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The Use of Rapid Diagnostic Tests for Transfusion Infectious Screening in Africa: A Literature Review

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ABSTRACT

Infectious risk associated with blood transfusion remains a major public health challenge in Africa, where prevalence rates of the major transfusion-transmissible infections (ie, hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis) are among the highest in the world. Resource-limited blood services often operate with minimal predonation screening safeguards, prompting exclusive reliance on laboratory testing to mitigate infectious risk. Transfusion screening with rapid diagnostic tests (RDTs) has been adopted in areas that lack the capacity to support the routine use of more sophisticated technologies. However, uncertainty surrounding the performance of some RDTs in the field has spurred debate regarding their application to blood donation screening. Our review of the literature identified 17 studies that evaluated RDTs for the infectious screening of blood donors in Africa. The review highlights the variable performance of available RDTs and the importance of their use in a quality-assured manner. Deficiencies in performance observed with some RDTs underscore the need to validate test kits prior to use under field conditions with locally acquired samples. Suboptimal sensitivities of some available tests, specifically hepatitis B virus rapid assays, question their suitability in single-test algorithms, particularly in high-prevalence regions. Although RDTs have limitations, many of which can be addressed through improved training and quality systems, they are frequently the only viable option for infectious screening in resource-poor African countries. Therefore, additional studies and specific guidelines regarding the use of RDTs in the context of blood safety are needed.

Contents

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Blood transfusion is a critical therapy for an array of clinical indications. In contrast to high-resource settings, where the risk of transfusion-transmitted infections (TTIs) has been virtually eliminated, transfusion-associated risk remains a major public health challenge in resource-limited countries [1,2]. Transfusion-transmitted infections are of particular concern in Africa, where the prevalence of the major TTIs in blood donors (ie, hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], and syphilis) are among the highest in the world and the need for blood is substantial [3,4]. Many African blood services operate in the absence of safeguards, such as recruitment of low-risk donors, prompting reliance on laboratory testing as the sole means to mitigate the risk of TTIs [5].

Although most African countries report infectious screening of blood, existing testing may be incomplete or fail to meet the World Health Organization (WHO)–recommended standards [5,6]. Laboratory screening is complicated by deficiencies in infrastructure, transportation, training, financial support, and quality systems. Highly sensitive, yet expensive and technically demanding laboratory screening methods (eg, nucleic acid testing [NAT]) are not routinely available in resource-constrained settings [7]. Even automated serologic testing platforms require formal training, reagent management, and rigorous quality systems to ensure output reliability.

Given the barriers to automated testing, many resource-limited countries are resorting to rapid diagnostic tests (RDTs) for TTI screening. Although quality RDTs hold promise for increasing the safety of the region's blood supply, uncertainty surrounding the performance of some RDTs in the field has spurred debate regarding their application to TTI screening [8–12]. An improved understanding surrounding the conditions of their use and reasons underlying deficient RDT performance is needed. Therefore, we sought to review the existing literature on performance and operational characteristics of RDTs for transfusion screening in Africa to inform the reader with recommendations for their use.

Methods

To identify relevant literature, we searched PubMed and Medline databases using combinations of the following search terms: “rapid diagnostic test,” “rapid test,” “RDT,” “dipstick,” “transfusion,” “blood safety,” “transfusion-transmitted infections,” “TTI,” “human immunodeficiency virus,” “HIV,” “hepatitis B,” “hepatitis C,” “HBV,” “HCV,” “syphilis,” “malaria,” “bacterial contamination,” and “(sub-Saharan) Africa.” The search was confined to English-language publications. We extended the search to the Google Scholar database and included relevant data from WHO and national blood transfusion program reports. Additional literature was identified through manual searches of reference lists of identified studies and contacting researchers in the field.

We included studies evaluating the performance of RDTs for the infectious screening of blood donors or donated blood in Africa. Studies of RDTs in alternative contexts and settings were excluded (eg, voluntary counseling and testing [VCT]). After scanning the titles and abstracts of identified records, we obtained full texts of relevant articles. A total of 390 relevant studies were identified using the search terms; 356 of these were rejected because they did not fulfill the selection criteria. Six additional articles were identified through contacts and reference list searches. After a review of the full publications, 23 studies were rejected and 17 articles were included for review.

Transfusion-Transmitted Infections

The WHO recommends mandatory screening of blood donations for the 4 major TTIs and, depending on local epidemiological evidence, all additional agents that may compromise blood safety [4,6]. However, per a blood safety report on the WHO African Region in 2010, only 95.3%, 88.9%, 90.1%, and 79.9% of blood donations were screened in a quality assured manner for HIV, HBV, HCV, and syphilis, respectively [5]. Blood is not routinely screened for other endemic pathogens (ie, bacteria, protozoa, and viruses) that may also pose infectious risk. Of note, data on blood donor seroprevalence and TTIs in Africa are limited due to incomplete surveillance and hemovigilance.

Fundamental differences between the general and blood donor populations necessitate a higher performance standard for blood donor screening tests. Specifically, blood donors are typically lower risk for TTIs than the general population, given the need to pass a risk factor questionnaire, clinical assessment, and feeling sufficiently healthy to donate blood [13–15]. However, donors in the early stages of a viral infection (eg, HIV) may have high viral loads yet lack detectable serologic markers and remain asymptomatic. In the context of bacterial or parasitic infection, the absence of symptoms may correlate with lower levels of bacteremia or parasitemia (eg, malaria) than might be encountered if an individual was symptomatic [16]. Low levels of pathogen and low antibody titers affect laboratory screening, thus requiring optimal test performance with high sensitivity to capture infected donors. Given the direct impact on blood safety, the WHO recommends a minimum sensitivity and specificity of 99.5% for assays used for transfusion screening (Table 1) [6].

HIV

Africa is disproportionately affected by the HIV epidemic. Two-thirds of all people living with HIV and 70% of all newly reported HIV infections occurring in 2012 were concentrated in sub-Saharan Africa [17]. The UNAIDS 2013 Global report estimated the HIV prevalence in the general adult population in sub-Saharan Africa to be 4.7%, ranging across the continent from 0.2% in Cape Verde to 26.5% in Swaziland [17]. Reports of HIV prevalence in blood donor populations range geographically from less than 0.1% in South Africa up to 15.4% in Mozambique [18–20].

