardised classification system for adverse events of transfusions. The classification is based on whether the event is acute (within 24 hours of transfusion) or delayed (more than 24hours), or whether it is haemolytic or non haemolytic. The severity of transfusion reactions was graded into mild, moderate or severe reactions. A determination of whether an event was attributable to the blood transfusion (imputability) was performed according to the revised SHOT classification and classified into Unlikely, Possible, Likely/Probable and Certain **(Serious Hazards of Transfusion, 2011)**. To ensure an objective assessment of the classification, three authors (AOO, SOO and IB) independently analysed and categorised each recorded adverse event. It was agreed prior to the independent categorization that a majority decision was needed to enable a final decision to be taken (i.e. at least two of the three authors must agree on each categorisation). Any discrepancies were resolved by discussion between the authors.

**Results**

The total number of transfusions monitored for this study was 432 and the median age of transfusion recipients (N=372) was 36 years, ranging from one to 86 years. Whole blood made up 97.7% (422/432) of all the transfused blood units. The mean duration (± SD) of individual transfusions during the study was 3.0 ± 1.2 hours.

The most common abnormal findings among the vital signs measured at pre-transfusion were tachycardia (21.1%), fever (12.5%) and tachypnea (12.0%). The frequency of all the abnormal vital signs progressively decreased to between 0 and 2.5% by the third hour of transfusion (Figure 1). The mean pre-transfusion haemoglobin was 6.6g/dl and it improved gradually to 7.9g/dl by day 7.

The incidence of adverse events was 21.3% (92/432). Acute transfusion reactions accounted for the majority of these events (88/92), the most common of which were acute allergic reactions, accounting for 49% of all reactions (Table 2). The least common reactions were transfusion-associated dyspnoea (TAD) and transfusion associated circulatory overload (TACO) making up 1.1% and 2.3% respectively of the total reactions. **The ‘unclassified’ category, making up 12.5% of acute reactions, was a combination of symptoms such as anxiety, difficulty in breathing, headaches, palpitations and restlessness.** These symptoms have not been classified within the SHOT haemovigilance system. Thepresence of blood clots in the donated blood made up the rest of the adverse events (4/432).

Of the 88 acute transfusion reactions, the majority (87.5%) of them were mild, 11.4% were moderate and only 1.1% was severe. The only transfusion reaction classified as severe was a death that occurred in a very ill patient with cervical cancer about 1 hour into the transfusion. However, the death was not attributed directly to the blood transfusion. For imputability of the event to the blood transfusion, 79.4% (73/88) of the reactions were classified as possibly due to the transfusion and 14 (15.2%) was seen as likely/probably due to the transfusion received by the patient. Only one event (1.1%) was seen as unlikely to be due to the blood transfusion received.

Twenty of the 432 (4.6%) transfusions monitored were stopped before the transfusion was completed (Table 3). Four transfusions were stopped because blood clots were found in the blood bags thus hindering flow. The most frequent (43.8%) reason for stopping a blood transfusion was acute febrile transfusion reaction (AFTR) followed by acute allergic transfusion reactions (Table 3). There were no bacterial isolates from the blood culture of either the blood transfused or the blood of all the seven transfusion recipients who developed AFTR.

**Discussion**

This study shows that acute transfusion reactions are occurring at a high rate of 213 reactions per 1000 transfusions in KATH. **It is in contrast with 0.046% found in Zimbabwe in 2013 (**[**Mafirakureva *et al*. 2014**](#_ENREF_9)**). The study from Zimbabwe was a retrospective study that relied on passive reporting whereas the present study from Ghana used a prospective and active follow-up design to capture adverse events**. In passive systems, symptoms such as itching could be considered as unimportant by the patient who will not volunteer that information unless specifically asked. The higher incidence of adverse events in our study was likely to be because the study was conducted in a rigorous manner and included detailed questioning of recipients about wide range of named symptoms immediately after receiving the transfusion. The immediate questioning prevented recall bias and the direct questioning provided a greater chance of eliciting symptoms that may not have been volunteered to health personnel by recipients and would not have been captured in a retrospective study. Although under study conditions, intensive and regular monitoring could be done, this may be a challenge for routine hospital care. This is because hospitals usually lack adequate staff to provide the required healthcare needs to patients.

Two other studies from Africa are known to have also reported on adverse events of transfusion. A prospective study from Cameroon, conducted more than a decade ago, established an even higher incidence of 59% unfavourable outcomes of transfusion. That study was a direct patient observation and a review of patient records spanning a five-year period and involving 26,973 transfusions ([Mbanya *et al.* 2001](#_ENREF_10)). A more recent study reviewing 785 transfusions from 6 hospitals in Namibia estimated a rate of 11.5 acute transfusion reactions per 1000 transfusions. The estimated rate was however far higher than the 0.2% rate that was been reported for the Namibia haemovigilance system within the same period. It is well recognised that under-reporting of transfusion events is a common problem in passive reporting systems.([Meza *et al.* 2014](#_ENREF_11))

Tachycardia and fever were common findings at pre-transfusion and malaria may be the major contributory factor. This is because malaria is among the commonest cause of anaemia in Kumasi and generally in subSaharan Africa. Malaria also usually presents with fever. A combination of fever and anaemia contributes to tachycardia.

