Screening Donated Blood for Transfusion-Transmissible Infections

Recommendations

World Health Organization

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Preface

Blood transfusion is a life-saving intervention that has an essential role in patient management within health care systems. All Member States of the World Health Organization (WHO) endorsed World Health Assembly resolutions WHA28.72 (*1*) in 1975 and WHA58.13 (*2*) in 2005. These commit them to the provision of adequate supplies of safe blood and blood products that are accessible to all patients who require transfusion either to save their lives or promote their continuing or improving health.

WHO recommends the following integrated strategy for the provision of safe blood and blood products and safe, efficacious blood transfusion (*3*).

1 Establishment of well-organized blood transfusion services that are coordinated at national level and that can provide sufficient and timely supplies of safe blood to meet the transfusion needs of the patient population.

2 Collection of blood from voluntary non-remunerated blood donors at low risk of infections that can be transmitted through blood and blood products, the phasing out of family/replacement donation and the elimination of paid donation.

3 Quality-assured screening of all donated blood for transfusion-transmissible infections, including HIV, hepatitis B, hepatitis C, *Treponema pallidum* (syphilis) and, where relevant, other infections that pose a risk to the safety of the blood supply, such as *Trypanosoma cruzi* (Chagas disease) and *Plasmodium* species (malaria); as well as testing for blood groups and compatibility.

4 Rational use of blood to reduce unnecessary transfusions and minimize the risks associated with transfusion, the use of alternatives to transfusion, where possible, and safe clinical transfusion procedures.

5 Implementation of effective quality systems, including quality management, the development and implementation of quality standards, effective documentation systems, training of all staff and regular quality assessment.

The establishment of systems to ensure that all donated blood is screened for transfusion-transmissible infections is a core component of every national blood programme. Globally, however, there are significant variations in the extent to which donated blood is screened, the screening strategies adopted and the overall quality and effectiveness of the blood screening process. As a result, in many countries the recipients of blood and blood products remain at unacceptable risk of acquiring life-threatening infections that could easily be prevented.

In 1991, the World Health Organization Global Programme on AIDS and the-then League of Red Cross and Red Crescent Societies published *Consensus Statement on Screening Blood Donations for Infectious Agents through Blood Transfusion* (*4*). Since then, there have been major developments in screening for transfusion-transmissible infections, with the identification of new infectious agents and significant improvements in the detection of markers of infection in donated blood. The recommendations contained in this document have therefore been

developed to update and broaden the scope of the earlier recommendations. This document is specifically designed to guide and support countries with less-developed blood transfusion services in establishing appropriate, effective and reliable blood screening programmes.

It should be recognized, however, that all blood screening programmes have limitations and that absolute safety, in terms of freedom from infection risk, cannot be guaranteed. In addition, each country has to address specific issues or constraints that influence the safety of its blood supply, including the incidence and prevalence of bloodborne infections, the structure and level of development of the blood transfusion service, the resources available and special transfusion requirements. The safety of the blood supply also depends on its source, the safest source being regular voluntary non-remunerated donors from populations at low risk for transfusion-transmissible infections.

These recommendations are designed to support countries in establishing effective national programmes to ensure 100% quality-assured screening of donated blood for transfusion-transmissible infections. In countries where systems are not yet fully in place, the recommendations will be helpful in instituting a step-wise process to implement them.

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Key recommendations

POLICY RECOMMENDATIONS

1 Each country should have a national policy on blood screening that defines national requirements for the screening of all whole blood and apheresis donations for transfusion-transmissible infections.

2 There should be a national programme for blood screening which sets out the strategy for screening, with algorithms that define the actual tests to be used in each screening facility.

3 All whole blood and apheresis donations should be screened for evidence of infection prior to the release of blood and blood components for clinical or manufacturing use.

4 All donations should be screened for serological markers of HIV, hepatitis B, hepatitis C and syphilis.

5 Screening of donations for other infections, such as those causing malaria, Chagas disease or HTLV, should be based on local epidemiological evidence.

6 Where feasible, blood screening should be consolidated in strategically located facilities at national and/or regional levels to achieve uniformity of standards, increased safety and economies of scale.

7 Adequate resources should be made available for the consistent and reliable screening of blood donations for transfusion-transmissible infections.

8 A sufficient number of qualified and trained staff should be available for the blood screening programme.

9 There should be a national system for the evaluation, selection and validation of all assays used for blood screening.

10 The minimum evaluated sensitivity and specificity levels of all assays used for blood screening should be as high as possible and preferably not less than 99.5%.

11 Quality-assured screening of all donations using serology should be in place before screening strategies utilizing nucleic acid testing are considered.

12 There should be a national procurement policy and supply system to ensure the quality and continuity of test kits, reagents and other consumables required for the screening of all donated blood.

13 Quality systems should be in place for all elements of the blood screening programme, including standards, training, documentation and assessment.

14 There should be regulatory mechanisms for oversight of the activities of blood transfusion services, including blood screening.

TECHNICAL RECOMMENDATIONS

1 Every facility in which screening is performed should have a suitable infrastructure and quality system to perform effective blood screening for transfusion-transmissible infections.

2 All staff involved in blood screening should be trained to perform their functions to nationally required standards.

3 Specific indicators of performance of all assays should be designated and monitored continuously to assure the reliability of results.

4 All test kits and reagents should be stored and transported under appropriate controlled conditions.

5 All blood screening tests should be performed in a quality-assured manner following standardized procedures.

6 A quarantine system should be in place for the physical segregation of all unscreened donations and their blood components until all required tests have been completed and the suitability of donations for therapeutic use has been determined.

7 Only blood and blood components from donations that are non-reactive in all screening tests for all defined markers should be released for clinical or manufacturing use.

8 All reactive units should be removed from the quarantined stock and stored separately and securely until they are disposed of safely or kept for quality assurance or research purposes, in accordance with national policies.