Although sexual contact is the primary mode of transmission, HIV is readily transmitted via transfusion of an infected blood product. This prompted the US President's Emergency Plan for AIDS Relief (PEPFAR) to allocate resources to blood services as part of the program's broader HIV/AIDS initiative. PEPFAR has provided technical and financial support to national blood services in 12 sub-Saharan Africa since 2004 and 20 sub-Saharan African countries since 2010, which has contributed to a decrease in the number of HIV-reactive units and overall improvement in those blood services in PEPFAR-supported countries [21]. However, transfusions still contribute to new HIV infections in Africa, underscoring the need for improved screening on the continent [22,23].

Hepatitis B Virus

The prevalence of HBV in the general population ranges from moderately endemic in North Africa to highly endemic in regions of sub-Saharan Africa, where at least 8% of the population are chronic carriers

Table 1
Approaches to risk mitigation and screening for transfusion-transmissible agents

Method	Description	Advantages	Limitations
Immunoassay: EIA, CLIA, Ag/Ab combo	Immobilized antibodies and/or antigens in a solid-phase form immune complexes with target analytes present in a sample. Immune complexes are revealed through either color generation (EIA) or light emitted by a chemical reaction (CLIA).	· Amenable to automation and high through-put testing · Sensitivities and specificities approximating 100%[a]	· Technically demanding · Requires appropriate equipment and maintenance · Most automated platforms were validated in low-prevalence settings · Limited application to low through-put testing · Requires consistent supply of reagents and cold-chain management
NAT	In vitro amplification of a pathogen-specific segment of viral DNA or RNA. NAT can be done in minipools or on individual donations.	· Shortens the window period of transfusion-transmissible viruses · Amplification enables detection of samples with low viral levels · Enables the detection of some serologically negative infections · Amenable to multiplex screening (eg, HBV, HCV, and HIV simultaneously)	· Technically demanding · Requires high-level laboratory infrastructure · Cost
PI	PI technologies (ie, mechanical disruption, solvent-detergent methods, and photochemical treatment) serve to treat the blood component globally by disrupting replication and production of pathogens	· Addresses known TTIs not routinely subject to screening · Potential mitigation against newly emerging, reemerging, and unidentified pathogens	· Currently only available for plasma and platelets · Cost
RDTs	Single and easy-to-use test kits available in a variety of methods (ie, particle agglutination, solid phase tests, immunofiltration, and immunochromatography)	· Cheap (US$0.40-US$4.00 per test) · Technically undemanding · Rapid (turnaround time <20 min) · Most test kits contain all required reagents · No requirement for an electrical source or major equipment · Straightforward to operate and interpret	· Lack of permanent records and limited traceability · Limited application to medium to high through-put testing · Manual operation increases potential error · Effectiveness dependent on test quality and conditions of use

Abbreviation: CLIA, chemiluminescent immunoassay.
[a] With serologically positive and negative samples in a quality environment.

[24,25]. Between 15% and 40% of HBV infected individuals will eventually develop clinically significant sequelae such as cirrhosis, liver failure, and/or hepatocellular carcinoma [26]. The prevalence of the hepatitis B surface antigen (HBsAg) in blood donors in Africa has been reported to be from 0.07% to more than 10%, with most countries exceeding 3% [19,20]. Although HBsAg prevalence remains high, there has been progress in coverage as evidenced by the number of countries screening: between 2000 and 2011, the number of countries that reported screening most (95%-100%) of donations for HBsAg increased from 29 to 38 [27].

Unfortunately, the estimated risk of an HBV-infected blood donation entering the blood supply in most of sub-Saharan Africa remains relatively high [28]. The results of a mathematical model estimated the probability of acquiring HBV from contaminated blood in sub-Saharan Africa to be 4.3 infections per 1000 units compared with 1 and 2.5 for HIV and HCV, respectively [29]. In contrast, the residual risk of HBV estimated to be 1 in 981 000 in Australia [30]. Recent attention has been brought to occult HBV infections, defined as the presence of very low levels of HBV DNA in the liver and serum in the absence of detectable HBsAg [31,32]. Occult HBV differs from window period HBV in that antibodies to hepatitis B core antigen (HBc) are detectable in occult infections. Occult HBV may go undetected by even the most sensitive HBsAg serologic and molecular tests and has been shown to be transmissible through blood transfusion [33].

Hepatitis C Virus

Africa has the highest burden of HCV in the world with an estimated 32 million infected [34]. The estimated overall HCV prevalence in the general population in Africa falls between 3.0% and 5.3%, ranging from less than 1% in the countries of South and East Africa (Zambia, Kenya, Malawi, and South Africa) to a mean prevalence of 6% in the Central African region [35,36]. Egypt has the world's highest HCV prevalence in the general population (17.5%), which has been attributed to lack of sterile technique during mass campaigns of parenteral antischistosomal therapy during the 1920 to 1980s [37]. Like HBV, there has been an increase in the number of sub-Saharan African countries that report testing for HCV antibodies coupled with a decrease in the number of donations that screen positive for HCV [27].

Syphilis

Syphilis, caused by *Treponema pallidum*, remains a serious public health problem in Africa. This is in distinct contrast to developed countries, where the merits of continued screening have been questioned in view of a diminished reservoir of syphilis and poor survival of spirochetes after refrigeration prior to transfusion [38,39]. In contrast, syphilis prevalence is comparatively high in African blood donors, reaching a prevalence of more than 9% in some populations [40,41]. The transfusion of nonrefrigerated fresh, whole blood is common in remote settings, further supporting the need for continued syphilis screening in Africa.