Allergic and febrile reactions were the most common types of acute transfusion reactions seen in our study. This is similar to other studies from developing countries ([Mafirakureva *et al*. 2014](#_ENREF_9); [Mbanya *et al.* 2001](#_ENREF_10); [Meza *et al.* 2014](#_ENREF_11)). Our study was observational and did not focus on management of these acute transfusion reactions. However, as seen in figure 1, it is likely that the normalisation of abnormal signs was due to the direct response of health personnel to the abnormal recordings. For example, the use of tepid sponging and antipyretics accounts for the reduction of fever. Regular monitoring during transfusion therefore appears to be an added benefit to patients since they are likely to receive appropriate treatment early. Hospitals with inadequate staff who seek to implement the monitoring of adverse events of transfusion as part of a haemovigilance system should adapt a time schedule that is compatible with their tights schedules.

The signs and symptoms associated with transfusion reactions are very important considerations for their management. Guidelines from the British Committee for Standards in Haematology on the investigation and management of acute transfusion reactions recommend that the initial treatment should be guided by the signs and symptoms and not on the later classification which is done retrospectively ([Tinegate *et al.* 2012](#_ENREF_16)).

A major aspect of our study was to identify adverse events which are preventable by careful monitoring of transfusion (e.g. transfusion associated circulatory overload) or those that are caused by error (e.g. incorrect blood component transfused) ([Bolton-Maggs & Cohen, 2013](#_ENREF_4)). There were a few reactions such as palpitations, restlessness and difficulty in breathing, which were not severe and which did not fit strictly into the SHOT classification system ([SHOT, 2011](#_ENREF_14)). The International Haemovigilance Network has proposed standard definitions for non-infectious adverse transfusion reactions and more effort is encouraged to harmonise all definitions to make comparisons easier. Severe transfusion reactions were uncommon in this study. No ABO incompatibility was observed. One patient died while receiving a transfusion but the death was adjudged to be related to the patient’s advanced cervical cancer rather than the transfusion.

Uncompleted transfusions are not well documented in Africa, making it difficult to compare findings from this study with any other study. Twenty (4.6%) of the 432 transfusions we monitored were stopped prematurely. There were no published guidelines in Ghana for stopping transfusions, resulting in a lack of consistency in decisions about whether to stop the transfusion or not. Transfusion reactions such as the mild febrile and allergic reactions were in some cases managed with antipyretic and antihistamines but in other cases, the transfusion was stopped. All the cases of acute allergic and febrile transfusion reactions that triggered stopping the transfusion were mild reactions and could have been continued after an initial assessment and management with antipyretics or antihistamines. Chills are another transfusion reaction which could be managed by warm blankets rather than stopping the transfusion.

Some countries and regions have well documented guidelines for the investigation and management of acute transfusion reactions. In the UK for example, a guideline has been published by British Committee for Standards in Haematology and is available for use ([Tinegate *et al.* 2012](#_ENREF_16)). Clear guidelines on when to stop transfusion are needed in each country to prevent the unnecessary wastage of blood. Using the UK guidelines, we estimate that about 60% of transfusions that were discontinued should not have been stopped.

The presence of blood clots in blood bags is not a frequently reported problem in blood transfusion so the rate of 10 cases per 1000 transfusions is a cause for concern. It may be an indication of poor collection technique, where the donated blood may not have been well mixed with the anticoagulant. This can occur either due to small volumes of the anticoagulant or collecting more than the recommended volume of blood. Blood clots in transfusion bags is therefore avoidable by ensuring good mixing during blood donation sessions and by careful inspection of bags at the time of issuing blood for transfusion. A recent case report shows that despite standardized checks at all stages in the release of blood products for transfusion, clots in the bag may be missed initially and only detected when transfusion has started ([Bang *et al* 2013](#_ENREF_1)). **In the facility where this study was conducted, the blood bank has re-trained their staff to ensure proper collection and mixing of recommended volumes in the blood bag.**

**A limitation of this study was its inability to evaluate delayed transfusion reactions. In the study setting, investigations for delayed reactions could be extensive especially as there are other frequent causes of delayed haemolysis such as sickle cell disease or G6PD or worsening malaria. Acute adverse events of transfusion were therefore the focus of the study.**

This study has shown that the incidence of adverse events of transfusion in Ghana is high. Since this study was completed, the Transfusion Medicine Unit of the hospital has conducted several training workshops for clinicians on a regular basis, to emphasise the importance of monitoring for adverse events and how to manage them. The National Blood Service also holds regular workshops as part of Continuous Professional Development for practitioners. Although haemovigilance system can be relatively expensive to establish in resource limited countries, a gradual implementation is a pragmatic and feasible approach (Nel, 2008). Monitoring of blood transfusions can be the first step and this requires availability of staff to monitor, document and report the events that occur. Such reports enable corrective measures to be taken to prevent the recurrence of these events. In resource-limited countries, guidelines about how to investigate and manage transfusion reactions are essential to minimise the number of unnecessary terminations of blood transfusions and to contribute to preserving scarce blood stocks.

**Authorship:**

A. Owusu-Ofori and I Bates designed the study. A Owusu-Ofori performed the research. A Owusu-Ofori, S. Owusu-Ofori and I Bates reviewed, analysed and interpreted the data. A Owusu-Ofori, S. Owusu-Ofori and I Bates contributed to the writing of the manuscript.

**Conflict of interest:**

None

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**Figure and Table legends**

Figure 1: Vital signs measurements during the period of transfusion

Table 1 : A summary of definitions adopted and used from the SHOT classification of adverse events of transfusion.

Table 2: Types of acute transfusion reactions observed.

Table 3: Events for which the blood transfusion was discontinued.