9 Systems should be put in place to maintain the confidentiality of test results.

10 Confirmatory testing of reactive donations should be undertaken for donor notification, counselling and referral for treatment, deferral or recall for future donation, and look-back on previous donations.

1 Introduction

1.1 CONTEXT

It is the responsibility of governments to assure a safe and sufficient supply of blood and blood products for all patients requiring transfusion (*1*). Each country should formulate a national blood policy and plan, as part of the national health policy, to define how safe blood and blood products will be made available and accessible to address the transfusion needs of its population, including how blood transfusion services will be organized and managed.

The provision of safe and efficacious blood and blood components for transfusion or manufacturing use involves a number of processes, from the selection of blood donors and the collection, processing and testing of blood donations to the testing of patient samples, the issue of compatible blood and its administration to the patient. There is a risk of error in each process in this "transfusion chain" and a failure at any of these stages can have serious implications for the recipients of blood and blood products. Thus, while blood transfusion can be life-saving, there are associated risks, particularly the transmission of bloodborne infections.

Screening for transfusion-transmissible infections (TTIs) to exclude blood donations at risk of transmitting infection from donors to recipients is a critical part of the process of ensuring that transfusion is as safe as possible. Effective screening for evidence of the presence of the most common and dangerous TTIs can reduce the risk of transmission to very low levels (*5*). Blood transfusion services should therefore establish efficient systems to ensure that all donated blood is correctly screened for specific TTIs and that only non-reactive blood and blood components are released for clinical and manufacturing use.

The adoption of screening strategies appropriate to the needs, infrastructure and resources of each country can contribute significantly to improvements in blood safety. In countries where effective blood screening programmes have been implemented, the risk of transmission of TTIs has been reduced dramatically over the last 20 years (*6*–*7*).

Nevertheless, a significant proportion of donated blood remains unsafe as it is either not screened for all the major TTIs or is not screened within a quality system. Data on blood safety indicators provided in 2007 by ministries of health to the WHO Global Database on Blood Safety (GDBS) indicate that, of the 155 countries that reported performing 100% screening for HIV, only 71 screen in a quality-assured manner* (*8*). Concerted efforts are still required by a substantial number of countries to achieve 100% screening of donated blood for TTIs within quality systems.

1.2 CONSTRAINTS AND CHALLENGES

Various assay systems with differing sensitivities and specificities are available for blood screening. However, the efficacy of screening depends on their correct use in laboratories that are appropriately resourced and staffed and that have well-maintained quality systems.

* For the purposes of data collection, screening for TTIs in a quality-assured manner is defined as screening performed in blood centres/blood screening laboratories that (i) follow documented standard operating procedures and (ii) participate in an external quality assessment scheme.

Countries that are still unable to screen all donated blood for TTIs in a quality-assured manner face a variety of constraints. At national level, the main challenges are often ineffective policies, lack of national standards or screening strategies, and limited resources for implementing the national blood screening programme.

At the operational level, the effectiveness of blood screening is often constrained by the fragmentation and lack of coordination of blood transfusion services, inadequate infrastructures, shortages of trained staff and poor quality systems. This may result in:

- Inefficient screening systems and wastage of resources owing to differing levels of operation at multiple sites
- Lack of quality management and quality assurance systems
- Use of poor quality test kits and reagents
- Unreliable, inconsistent supplies of test kits and reagents due to poor logistics
- Equipment failure
- Variations in laboratory procedures and practices
- Incorrect storage or inappropriate use of test kits and reagents
- Inadequate procedures for identification, leading to the misidentification of patient or donor blood samples, donations or processed units of blood and blood components
- Technical failure in testing
- Misinterpretation of test results
- Inaccuracies in the recording or transcription of test results.

Leading to:

- Higher error rates in test results
- Increased risk of failure to detect TTIs
- Unnecessary discard of non-reactive blood
- Blood shortages and use of unscreened blood in urgent situations
- Incorrect donor notification and stigmatization.

Blood donors and blood screening

Screening of donated blood for TTIs represents one element of strategies for blood safety and availability. The first line of defence in providing a safe blood supply and minimizing the risk of transfusion-transmitted infection is to collect blood from well-selected, voluntary non-remunerated blood donors from low-risk populations, particularly those who donate regularly. The prevalence of TTIs in voluntary non-remunerated blood donors is generally much lower than among family/replacement (*9–11*) and paid donors (*12–14*). Each country should establish voluntary blood donor programmes which provide donor information and education and develop stringent national criteria for blood donor selection and deferral to exclude prospective donors at the risk of TTIs (*15*).

A lower prevalence of TTIs in the donor population also reduces the discard of donated blood and hence results in improved efficiency and use of resources.

1.3 AIM AND OBJECTIVES

In 1991, a *Consensus Statement on Screening of Blood Donations for Infectious Agents Transmissible through Blood Transfusion* (*4*) was published by the WHO Global Programme on AIDS and the League of Red Cross and Red Crescent

Societies. Recognizing that these recommendations were long outdated, the WHO Blood Transfusion Safety programme initiated a review process to develop new guidance on strengthening blood screening programmes.

Aim

The aim of *Screening Donated Blood for Transfusion-Transmissible Infections* is to support countries in establishing effective national blood screening programmes to protect the recipients of blood transfusion from TTIs.

Objectives

This document is designed primarily to support the strengthening and improvement of blood screening programmes in countries where systems are not yet fully developed. The specific objectives are to:

1. Provide policy guidance on ensuring safe and sufficient blood supplies through effective blood screening to minimize the risk of transmission of bloodborne infections through the route of transfusion.
2. Provide information and technical advice on the specific measures and actions needed to:
   - Develop and implement efficient, national blood screening programmes in which 100% of blood donations are screened
   - Identify TTIs to be screened for in blood donations
   - Develop appropriate screening strategies and algorithms
   - Develop systems for the selection and evaluation of assays
   - Implement quality systems in all aspects of blood screening
   - Develop policies and systems to manage positive or reactive blood donors.