Additional Transfusion-Transmissible Agents

Transfusion screening is focused on the major transfusion-transmitted viruses that have been prioritized by the WHO. However, blood still goes unscreened for a number of endemic and emerging transfusion-transmissible pathogens. For example, although an estimated 90% of all malaria infections occur in sub-Saharan Africa, only a minority of countries (eg, Malawi, Sao Tome, Principe, and Sierra Leone) had reported screening donors or donated blood for malaria as of 2010 [5,42]. Although vector-borne transmission (mosquitoes) is the more common mode of transmission, *Plasmodium* spp. are transfusion transmissible and can be fatal if transfused to recipients who lack "semi-immunity" acquired from repeated exposure [43]. According to a recent literature review, the median prevalence of malaria infection in blood donors is 10.2% (range, 0.7% Kenya and 55% in Nigeria) [44].

However, screening for malaria is complicated, particularly in endemic regions. High background prevalence in many African countries precludes an easy determination of transfusion-transmitted malaria vs

natural acquisition. Furthermore, rejecting blood donors with prior exposure or low-grade parasitemia would further deplete an already inadequate blood supply. Antimalaria prophylaxis of transfusion recipients has been proposed as an alternative to screening; however, widespread chloroquine resistance and the high relative cost of artemesinin-based combination therapy render this a cost-infective option [45,46].

Human T-cell lymphotropic viruses 1/2 (HTLV 1/2) remain a transfusion risk in many African countries. Currently, only Gabon is screening for HTLV-1 in Africa [5]. Worldwide, HTLV is geographically clustered in highly endemic areas, many of which are located in Africa [47]. Human T-cell lymphotropic virus 1 is the causative agent of adult T-cell leukemia/lymphoma and tropical spastic paraparesis/HTLV-1 myelopathy; it has also been linked to other inflammatory disorders. Human T-cell lymphotropic virus 2 is also associated with tropical spastic paraparesis/HTLV-1 myelopathy but not adult T-cell leukemia/lymphoma. Transmission of HTLV can occur via mother-to-child, via sexual transmission, or through contaminated blood products. Estimates of the seroprevalence of HTLV-1 in blood donors in Africa range from 0.0 to 5%, depending on the region [41,47,48]. A recent study conducted in South Africa demonstrated a seroprevalence of 0.062% for HTLV-1 in the donor population; the South African National Blood Service is currently considering whether to implement HTLV screening [49].

Bacterial contamination is the most frequent, albeit neglected, risk to blood safety. In the United States, approximately 1 of 2000 to 3000 platelet units and 1 in 30 000 red blood cell units are estimated to be contaminated with bacteria [50,51]. By comparison, the frequency of bacterial contamination of whole blood in Africa has been estimated to be 2500 times greater than that in industrialized countries [51]. Contamination of blood units with bacteria can occur consequent to bacteremia in the donor (eg, *Pseudomonas aeruginosa*, *Escherichia coli*, etc), or, more commonly, during collection, processing, or storage (eg, *Staphylococcus aureus*, *Staphylococcus epidermidis*, etc) [51,52]. Hot and humid conditions, poor cold chain management, allied with inattention or inability to preserve sterile technique increases the risk of contamination. Approaches to bacterial risk mitigation in platelets that have been adopted in high-middle income countries (eg, the United States) include the use of diversion pouches with testing and culture of the first aliquots of blood collected [53]. In contrast, although there is a growing awareness of bacterial risk in Africa, similar initiatives have yet to be widely undertaken [54].

Approaches to Risk Mitigation and Transfusion Screening

Donor Selection

Donor selection is the first line of defense against TTIs. For example, effective donor selection in South Africa has reduced the prevalence of HIV in blood donors by 100-fold compared with the general population [19]. The WHO advocates for the systematic recruitment and collection from low-risk donors and recommends, specifically, that 80% to 100% of donations be sourced from voluntary nonremunerated blood donors (VNRBDs), given lower reported rates of TTIs [14,55–57]. Despite much improvement in donor recruitment and the adoption of innovative and low-cost donor mobilization strategies (eg, Club 25, partnerships, and outreach through local FM radio stations), many African countries have yet to achieve the WHO-recommended target [58,59]. This is partly ascribed to the high cost of recruitment of VNRBD through a centralized system, which can be 2 to 3 times more expensive than replacement donation, often requiring the support of a national transfusion infrastructure to be sustainable [60].

Hospital-based replacement donors, typically comprising friends or family members of the recipient and at times paid donors, are used to amend the deficit [55,60]. Replacement donors are considered at higher risk for TTIs and make up more than 70% of the donor pool in many African countries [5,61]. Findings among blood donors in Africa also suggest that promoting repeat donations, from both VNRBD and replacement donors, can improve blood safety [62,63]. Prevalence of viral markers in repeat blood donors both in Africa and the rest of the world has been shown to be significantly lower than that in first-time donors [64]. However, most donations in some sub-Saharan African countries are collected from first-time donors, once again, underscoring the importance of laboratory testing.

Immunoassays (Enzyme, Chemiluminescent, and Antigen/Antibody Combination)

Enzyme and chemiluminescent immunoassays are based on the use of immobilized antibodies and/or antigens in a solid phase, which form immune complexes with target analytes present in a sample. Both methods reveal immune complexes through either color generation or light emitted by a chemical reaction. Immunoassays are amenable to high through-put testing and demonstrate sensitivities and specificities approximating 100% with serologic-positive and serologic-negative samples, respectively. Therefore, the automated serologic assay is the most commonly used method for transfusion screening in high-resource settings. Antigen/Antibody (Ag/Ab) combination enzyme immune assays, which detect both antigens and antibodies, have improved screening and diagnostic testing, specifically for the detection of HIV and HCV by their ability to identify infected donors in the preseroconversion window period [65]. Therefore, Ag/Ab combination assays may offer a cheaper alternative to NAT to detect serologically negative viral infections [66,67].

In Africa, where 70% of blood banks process fewer than 10 000 units per year and often collect from donors in high-prevalence areas, the use of automated serologic tests may not be optimal [11,68]. Automated serologic testing requires appropriate equipment (with concomitant maintenance and validation), trained personnel, and a reliable electrical supply. In addition, commonly used automated serologic testing platforms were validated using large numbers of specimens in settings with low TTI prevalences [6]. The overhead cost per sample to maintain calibration and quality evaluations of reagent batches may become prohibitive without economies of scale.

Molecular Testing

Nucleic acid testing uses in vitro amplification of a pathogen-specific sequence of DNA or RNA for detection of pathogens. It has been revolutionary to blood screening given the ability to identify infectious donors in the preseroconversion window period, which would otherwise go undetected by conventional serologic tests. Risk estimates suggest that individual donation NAT has reduced the time from infection to detection for HIV-1 and HCV from 22 and 70 days using antibody assays to 5.6 and 4.9 days, respectively [69]. Nucleic acid technology has been widely implemented in high- and middle-income countries but is not routinely performed in Africa, with the exception of South Africa, Namibia, and Egypt. South Africa (which also performed NAT testing for Namibia until March 2014) was the first country to initiate individual donation NAT screening in response to the high HIV burden in the general population (average prevalence 18% in adults aged 15-29 years) [7,17]. A total of 16 HIV, 20 HBV, and 1 HCV window-period "NAT-yield" (RNA/DNA positive, serologically negative) donations were detected in South Africa for 1 year of NAT screening, which would likely have resulted in TTIs [19]. Although NAT would confer benefits in other high-prevalence countries, lack of infrastructure and technical expertise, coupled with high cost, still precludes more widespread implementation. Furthermore, improved donor selection and education potentially represents a more cost-effective means to reduce transfusion risk [70].

Pathogen Inactivation

Unlike conventional testing, pathogen inactivation (PI) serves to inactivate pathogens present in the blood component prior to transfusion. Pathogen inactivation technologies use a variety of mechanisms (eg, mechanical disruption, solvent-detergent methods, or photochemical

treatment) to disrupt replication of pathogens (ie, enveloped and nonenveloped viruses, bacteria, and protozoa) rendering the blood product safe to the recipient [71]. One major advantage of PI is that the technology not only addresses risk from the major TTIs but also has the potential for mitigation against endemic TTIs that are not routinely subject to screening (eg, malaria, HTLV, bacteria, etc) as well as newly emerging, reemerging, and unidentified pathogens [72,73].

The safety and efficacy of PI has been well demonstrated in a number of European countries, but the current costs and technical complexity are still prohibitive for its use in resource-poor settings. Furthermore, PI is currently only available for plasma and platelets, whereas 87.4% of units transfused in Africa are whole blood or red cell concentrates [5]. Technologies for whole blood are underdevelopment and would be ideal for use in settings where conventional screening methods are not feasible [74].

Rapid Diagnostic Tests for Transfusion Screening

Rapid diagnostic tests offer a flexible and technically undemanding approach to diagnostics and blood screening. Most single-use RDT kits contain all the required reagents; importantly, they usually do not require electricity or a formal laboratory infrastructure. Compared with enzyme immunoassays (EIAs), RDTs are simple to operate and the results are easily interpreted if the manufacturer's directions are followed and the operator has been adequately trained. The turnaround time with RDTs is usually less than 20 minutes; in contrast, EIAs take from 30 minutes to 2 hours before results are available [68].

Compared with automated EIAs, RDTs are more affordable, particularly when the global costs (ie, training, equipment, reagents, maintenance, etc) are considered. The WHO established a centralized bulk procurement service in order to further reduce costs and facilitate access to prequalified diagnostics from approved suppliers [75]. The service provides improved access to selected HIV, HBV, HCV, and malaria serologic assays that meet stringent performance and feasibility criteria [76]. Rapid diagnostic tests that are purchased via the procurement service cost significantly less than those obtained from commercial vendors and range from approximately US$0.40 to US$4.00 per test [77–79].

Mode of Action

Commercially available RDTs are presented in a range of formats (eg, dipstick, strip, and cassette) and can be applied to a variety of specimens such as whole blood (finger stick or venipuncture), serum, plasma, or saliva. Test kits are based on 4 major types of methods: particle agglutination, solid phase tests, immunofiltration (flow-through), and immunochromatography (lateral flow) [68,80]. Particle agglutination tests are based on clumping or settling patterns of coated particles when in contact with a captured analyte. Flow-through devices are based on the principle of immunofiltration where antigens on the device bind antibodies that are present in the patient or donor sample; a positive result is indicated by color formation, as noted by a dot on a membrane. Similarly, solid phase tests, including dipstick assays, present a spot or dot when antigens fixed to a solid matrix bind with antibodies in a sample. The immunochromatographic lateral flow test was initially introduced as a point-of-care pregnancy test but has become a popular method in a variety of applications [81]. The mechanism of detection is as follows: a dye-labeled signal reagent, located either on a strip or a well, binds with a target analyte (if present), which is transported by capillary action over the test and control bands. The test band captures the immune complex and the accumulation of dye produces a visible line, the intensity of which is determined by the analyte concentration [81].

Rapid Diagnostic Tests for Transfusion Infectious Screening

In the clinical arena, rapid testing has been successfully used in remote clinics, as a surveillance mechanism of hard to reach populations, and in circumstances where results are required urgently (eg, rapid HIV testing of mothers during labor and delivery to prevent mother-to-child transmission). As one seminal example, rapid HIV tests have revolutionized VCT services: they have enabled large-scale testing by minimally trained workers, where rapid turnaround has facilitated early posttest counseling and access to treatment [82,83]. In the transfusion setting, RDTs have been adopted for donor infectious screening in countries and settings where the skill base, time, or resources do not support the use of EIAs or more sophisticated technologies [84,85].

Rapid Diagnostic Tests for HIV

The performance of the latest RDTs for HIV approximates that of automated EIAs (Table 2). Multiple studies evaluating rapid HIV tests for transfusion screening in Africa have reported sensitivities approximating 100%, supporting their use in a quality assured manner for transfusion screening [86–89]. However, 3 studies reported low sensitivities (60.5, 72.4, and 79.2, respectively) [8,66,90]. A cross-sectional assessment of test performance at 51 blood centers in 17 African countries found 5 HIV rapid tests to have an average sensitivity of 72.4% [8]. False negatives have been noted when testing specimens with low antibody titers, which may result in weak or unclear test reactions [8,87]. Specificities of HIV RDTs for the screening of donated blood in Africa range from 94.0% to 100.0% [67,87]. Low specificities have been ascribed to the misinterpretation of indistinct results (eg, weakly reactive bands) either due to technical error (ie, mistakes in labeling or sample misidentification) or due to potential immune cross-reactivity [86].