The recommendations and algorithms provided in this document are specific to the screening of donated blood for TTIs and are not designed for diagnostic testing for infections. However, they may be applied to screening requirements for plasma for fractionation, stem cells and tissues.

1.4 TARGET AUDIENCE

This document is primarily intended for use in developing and transitional countries with limited resources in which blood transfusion services are in the early stages of development. It is designed for use by:

- Policy makers responsible for health, finance, education, quality and other areas that directly and indirectly influence blood safety
- National blood programme managers in ministries of health
- National blood transfusion service personnel, including directors, senior managers, quality and laboratory staff, especially those directly responsible for screening blood for TTIs
- Laboratory managers and technical staff in hospital transfusion laboratories/blood banks
- Laboratory managers and technical staff in reference laboratories.

The document may also be useful for other relevant stakeholders such as education and training institutions, transplantation services, plasma fractionation facilities and disease prevention programmes focusing on infections such as HIV and hepatitis.

1.5 METHODOLOGY

Informal Consultation of Experts on the Screening of Donated Blood for Transfusion-Transmissible Infections

In October 2004, the WHO Blood Transfusion Safety programme convened an Informal Consultation on the Screening of Donated Blood for Transfusion-Transmissible Infections. The specific objectives of the consultation were to review the guidelines contained in the earlier *Consensus Statement*, address current scientific issues in relation to the characterization of new infections and the development of new technologies for blood screening and define the scope for updating the guidelines.

The consultation was convened as a Working Group consisting of 11 international experts, including members of the WHO Expert Advisory Panel on Blood Transfusion Medicine. These experts were nominated by the WHO Regional Advisers on Blood Safety and selected on the basis of their expertise in the field of transfusion microbiology. The selection process was also designed to ensure a regional balance and participation from both developing and developed countries. The consultation was also attended by observers from the European Commission, Health Canada, the International Consortium for Blood Safety, the International Society of Blood Transfusion and the Thalassaemia International Federation.

Scope of the recommendations

The focus of the consultation was primarily on the needs of developing and transitional countries in which blood screening programmes are not yet well-developed or where quality systems are lacking. The need for updated guidelines on screening donated blood was identified, including policy and organizational issues as well as the technical and scientific aspects of blood screening. The Working Group recommended that the updated guidelines should include information on the importance of a sustainable blood screening programme for an adequate supply of screened blood and blood components; economic considerations; the benefits of the centralization or regionalization of blood screening; legislative issues; an emphasis on voluntary, non-remunerated blood donation and donor selection criteria; policy development for the evaluation, selection, procurement and validation of test kits/assays; confirmatory testing and blood donor management; dealing with emergencies and remote populations; and the link with requirements for the plasma industry.

The following sections were proposed as constituting the main framework of the recommendations:

- Developing national programmes for screening donated blood
- Screening assays
- Screening for transfusion-transmissible infections
- Blood screening, quarantine and release
- Confirmatory testing and blood donor management
- Quality systems in blood screening.

The Working Group emphasized the need for the recommendations to be evidence-based and particularly relevant for blood transfusion services that are not yet well-developed. They stressed that the recommendations should be designed to promote a consistent approach to ensuring blood safety and availability while being sufficiently flexible to allow for differences in screening strategies and infections to be screened for.

Evidence

A literature search was conducted by the WHO Blood Transfusion Safety team using PubMed, MedLine, the WHO library database and regional databases. Particular efforts were made to identify systematic literature reviews and evidence related specifically to screening for TTIs in developing countries.

Peer review and technical editing

An initial draft of the document, based on the evidence and recommendations from the informal consultation, was prepared by Dr Alan Kitchen, chair of the Working Group and a member of the WHO Expert Advisory Panel on Blood Transfusion Medicine.

Following internal review and revision, an advanced draft of the document was circulated to participants at the Plenary Meeting of the Global Collaboration for Blood Safety (GCBS), a WHO-hosted network, held in 2006, and members of the Working Party on Transfusion-Transmitted Diseases of the International Society of Blood Transfusion. The draft was thus subjected to an extensive consultative and review process by international experts, directors of WHO Collaborating Centres on blood transfusion, international and governmental agencies and non-governmental organizations.

A consultative meeting of selected experts was convened in 2007 specifically to review and address the comments received on the advanced draft. The technical editing of the draft document in its various stages of development was undertaken by an editorial team and a further peer review was undertaken of the final draft.

Declaration of interests

Conflict of interest statements were collected from all major contributors. No conflict of interest has been declared by any contributors to the document.

Review and updating of the recommendations

It is anticipated that the recommendations in this document will remain valid until 2014. The Blood Transfusion Safety Team, Department of Essential Health Technologies at WHO Headquarters in Geneva will be responsible for initiating a review of these recommendations at that time.

2 National blood screening programme for transfusion-transmissible infections

2.1 DEVELOPING A NATIONAL BLOOD SCREENING PROGRAMME

National health authorities and blood transfusion services are responsible for ensuring that relevant policies, standards, strategies, systems and infrastructure are in place for the screening of all whole blood and apheresis donations for TTIs prior to their release for clinical or manufacturing use (*2*).