Rapid Diagnostic Tests for HBV

Reports of the performance of RDTs for HBV for screening donated blood vary considerably (Table 2). Sensitivities of RDTs that target HBsAg range from 14.3% to 98.6% [8,91,92]. Hepatitis B surface antigen is most commonly targeted by HBV RDTs, but assays that target non-HBsAg HBV biomarkers are also available. A study with donor samples in Egypt found non-HBsAg RDTs to be highly specific; however, the sensitivities of rapid anti-HBsAg, anti-HBc, and anti–hepatitis B “e” antigen (HBe) tests (64.2%, 85.5%, and 82.78%) were lower than those stated by the manufacturers [93]. The authors proposed that the low sensitivities of the rapid anti-HBc and HBe tests may have been related to deficient detection of selected genotypes or subtypes [93]. Studies evaluating RDTs for HBsAg blood screening in Africa have found specificities ranging from 95.1% to 100% (Table 2). Discrepancies between reported and observed sensitivities have been attributed to the inability of some HBsAg RDTs to detect low HBsAg concentrations [87,94]. An assessment of 10 HBsAg rapid tests found that samples that contained less than 1 ng/ml HBsAg tested negative with all rapid tests [8].

Rapid Diagnostic Tests for HCV

Studies conducted in Egypt and Mozambique reported sensitivities of anti-HCV rapid tests to be 97.0% and 100%, respectively, supporting their use as an alternative to EIAs [91,95]. However, 3 studies demonstrated low sensitivities for rapid anti-HCV assays, one as low as 47.0% [8]. False-negative results occurred frequently with samples containing low HCV Ab levels [8]. Authors suggested that weak antibody reactivity and use of RDTs in “real-world” conditions (actual rather than ideal) likely contributed to the observed suboptimal sensitivities of HCV rapid tests [96].

Rapid Diagnostic Tests for the Screening of Additional Transfusion-Transmissible Agents

Rapid diagnostic tests are also available for the screening of TTIs other than the major transfusion-transmissible viruses. Examples include RDTs for syphilis and malaria. Syphilis screening with RDTs is typically based on the detection of *T pallidum* antibodies [97]. Most syphilis RDTs are specific treponemal tests in dipstick or cassette format and perform

sufficiently well for use in transfusion screening [98,99]. An evaluation of 9 rapid syphilis tests in 8 geographically diverse laboratories found overall sensitivities (85%-97.7%) and specificities (92.8%-98%) comparing favorably to the best available laboratory-based diagnostics [100].

Blood services in Africa that screen for malaria commonly rely on microscopic evaluation, although numerous RDTs are available [101]. Most malaria RDTs are immunochromatographic devices that target malaria antigens such as HRP-2, pLDH, and *Plasmodium* aldolase [102]. However, both RDTs and microscopy lack the sensitivity to detect low-grade parasitaemia (<0.002%), which occurs in many semi-immune and asymptomatic donors [102,103]. An evaluation of malaria screening methods among Sudanese blood donors found the sensitivity and specificity of an RDT to be 66.7% and 94.9%, respectively, when compared with polymerase chain reaction [104].

Application of RDTs to Predonation Infectious Screening

Although controversial and not endorsed by the WHO, predonation screening for TTIs with RDTs is a strategy that has been proposed for use in resource-poor, high-prevalence settings without access to a stable pool of low-risk donors [105]. Prescreening of potential donors using only a blood sample can reduce blood bag wastage and associated costs of consumables given that blood is not collected from donors who test positive during predonation screening. Furthermore, this avoids the costs of blood grouping and infectious testing (screening and confirmation). One study in Ghana demonstrated savings of more than $11 000 in blood bag and testing costs over a 1-year period of predonation screening [89]. In settings where postdonation communication is limited, prescreening also facilitates the early referral of reactive donors to counseling and management, thereby serving to interrupt further transmission [106].

Despite its benefits, predonation screening raises multiple concerns [107]. Prescreening each donor, with pretest and posttest counseling, may increase wait times and discourage donors. In settings without follow-up testing, false-positive results could lead to the misdiagnosis of healthy donors. In addition, blood services that implement predonation screening may unintentionally serve as alternate VCT sites and risk the attraction of test-seeking individuals and deterrent of potential donors due to potential stigmatization of donors who are barred from donation. Moreover, donors who are prescreened may not be documented in the same way as those associated with actual donations. For example, if donors are only prescreened for the most prevalent TTI marker in their region, data related to the seroprevalence of alternative TTI markers are not generated. Therefore, a useful surveillance mechanism is foregone.

Discussion

High-quality RDTs hold promise for blood safety in resource-poor settings where infrastructure to support formal laboratory testing is often lacking. However, recent studies highlight variable and suboptimal performance for RDTs in the transfusion setting, thus prompting debate as to the merits of their continued use, particularly in single-test screening algorithms in high-prevalence regions. Although grouped together, deficiencies in RDTs are not uniform across the targeted TTIs. For example, a higher level of performance has been reported with HIV RDTs as compared with HCV and HBV, which may reflect the broader investment in HIV prevention and testing. In contrast, there are several reports of suboptimal performance of other RDTs, particularly for HBV markers,

Both deficiencies in sensitivity and specificity have been reported for RDTs, which represent separate challenges for blood safety. Test sensitivity is of foremost concern, where a false-negative result confers both risk of a potential TTI as well as ongoing transmission in the general population. In contrast, deficient specificity, although not of immediate risk to transfusion recipients, indirectly burdens the transfusion service through unnecessary deferral of noninfectious donors. This is pertinent to Africa where only 40% of transfusion demand is currently being met and RDTs are frequently used in the absence of confirmatory testing [5]. Furthermore, disclosure of test results (eg, HIV), whether real or false, is likely to provoke significant distress in the donor [108].

Of note, performance characteristics of some RDTs in the field have been shown to be significantly below those claimed by manufacturers [93,109]. There are a number of factors that could account for the reported discrepancies. Foremost is human error such as lack of training and supervision of personnel who are tasked with performing testing. This problem is shared by point-of-care tests in general, yet is accentuated in under-resourced areas given the lack of quality systems, where RDTs are used. Manual operation and interpretation of RDTs in particular are sources of inconsistency and error. One study of RDTs for predonation screening in Ghana found premature reading of test strips (5-10 minutes early), which prevented the identification of 5 weakly positive results [89]. Selected deficiencies, for example, individual operator error and the subjectivity of interpretation may be remedied through improved training and provision of guidelines. However, systematic improvement in quality systems of which oversight of RDT use is only one component is likely needed.

Although RDTs are simpler than EIAs, they still require basic equipment and controlled transportation and storage conditions. At a minimum, pipettes and tips are needed and some kits require additional solutions, which demand proper cold chain management. Some assays require storage between 2°C and 10°C and all those that have been evaluated by the WHO require storage lower than 20°C to 35°C [77–79]. High ambient temperatures and humidity can degrade rapid tests, and inappropriate storage has been shown to contribute to poor performance [99,109]. Furthermore, the use of RDTs is reliant on a consistent supply of test kits, which is highly contingent upon funding and stock management. In one study, occasional shortages of rapid tests led to the collection of blood, which was untested and ultimately transfused. Many blood services in Africa are hospital based and do not control the procurement process, which can result in the purchase of consumables by the hospital based on price and availability rather than that which has been requested [110].

Assay performance may also be impacted by viral and subtype variation. For example, most RDTs target serologic markers of HIV infection such as HIV-1, group-O, and HIV-2 antibodies. Frequently used recombinant proteins or synthetic peptide antigens are specific to a subtype and are primarily optimized to detect HIV-1 subtype B strains, the most prevalence clade in the United States [111]. Evaluations of HIV-1 rapid tests found that selected tests were unable to accurately detect antibodies from subtype C or D [112,113]. The variability of RDTs to detect non–subtype B infections is concerning for their use for transfusion screening in Africa where subtypes A and C and circulating recombinant forms are most frequent [111].

There may be ways to improve sensitivity both in how RDTs algorithms are implemented and via selection of assays that are known to perform well under field conditions. However, each has barriers to implementation. First, the use of multiple RDTs in a serial or parallel algorithm could improve overall performance; however, this may offset the low-cost benefit of RDTs [7] Second, a formal head-to-head comparison of RDTs for all 3 major transfusion-transmissible viruses (ie, HIV, HBV, and HCV) has not been undertaken in the transfusion setting. There are platforms that may offer benefit and additional comparison studies between test kits would be of value. One study in Uganda compared 4 HIV RDTs (Uni-Gold Recombigen HIV (Trinity Biotech, Wicklow, Ireland), HIV-1/2 STAT-PAK (Chembio, Medford, NY), Determine HIV-1/2 (Abbot Abbott, Tokyo, Japan), and OraQuick HIV-1 (Orasure, Bethlehem, PA; assembled in Thailand)) in parallel against a serologic reference; the findings informed development of a serial algorithm which reportedly achieved a sensitivity of 98.6% and a specificity of 99.9% [86].

A fundamental problem remains a paucity of data on RDTs: even the true scope of their use is limited. To date a comprehensive survey of countries that conduct transfusion screening with RDTs has not been undertaken. Instead, the extent of use is inferred by a small number of