An effective, well-organized blood screening programme with quality systems is essential for the provision of safe blood supplies that are sufficient to meet the transfusion requirements of patients at all times and in all parts of the country, including remote regions. The design and development of a national blood screening programme for TTIs requires certain questions to be considered:

- Are there systems for the education and recruitment of low-risk voluntary non-remunerated blood donors?
- How much of the blood supply is contributed by voluntary non-remunerated blood donors?
- Are national criteria for blood donor selection and deferral in place?
- Which TTIs are to be screened for?
- What are the incidence and prevalence of these specific infections in the general population and blood donor population?
- For each infection, which specific marker(s) are to be screened for?
- Are suitable screening assays available?
- Has a suitable screening algorithm been developed for each TTI?
- Has a specific and sufficient budget been allocated for the blood screening programme?
- Are there a suitable infrastructure, facilities and equipment for efficient blood screening?
- Is there an adequate and consistent supply of quality test kits and reagents?
- Is there a national reference laboratory or access to such services?
- Are facilities for confirmatory testing, donor counselling and referral available?

From the answers to these questions, a screening programme can be developed to implement the national policy on blood screening to identify and prevent the release of any donations reactive for specific TTIs in the most reliable and cost-effective manner.

2.2 NATIONAL POLICY ON BLOOD SCREENING

Each country should have a national policy on blood screening, incorporated into the national blood policy, that defines national requirements for the screening of all whole blood and apheresis donations for TTIs.

The policy should define mandatory screening for specific infections and their markers and screening for other TTIs, based on national epidemiological data on bloodborne pathogens. It should also outline the measures that will be taken to ensure that all screening is performed in the context of effective, quality-managed blood transfusion services and the consistent provision and most efficient use of available resources. The need for, and the role of, confirmatory testing should also be clearly defined.

2.3 NATIONAL SCREENING STRATEGY

Laboratory screening of donated blood is the step that determines whether or not a donation is non-reactive for specific markers of infection and is therefore safe to release for clinical or manufacturing use. Each country should decide on the TTIs to be screened for as part of the blood screening programme and develop a screening strategy appropriate to its specific situation. This will be influenced by the incidence and prevalence of infection, the capacity and infrastructure of the blood transfusion service (BTS), the costs of screening and the available resources. The critical factor is that whichever strategy is selected, it is implemented effectively, consistently and within a well-managed quality system.

The national screening strategy provides an overall decision-making process on how tests are to be used and interpreted and defines the outcomes of screening with regard to whether a blood unit will be released or discarded. The strategy should define in general terms how screening is to be performed and provide specific guidelines on:

- Marker(s) to be screened for each infection
- Assay(s) to be used for each marker
- Standards for the performance of testing, including assay performance characteristics
- Quality systems within which the screening is to be performed
- Blood screening in specific situations; for example, in remote areas with low workloads and limited facilities, when equipment is lacking or where there may be no electricity
- Emergency screening when blood is needed urgently
- Interpretation of the results of screening tests, including:
  - The definition of initially reactive and non-reactive blood donations and the decision points for the release of non-reactive units of whole blood and blood components
  - Whether initially reactive tests should be repeated or initially reactive donations should be discarded; the inclusion of repeat testing in the screening strategy is determined by the effectiveness of the quality system in place (see Section 5)
  - The fate of initially reactive donations that are non-reactive on repeat testing
- Procedures for the quarantine and release or discard of blood and blood components
- Whether confirmatory testing should be performed to distinguish between true reactivity and non-specific reactivity for donor management
- The subsequent actions to be taken for donors whose blood tests are repeat reactive, but are not confirmed positive: i.e. whether donors should be notified and counselled concerning possible non-specific or biologically false reactive results.

- Donor look-back and recipient follow-up
- Safe disposal of reactive and positive units.

The national blood screening strategy should be reviewed periodically to determine whether there is a need for any amendment because of new evidence or changes in the epidemiology of infection in the general population. A rising incidence of infection, for example, increases the probability of blood donation by recently infected donors. Additional blood screening measures may be required to ensure that such early infections are detected on screening. Conversely, a falling or low incidence and a low prevalence of infection may also require the current strategy to be re-examined.

Screening and confirmatory strategies are explained in more detail in Sections 5 and 6.

2.3.1 Screening algorithms

A screening algorithm defines the specific tests and testing processes to be followed in each facility to determine the suitability of each unit of donated blood and any components derived from it. The use of screening algorithms helps to ensure consistency in screening tests and decisions regarding the release of screened blood and blood components, the discard of unsuitable units and the management of blood donors with confirmed positive screening results.

A screening algorithm should be developed for each TTI. The design of an algorithm will be determined by the specific infection marker to be screened for, the expertise of the users, the infrastructure, testing conditions and quality systems of individual screening facilities. Once an algorithm has been defined, this will guide the procurement of the specific test kits, reagents and laboratory testing systems required.

Algorithms for blood screening and blood donor management are addressed in more detail in Sections 5 and 6.

2.4 ORGANIZATION AND MANAGEMENT

2.4.1 Blood transfusion service(s)

The efficient coordination of blood transfusion services at national level is a prerequisite for an effective and sustainable national blood screening programme. It is also required for the uniform application of national standards and procedures across an entire country. Coordination is essential to maintain continuity in operations and consistency in performance in all facilities in which screening is performed, including blood centres and hospital-based services. Each screening facility requires a specific and sufficient budget, a suitable infrastructure, with reliable water and power supplies, well-maintained equipment and efficient transportation and telecommunications systems.

Greater efficiency and safety can be achieved by bringing together key blood screening activities into a network of strategically located central and/or regional blood centres with well-trained staff, suitable equipment and efficient procurement and supply systems (*16*). By facilitating economies of scale, this enables overall costs to be minimized without compromising quality. Conversely, the screening of blood in multiple small centres usually leads to the wastage of precious resources and a lack of uniform standards (*17*).

In countries with hospital-based blood services, national health authorities should assess the need and feasibility of consolidating screening activities at

national and/or regional levels so that the national screening programme can be implemented more efficiently and cost-effectively. This requires a situation analysis through the identification and mapping of all existing facilities that screen blood donations and an assessment of their organizational structure, infrastructure, technical and human resources. From this, a needs assessment can be carried out to identify requirements and priority interventions to strengthen TTI screening of donated blood. This will enable the development of national and regional operational plans involving all relevant stakeholders for strengthening and, if appropriate, reorganizing the structure and network of facilities for blood screening. Plans should include a monitoring and evaluation mechanism, with a baseline, targets and indicators in order to measure progress and impact in all facilities in which TTI screening of donated blood is performed.

2.4.2 Reference laboratory

Most countries have at least one well-established laboratory with the relevant expertise and experience that could be designated as a reference laboratory. A national public health/reference laboratory is generally suitable for this work. Alternatively, the role of the reference laboratory may be delegated to a blood transfusion service laboratory if it has suitable facilities, adequate resources and an effective quality system. An assessment of requirements for the strengthening of the reference laboratory may be needed to ensure its capacity to support the blood screening programme.

The role of the reference laboratory may include:

- Evaluation and selection of assay systems and equipment
- Confirmatory testing on screen reactive donations for blood donor management
- Provision of quality control samples
- Organization of external quality assessment schemes.

2.5 FINANCIAL AND HUMAN RESOURCES

An investment in blood safety measures to prevent transfusion-transmitted infection is more cost-effective than allowing the further spread of TTIs which places additional, avoidable pressures on the healthcare system. Every country should ensure that sufficient and sustained resources are available for an effective and comprehensive blood screening programme that ensures the high quality screening of all donations for TTIs. In order to make optimal use of limited healthcare resources, the screening programme should ensure a balance between the application and implementation of good scientific principles and the best use of the resources available. The implementation of new systems for screening is best undertaken in a stepwise fashion with appropriate resources allocated for establishing functional quality systems.

A sufficient number of qualified and trained staff should be available to perform the laboratory activities associated with blood screening, including the implementation of quality systems. In-service training programmes should be established and reviewed at appropriate intervals to define areas where further training or re-training is necessary. The competency of all staff to perform their roles to the required standards should be assessed on a regular basis. Blood transfusion services should work with national health and education authorities to ensure that education and training institutions provide suitable opportunities for qualifications and training. Measures should be adopted to provide opportunities

for career progression and to retain experienced staff in order to ensure that laboratories function effectively.

2.6 EVALUATION, SELECTION AND VALIDATION OF ASSAY SYSTEMS

Assay systems should be systematically evaluated and selected before procurement and then validated in each screening facility before their introduction for routine use. In situations where resources and expertise are limited, it may be appropriate to utilize evaluation data from external sources to assess potential assays and systems. In all cases, however, it is essential that an effective process is defined and put in place to ensure that new assays and systems are introduced only following proper investigation, evaluation and validation. Cost should not be used as the basis for the selection of an assay unless the performance of other assays under consideration is comparable.

The evaluation, selection and validation of screening assays are covered in more detail in Section 3.

2.7 LABORATORY QUALITY SYSTEMS

Effective quality systems are essential for the overall effectiveness of the blood screening programme and to minimize the transmission of infection through the route of transfusion. Quality systems should not be limited to laboratories only, but should encompass all activities of the blood transfusion service to ensure that all donations are screened correctly and handled appropriately before and after laboratory testing. The implementation of quality standards will ensure the safety and clinical efficacy of blood and blood products for patients as well as protecting the health and safety of staff.

Quality systems in blood screening are addressed in Section 7.

2.8 PROCUREMENT AND SUPPLY OF ASSAYS AND REAGENTS

Continuity in the supply of the assays, reagents and consumables required for testing depends on reliable procurement and supply systems. Frequent variations in assays and reagents could affect the quality system as they would each require evaluation and validation, and appropriate documentation and training before their use. Interruptions to supplies of assays and reagents may result in the temporary inability of screening facilities to screen for TTIs and having to issue unscreened blood for transfusion.

A national procurement system will require the development of specifications for equipment, test kits, reagents and consumables and assessment of the quantity and types required. The implementation of centralized bulk procurement with an efficient distribution system is likely to provide significant cost savings, simplify stock management and enable an uninterrupted supply of assays and reagents to be maintained. WHO and other technical agencies operate procurement services to increase access to affordable assays of assured quality that are appropriate for use in resource-limited settings (*see*: www.who.int/diagnostics_laboratory/procurement/en/).

The blood transfusion service should have appropriate systems in place to monitor stocks and expiry dates of test kits and reagents and have an adequate supply chain system to ensure that stocks are managed efficiently. These systems should include procedures to identify the manufacturers and ensure the traceability of the batch numbers of all test kits and reagents. A reliable procurement and supply system helps to ensure that each supplier is fully aware of the test kits and reagents required, the usage rates and the quantities needed. This should enable suppliers to ensure that stocks are always available for delivery, when required.

2.9 STORAGE AND TRANSPORTATION

All test kits and reagents should be stored and transported under controlled conditions. The blood transfusion service should ensure that reliable cold chain systems are in place in each screening laboratory to assure compliance at all times (*18*). Appropriate temperature-controlled storage equipment which conforms to defined specifications should be made available for normal maximum stocks of all test kits and reagents (*19*).

Test kits and reagents should always be transported and stored in accordance with the manufacturers' instructions. Most test kits and reagents require storage within a specific temperature range, usually between +2°C and +8°C. Transportation at ambient temperatures may be acceptable for short periods of time and in moderate climates. In climates with extremes of hot or cold, test kits and reagents should be transported under fully controlled conditions at specified temperatures, such as between +2°C and +8°C.

2.10 REGULATORY MECHANISMS

Each country should establish regulatory mechanisms that legislate and perform oversight functions for the activities of the blood transfusion service. These may operate through licensing procedures and inspection by representatives of the national health authority or through an appropriate governmental agency. They should have the expertise and competence in blood transfusion activities to assess the BTS against appropriate national and international standards, as they become applicable. These assessments may be formalized as a system of licensing, certification and/or accreditation and may involve not only the BTS, but also transfusion-related activities at hospital level. An effective oversight system gives confidence in the blood transfusion service to all stakeholders.