Table 2
Characteristics of studies included in the review

Reference	Country	Product name	Target agent	Comparison assay(s)	Reference/ Confirmation assay(s)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cost (USdollars)
[88]	Tanzania	Determine HIV 1/2 (Inverness Medical Japan Co. Ltd., Tokyo, Japan)	HIV-1/HIV-2		Immunoblot	100.0	99.6			0.80
		SD Bioline (Standard Diagnostics Inc., Kyonggi-do, Korea)	HIV-1/HIV-2		WB	100.0	99.2			0.47
		Uni-Gold (Trinity Biotech, Wicklow, Ireland)	HIV-1/HIV-2		WB	100.0	100.0			1.80
		First Response (PMC Medical India Pvt. Ltd., Daman, India)	HIV-1/HIV-2		WB	91.7	99.6			0.65
		Stat-Pak Dipstick (Chembio Diagnostic System, Inc., Medford, NY)	HIV-1/HIV-2		WB	100.0	100.0			0.80-0.95
[67]	Cameroon	Camstix–HIV 1 + 2 (Camdiagnostix, Yaounde, Cameroon)	HIV-1/HIV-2 Ab	EIA	WB, NAT	100.0	98.3	(94.4, 91.5)[a]	(100, 100)[a]	1.50
		Determine HIV 1 + 2 + 0 (Abbott Laboratories, Tokyo, Japan)	HIV-1/HIV-2 Ab	EIA	WB, NAT	100.0	98.3	(94.4, 91.5)[a]	(100, 100)[a]	2.50
		Genie II HIV-1/HIV-2 (Bio-Rad, Marnes la Coquette, France)	HIV-1/HIV-2 Ab	EIA	WB, NAT	98.9	100.0	(100, 100)[a]	(99.3, 99.3)[a]	4.00
		ImmunoComb II HIV 1/2 BiSpot (Orgenics, Yavne, Israel)	HIV-1/HIV-2 Ab	EIA	WB, NAT	99.3	99.5	(98.1, 97.5)[a]	(99.6, 99.6)[a]	3.70
[90]	Ethiopia	Determine HIV 1/2 (Abbott, Tokyo, Japan)	HIV-1/HIV-2 Ab	EIA	WB	60.5	98.9	88.5	94.9	
[66]	Cameroon	Determine HIV 1/2 (Determine HIV-1/-2, Inverness Medical France, Courbevoie, France)	HIV-1/HIV-2 Ab	EIA, HIV Ag/Ab	WB, NAT	79.2	99.1	71.2	99.4	
[86]	Uganda									
		Uni-Gold Recombigen HIV (Trinity Biotech, Wicklow, Ireland)	HIV-1 Ab	EIA	N/A	100.0	99.1	55.6	100	
		HIV 1/2 STAT-PAK (Chembio, Medford, NY)	HIV-1/HIV-2 Ab	EIA	N/A	100.0	99.6	76.9	100	
		Determine HIV 1/2 (Abbott, Tokyo, Japan)	HIV-1/HIV-2 Ab	EIA	N/A	100.0	96.2	22.2	100	
		OraQuick HIV-1 (Orasure, Bethlehem, PA; assembled in Thailand)	HIV-1 Ab	EIA	N/A	100.0	99.8	83.3	100	
[109]	Zambia	HIV-spot (non-expired)[b] (Diagnostic Biotechnology Ltd., Singapore, Singapore)	HIV-1/HIV-2 Ab		EIA/ Immunoblot	91.7	98.8	90.9	98.9	
[93]	Egypt[c]	ADVANCED QUALITY ONE STEP TEST (Intec Products, Fujian, China)	Anti-HBs		EIA	64.2	95.1	71.23	93.33	
		ADVANCED QUALITY ONE STEP TEST (Intec Products, Fujian, China)	Anti-HBc		EIA	85.5	98.4	94.64	95.45	
		ADVANCED QUALITY ONE STEP TEST (Intec Products, Fujian, China)	Anti-HBe		EIA	82.8	100.0	100	98.97	
[92]	Ghana	Latex agglutination (VEDAlab) (VEDAlab, Alençon, France)	HBsAg		EIA, NAT	53.8	97.0			
		Dipstick assay (VEDAlab) (VEDAlab, Alençon, France)	HBsAg		EIA, NAT	71.0	99.4			
[95]	Egypt	ImmunoComb II HCV (Inverness Medical Innovations, Waltham, MA)	Anti-HCV	EIA	NAT	97.0	78.5	70.8	98.1	
		HCV one-step (ACON Laboratories, San Diego, CA)	Anti-HCV	EIA	NAT	97.0	77.0	69.4	98.0	
		HCV TRI-DOT (J. Mitra, New Delhi, India)	Anti-HCV	EIA	NAT	97.0	77.0	69.4	98.0	
[96]	Cameroon	HCV rapid test (Human Diagnostics, Berlin, Germany)	Anti-HCV	Ag/Ab assay	Immunoblot, NAT	70.3	99.4			
[85]	Zimbabwe	HCV-SPOT (Genelabs Diagnostics, Singapore, Singapore)	anti-HCV	EIA	EIA	N/A	97.0			4.00
		SimpliRED HBsAg (AGEN, Brisbane, Australia)	HBsAg	EIA	N/A	93.3	100.0			1.50
		Dipstick-HBsAg (PATH, Seattle, WA/ Immuno-Chemical Laboratories, Bangkok-RIA)	HBsAg	EIA	N/A	93,3	100.0			0.64
[89]	Ghana									
		HBsAg Rapid test (Vedalab, Alençon, France)	HbsAg		EIA, NAT	93.0	99.0			0.80
		Anti-HCV (Intec, Hong Kong, PRC)	Anti-HCV		EIA, NAT	N/A	N/A			0.90
		Determine HIV-1/HIV-2 (Determine, Abbott Laboratories, Delkenheim, Germany)	HIV-1/HIV-2 Ab		EIA, NAT	N/A	N/A			
[91]	Mozambique	Determine HIV 1/2 (Abbott Laboratories, Chicago, IL)	HIV-1/HIV-2 Ab		RDT					
		Healtheasde HBsAg (Neomedic Ltd., Sea Cow Lake, South Africa)	HBsAg		EIA	98.6	80.4			
		AraGen RPR test (AraGen Biotech, Amman, Jordan)	Nontreponemal Ab		TPPA	100.0	98.8			
		SD Bioline HCV (Standard Diagnostics, Kyonggi-do, Korea)	Anti-HCV		EIA	100.0	99.1			

(continued on next page)

Table 2 (*continued*)

[87]	6 sub-Saharan African blood centers	Determine HIV-1/HIV-2 (Abbot)	HIV-1/HIV-2 Ab		EIA	100.0	94.0
		ImmunoComb II Trispot (Orgenics, in association with Genedia)	HIV-1/HIV-2 Ab		EIA	86.0	100.0
		SD Bioline HBsAg (Standard Diagnostics, Suwon, Korea)	HBsAg		EIA	43.0	100.0
		Core HBsAg (Core Diagnostics, Birmingham, UK)	HBsAg		EIA	43.0	100.0
		SD HCV Multi (Bioline, Standard Diagnostics)	anti-HCV		EIA	100.0	74.0
		Hexagon HCV	anti-HCV		EIA	50.0	100.0
[8]	17 Francophone African countries	5 rapid HIV tests[d]	HIV-1/HIV-2 Ab		EIA	72.4[e]	99.5[e]
		10 rapid HbsAg tests[f]	HbsAg		EIA	47.4[e]	99.1[e]
		8 rapid HCV tests[g]	Anti-HCV		EIA	63.7[e]	97.4[e]
[100]	8 laboratory sites	Determine Syphilis TP (Abbot, Chicago, IL)	Anti-TP		TPPA, TPHA	97.2	94.1
		Syphilis Fast (DIESSE Diagnostica, Senese SpA, Milan, Italy)	Anti-TP		TPPA, TPHA	86.0	92.8
		Espline TP (Fujirebio Inc, Tokyo, Japan)	Anti-TP		TPPA, TPHA	97.7	93.4
		Syphicheck-WB (Qualpro Diagnostics, Goa, India)	Anti-TP		TPPA, TPHA	84.5	97.7
		SD Bioline Syphilis 3.0 (Standard Diagnostics, Inc, Kyunggi-do, Korea)	Anti-TP		TPPA, TPHA	95.0	94.9
		Visitext Syphilis (Omega Diagnostics Ltd, Scotland, UK)	Anti-TP		TPPA, TPHA	85.0	98.0
		Syphicheck-WB (new version) (Qualpro Diagnostics, Goa, India)	Anti-TP		TPPA, TPHA	95.3	93.7
		Bioline Syphilis 3.0 (Pacific Biotech Co, Ltd, Petchaboon, Thailand)	anti-TP		TPPA, TPHA	92.2	97.0
		Syphilisonsite[onsite] Rapid Screening Test (CTK Biotech, Inc., San Diego, CA)	Anti-TP		TPPA, TPHA	96.3	94.6
[104]	Sudan	Qurum ICT	*Plasmodium falciparum*	Microscopy	PCR	66.7	94.9

Abbreviations: N/A or blank, not available or unknown; WB, Western blot; TP, *T pallidum*; TPPA, *T pallidum* particle agglutination assay; TPHA, *T pallidum* hemagglutination; PCR, polymerase chain reaction.