3 Screening assays

3.1 TYPES OF ASSAY

Various types of assay have been developed for use in blood screening over the past three decades. The assays most commonly in use are designed to detect antibodies, antigens or the nucleic acid of the infectious agent. However, not all assays are suitable in all situations and each assay has its limitations which need to be understood and taken into consideration when selecting assays.

The main types of assay used for blood screening are:

- Immunoassays (IAs):
  - Enzyme immunoassays (EIAs)
  - Chemiluminescent immunoassays (CLIAs)
  - Haemagglutination (HA)/particle agglutination (PA) assays
  - Rapid/simple single-use assays (rapid tests)
- Nucleic acid amplification technology (NAT) assays.

In the context of blood screening, appropriate evaluation is required in selecting the type of assay for each TTI, based on critical assay characteristics, such as sensitivity and specificity, as well as cost and ease of use.

3.1.1 Immunoassays

Immunoassays are assay systems available in several formats that may be used to detect antibody, antigen or a combination of the two. Generally, the simplest antibody detection assays are based on the use of immobilized antigen which captures any specific antibody present in the test sample (indirect IA). Commonly used antigen detection assays are based on the use of immobilized antibody to capture pathogen-specific antigens present in the sample.

Immunoassays can be used in different situations from high through-put laboratories with full automation to medium-sized laboratories with semi-automation to small laboratories, such as those in remote areas, which conduct a small number of tests manually.

Enzyme immunoassays (EIAs) and chemiluminescent immunoassays (CLIAs)

Enzyme and chemiluminescent immunoassays are currently the most commonly used assays for screening donated blood for TTIs. The design of EIAs and CLIAs is similar and they differ only in the mode of detection of immune complexes formed – colour generation in EIAs and measuring light produced by a chemical reaction in CLIAs. Any of these types of IA with high sensitivity will generally detect the target markers of infection required if they have been properly evaluated for blood screening and are then used within a quality environment.

EIAs and CLIAs are suitable for the screening of large numbers of samples and require a range of specific equipment. These assays may be performed either manually or on non-dedicated automated assay processing systems (open system). They may also be manufactured specifically to operate on specific dedicated automated systems (closed system).

EIAs and CLIAs have different solid phases to immobilize the antigen or antibody. Most commonly, the solid phases used are:

- Base and sides of a polystyrene microwell
- Surface of polystyrene or other material
- Micro-particles
- Surfaces of specific dedicated disposable devices used in automated self-contained assay systems; these vary according to the manufacturer, but are usually polystyrene
- Strips of nylon or nitro-cellulose membrane, specifically used in Western blots and line assays.

Particle agglutination assays

Particle agglutination assays detect the presence of specific antibody or antigen in a test sample through the agglutination of particles coated with the complementary specific antigen or antibody respectively.

Agglutination assays, mainly antibody assays, use a range of particles including red cells (haemagglutination) and inert particles such as gelatin and latex. This use of inert particles has the advantage of reducing non-specific reactivity against cross-reacting red cell antigens. The basic principles of haemagglutination and particle agglutination assays are the same, irrespective of the type of particles used. PA assays are still used extensively for the detection of syphilis antibodies.

PA assays do not involve multiple steps or need wash equipment. In a manual system, they are read visually, the reading of results is dependent on subjective evaluation and no permanent record of the test results can be kept. PA assays are suitable for the screening of large numbers of blood samples, including by automation.

Rapid/simple single-use assays (rapid tests)

Rapid/simple single-use assays are discrete, individual, disposable assays: i.e. they are used once and discarded. These assays exist in a number of different presentations. Many rapid tests are based on a form of immunochromatography in which the added sample flows down an inert strip and reacts with previously immobilized reagents. The sample can be serum, plasma or even whole blood in some cases. Any positive reaction is visualized as a dot or a band appearing on the device strip. Most of the assays also include a control dot or band that is used to validate the results of each individual device, irrespective of the specific test result.

Rapid tests are provided in simple-to-use formats that generally require no additional reagents except those supplied in the test kit. They are read visually and give a simple qualitative result within minutes. The reading of results is dependent on subjective evaluation and no permanent record of the original test results can be kept. Rapid tests are generally not suitable for screening large numbers of blood samples.

3.1.2 Nucleic acid amplification technology assays

Nucleic acid amplification technology (NAT), as applied to blood screening, detects the presence of viral nucleic acid, DNA or RNA, in donation samples. In this technology, a specific RNA/DNA segment of the virus is targeted and amplified in-vitro. The amplification step enables the detection of low levels of virus in the original sample by increasing the amount of specific target present to a level that

is easily detectable. The presence of specific nucleic acid indicates the presence of the virus itself and that the donation is likely to be infectious.

NAT assays can either be performed on individual donations (ID) or on mini-pools (MP) to detect the nucleic acid of the infectious agent. In addition to NAT assays which target individual viral nucleic acids, multiplex NAT screening assays have been developed which can detect DNA or RNA from multiple viruses simultaneously.

3.2 SELECTION OF ASSAYS

The selection of appropriate assays is a critical part of the screening programme. Reliable results depend on the consistent use of well-validated and effective assays. A number of factors need to be considered in selecting the most appropriate assays. In general, a balance has to be found between screening needs and the resources available, including finances, staff and their expertise, equipment, consumables and disposables.

Each screening system has its advantages and limitations that should be taken into consideration when selecting assays. Some limitations include:

- The length of time following infection before the screening test becomes reactive (window period)
- Rates of biological false positives which may result in the wastage of donations and unnecessary deferral of donors
- The complexity of some systems that require automation.