[a] First value based on the highest HIV prevalence reported in Cameroon, second value based on the lowest reported prevalence.

[b] Reagents and kits were stored outside the refrigerator at room temperature, varying from 18°C to 35°C.

[c] All donors were HBsAg negative.

[d] Determine HIV-1/HIV-2 (Abbot), ImmunoComb II HIV 1/2 Bispot (Orgenics), GENIE II HIV1/2 (Bio-Rad), SD Bioline HIV 1/2 Version 3.0 (SD Standard Diagnostics), Rapid 1-2-3 HEMA Express HIV (Hema Diagnostic Systems).

[e] Overall performance of rapid assays.

[f] One-step HBsAg test (AccuBio Tech), HEXAGON HBsAg(Human), Immunocomb II HBsAg (Orgenics), Determine HBsAg (Abbot), SD Bioline HBsAg (SD Standard Diagnostics), Rapid Signal HBsAg Dipstrip (Orgenics), HEP-CHECK-1 (Vedalab), One-step HBsAg test (Pistis), AgHBs STRIPS test (Taytec), One-step HBsAg test strip (Plamatec).

[g] Rapid anti-HCV test (AccuBio Tech), HCV TRI-DOT (J. Mitra & Co.), Hexagon HCV (Human), ImmunoComb II HCV (Orgenics), Rapid signal HCV Dipstrip (Orgenics), SD Bioline HCV(SD Standard Diagnostics), One-step HCV test (Pistis), CYPRESS anti-HCV (Cypress Diagnostics).

published studies coupled with communication with groups that conduct operational outreach in Africa. This suggests that RDT use for transfusion screening is widespread in the African region [12]. In 2 studies alone, almost a quarter (at least 23/95) of participating laboratories reported use of rapid testing for at least one of the major TTIs [8,114]. Most laboratories that use RDTs are located in regional blood banks rather than major cities and appear to be more common in Francophone Africa [8]. Although not unique to RDTs, their use reflects wide heterogeneity in blood bank practices not only between countries but also within individual countries according to organizational, infrastructure and financial constraints.

Heterogeneity in the literature poses a limitation to inform recommendations. The studies included in this review were conducted in different regions with a variety of methodologies. Furthermore, several of those studies, which concluded that RDTs were deficient, used an external quality assurance (EQA) design [8,87,114]. The latter has inherent limitations: first, given the low number of samples in a given panel, there is a disproportionate adverse effect on sensitivity or specificity even with a single error. In addition, the positive samples were diluted and may not reflect levels of infection encountered in asymptomatic donors. Most important, these studies lack direct observation and root cause analysis to account for the reported deficiencies between manufacture reporting and field use.

Recommendations

This review has led us to propose several recommendations to improve outcomes of RDT-based blood screening strategies. These recommendations are reasonably inexpensive and can be implemented even in remote or resource-poor locations. Foremost, the use of RDTs, or any other laboratory screening method, should occur in concert with recruitment of low-risk donors. Second, blood services should strive to select quality rapid tests, such as those that are prequalified by the WHO and included in the WHO bulk procurement list [115]. It important to validate quality rapid tests under field conditions with locally acquired samples to ensure adequate detection of circulating subtypes. Ideally, screening algorithms should be informed both by the assay in use as well as the prevalence of TTIs in the local environment. Similar to formal laboratory testing, a serial algorithm that uses an initial screening test with a highly sensitive RDT followed by a highly specific RDT for the same marker may serve to improve overall performance.

Quality systems are indispensible to minimizing risks throughout the blood transfusion process and are integral to the output reliability of RDTs. Therefore, laboratories testing with RDTs should adopt a rigorous quality management approach. A robust quality system includes routine quality control, quality assurance, and participation in EQA programs to ensure confidence in performance [116]. Quality control procedures should be performed and documented daily with known positive and negative samples. Tapid diagnostic test operators must receive specific training by qualified instructors not only on RDT operation but also on the related quality procedures and should be subject to a competency evaluation. There is a role for international organizations and regional transfusion-focused research networks in assisting in EQA and supporting transfusion-related research.

The potential value of RDTs is marred by the lack of technical guidelines. The necessity of well-designed algorithms used with quality RDTs

with rigorous quality systems was emphasized throughout the literature; however, current recommendations and guidelines related to RDTs are not tailored for use in transfusion screening. Contemporary guidelines are needed that support context-specific algorithms and the procurement and validation processes relevant to resource-poor blood banks. In addition, studies are needed to address some of the deficiencies highlighted in this review.

Conclusion

The risks and benefits of RDTs in transfusion screening in Africa seem similarly weighted leaving uncertainty as to their role. However, in some settings, RDTs may well be the only realistic option for testing with use borne by necessity rather than choice. Rapid diagnostic tests have a number of advantages, presenting an affordable option for blood safety where conventional laboratory testing remains unfeasible. However, the effectiveness of RDTs in the field is dependent on test quality and conditions of use. Studies evaluating their use in transfusion screening in Africa highlight the variability in performance, specifically those for HBV and HCV. Nevertheless, until more advanced screening or inactivation technologies are achievable, RDTs should be used in an informed and quality-assured manner to improve the safety of the regions blood supply. Ultimately, resource-constrained countries should continue to strive for the development of national transfusion services and low-risk donor recruitment networks to support safe and reliable blood systems.

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