In most situations, EIAs, CLIAs and particle agglutination assays developed specifically for blood screening are the assays of choice as they are suited to screening from relatively small to large numbers of samples. In addition, the formats allow more objective recording and analysis of the results than rapid tests. However, a rigorous scientific evaluation of all assays prior to use is needed to determine their suitability in terms of sensitivity, and where possible, specificity in the situations in which they are to be used. While immunoassays may most often be microplate-based EIAs or specific system-based CLIAs, the use of simple/rapid disposable devices may be appropriate in some situations.

Most EIAs and CLIAs have greater sensitivity and specificity than particle agglutination assays or rapid tests. Their manufacture and performance are generally more reliable and consistent and have better outcomes for blood screening. High quality particle agglutination assays are not available commercially for all the routine markers for which blood is screened.

The use of rapid/simple assays is generally not recommended for blood screening as they are designed for the immediate and rapid testing of small numbers of samples, mainly for diagnostic purposes. These assays are performed using manual techniques; the results therefore have to be transcribed by staff and there is a lack of permanent records and traceability. As a result they may have limited use in laboratories where through-put is medium to high. They may, however, be considered for use in small laboratories that have limited resources and perform only a small number of tests daily as they provide flexibility and no major items of equipment are needed. They may also be appropriate when a laboratory needs to screen specific donations on an emergency basis for immediate release of products due to a critically low blood inventory or when rare blood is required urgently. In such emergency situations, the use of the rapid/simple assay should be followed up with repeat testing using an EIA, CLIA or particle agglutination assay if these assays are routinely used.

The introduction of NAT should be considered only when an efficient and effective programme based on antibody/antigen testing is in place (*20*) and there is a clear, evidenced, additional benefit. Although NAT reduces the window period of infection, in countries with a low incidence of infection, the incremental gain is minimal as the number of donors in the window period at the point of donation is generally very low. However, in countries with a high incidence of infection there are likely to be significant numbers of window period donations that can be identified by NAT (*21*). Thus although the risk of transfusing a blood unit collected during the window period may be decreased using NAT, the actual benefit in most populations has first to be determined and should be balanced against the complexity and high cost of performing NAT, including the infrastructure required (*22–24*).

For countries with sufficient resources, NAT offers certain benefits when combined with antibody/antigen testing. However, the potential benefit of detecting early infections and preventing possible transmissions of infection should be assessed in relation to such factors as the incidence and prevalence of infection in the blood donor population, the effectiveness of the blood donor selection process, the sensitivity of the serological screening currently undertaken and the ability to enhance this through, for example, the use of more sensitive serological assays such as combination antigen-antibody assays.

3.3 CRITICAL ASSAY CHARACTERISTICS

Sensitivity and specificity are the key factors to be considered in selecting a specific assay. For the screening of blood donations, both sensitivity and specificity should be the highest possible or available. Each assay should be evaluated within the country or region to confirm the technical data provided with regard to assay performance and, where possible, data from other studies should be analysed. The performance actually achieved in routine screening situations may not always meet the expected performance because assays are conducted by a range of staff under differing conditions. The reliability and consistency of the assay will be determined by a number of factors related both to the assay and the specific laboratory in which it is used. Each assay should be validated in its place of use to assure that the performance is as expected according to the results of evaluation.

Assay specific factors include:

- Assay presentation
- Clarity of instructions
- Ease of use
- Assay characteristics, including sensitivity and specificity
- Sample volume
- Sample and reagent addition monitoring
- Robustness
- Assay reproducibility and precision
- Number of tests per assay
- Kit size
- Total assay time.

Laboratory specific factors include:

- Number of samples to be tested
- Staff levels

- Staff competence
- Available equipment
- Level of laboratory quality system.

Logistics that need to be taken into consideration include:

- Vendor selection and validation
- Price
- Procurement system
- Availability and reliability of the supply of test kits and reagents
- Shelf-life of test kits and reagents
- Infrastructure: e.g. controlled storage conditions and uninterrupted power supply
- Technical support for trouble-shooting
- Equipment maintenance, servicing and repair.

3.4 EVALUATION OF ASSAYS

Assays produced by the major international diagnostics companies are generally well-designed and are normally evaluated scientifically, both by the manufacturers themselves and by independent laboratories, prior to release onto the market (*see* www.who.int/diagnostics_laboratory/evaluations; www.who.int/diagnostics_laboratory/publications/evaluations/en/index.html and www.who.int/bloodproducts/ref_materials/en/). Data published in kit package inserts and the scientific literature also provide useful information guiding selection of vendors, testing platforms and specific assays. However, well-planned and documented assay evaluations prior to their procurement are essential to ensure that the most appropriate selections are made from the available options. Assay evaluations are required to determine scientifically the most suitable assays for use in particular situations.

Evaluations should be carried out in at least one major facility, but some blood transfusion services may not have the necessary resources, expertise, experience and, importantly, panels of samples required. In such situations, the evaluations should be undertaken on behalf of the blood transfusion service, and in close conjunction with it, by an appropriate laboratory, such as the national reference laboratory. If none is available, the evaluation data required should be obtained from a blood transfusion service or reference laboratory in another country with similar demography, infection incidence and prevalence and BTS requirements, preferably in the same region. Reference should also be made to information available from laboratories elsewhere in the region or globally.

The evaluation process normally consists of performing each assay under consideration against selected panels of samples that will challenge the assay and deliver statistically valid results. The panels are generally comprised of:

- True positive samples and true negative samples in which the sensitivity and specificity respectively are determined
- Samples collected during seroconversion
- Low-level positive samples: for example, samples from very early or very late in the course of infection
- Samples covering a range of different genotypes and/or serotypes with emphasis on local samples
- Known non-specifically reacting samples or potentially cross-reactive samples: i.e. samples from patients not infected with the target

infection, but with a range of clinically relevant conditions such as hypergammaglobulinaemia, other infections or autoimmune disease.

The overall size of the panels will be determined by local availability but, generally, the more samples tested, the more useful and reliable is the information generated. It is particularly important to include as many examples of locally-acquired infections as possible, especially samples from blood donors found previously reactive and confirmed to be infected. Analysis of the results will identify the assay that gives the best overall performance against all samples tested. It is therefore important that the panels are as broad as possible and that overall performance is assessed in the context of the planned use of the assay.

Each country should determine the minimum sensitivity and specificity levels required for each assay. Evaluation should be conducted on sufficient numbers of known antibody positive and negative samples to ensure that evaluation results are statistically significant. It is recommended that the minimum evaluated sensitivity and specificity levels of all assays used for blood screening should be as high as possible and preferably not less than 99.5%.

3.5 MONITORING ASSAY PERFORMANCE

In blood screening, assay performance should be continually monitored in order to identify any changes in performance that are occurring and that, without correction, might ultimately lead to a failure in either the assay runs or the detection of low-level true positive samples. Performance is usually assured by monitoring one or more parameters that can reasonably be expected to change relatively quickly as a result of any change in the performance or use of the assay (the assay or the operator/system performing the assay). These parameters include:

- Quality control sample results
- Assay control values
- Repeat reactivity.

The use of appropriate quality control (QC) samples included with every batch of tests performed will rapidly generate useful and reliable data for monitoring. In this context, a batch of tests can be any defined block of tests; for example, a single microplate is a batch of tests and at least one external QC sample could be included on each plate. External quality controls do not substitute for internal (kit) controls.

QC samples are normally well-characterized samples, individual or pooled, that are calibrated against international standards, where possible, and are diluted in an appropriate matrix. These samples may be used as external go–no–go controls, in which case the QC sample(s) has to be reactive for the assay run to be valid. If QC samples are not available, tracking the assay control values may be used as an alternative for assessing the consistency of performance.

In all cases where quantitative values are used, such as EIA optical density (OD) values, the results should be normalized to allow comparison between different runs and, to a certain degree, between different assays. The normalized OD value is calculated as follows:

- Non-competitive EIAs: divide the sample OD value by the cut-off OD value
- Competitive assays: divide the cut-off OD value by the sample OD value.

The ratio generated can then be directly compared to the ratios generated by any other runs of the assay, including different manufacturers' lots. The analysis is less objective in situations where assay results are qualitative, such as in the use of particle agglutination assays. However, the QC sample can be used to determine whether the results of the assay run are valid. Where it is not, the assay run should be repeated.

3.6 USE OF AUTOMATION FOR PERFORMING ASSAYS

The use of automation is a major consideration for blood transfusion services that perform a large number of screening tests. While all EIAs need a basic level of automation (automated plate washers and readers), highly sophisticated automated screening systems are available that can perform all aspects of an immunoassay from sampling through to the final analysis of the results. These systems perform immunoassays from any major manufacturer and are referred to as "open" systems; they are generally microplate-based and the equipment and assays are not linked. Dedicated systems, known as "closed" systems, are fully automated and use only specific, dedicated assays with all the necessary reagents and controls produced by or in collaboration with the equipment manufacturer.

Depending on the number of donation samples to be screened each day and the resources available, the use of a fully automated system can offer substantial advantages in terms of quality, especially if the system handles the samples as well as performing all the steps of the assay. Automated systems generally offer a high level of consistency and reproducibility in assay performance and can also help to reduce operator errors. However, they have specific additional requirements, including special staff training needs, regular and effective maintenance and calibration and may involve higher capital and running costs. Open and closed systems each have their advantages and disadvantages but, in general, an open system offers greater flexibility and may be more cost-effective, although the technical input and skill required from the user is often greater.

As in the selection of assay types, the overall workload is a major factor in determining whether automation is appropriate. Automated systems are particularly useful where large numbers of samples are screened regularly. At lower workload levels, where EIAs are performed, at the very least automated plate washers and plate readers are essential.

3.7 NEW ASSAYS AND TECHNOLOGIES

New blood safety technologies are constantly becoming available which may offer new opportunities to blood screening programmes. Although it is important to be aware of scientific and technological developments, these may or may not offer any advantages or significant improvements over current practice. In the context of screening donated blood, the use of a new technology is generally an advantage only if the technology currently in use is failing to identify infected donations or if the new technology offers significant cost savings and efficiency benefits without reducing the overall effectiveness of the current screening programme.

Before any new technology is introduced into a blood screening programme, it should be fully investigated and systematically evaluated. Even if there is a potential advantage, the feasibility of implementing a new technology should be fully considered, including the requirements for infrastructure, financing, staffing levels, training and quality systems. Since the overall costs of implementation may far outweigh any potential benefit in terms of increased blood safety, a cost-benefit analysis should be performed and found to be favourable.

4 Screening for transfusion-transmissible infections

4.1 TRANSFUSION-TRANSMISSIBLE INFECTIONS

The microbial agents of importance to blood transfusion services are those that are transmissible by blood transfusion and can cause morbidity and mortality in recipients. In order to be transmissible by blood, the infectious agent or infection usually has the following characteristics:

- Presence in the blood for long periods, sometimes in high titres
- Stability in blood stored at 4°C or lower
- Long incubation period before the appearance of clinical signs
- Asymptomatic phase or only mild symptoms in the blood donor, hence not identifiable during the blood donor selection process (*25*).

Infections that consistently meet these criteria include those described in Section 4.2.

As large volumes of blood or blood components are given to patients during transfusion therapy, even a blood unit with a low viral load may cause infection in the recipient. It is imperative that blood transfusion services have effective screening systems to detect, segregate and remove reactive blood donations and all components derived from these donations from the quarantined useable stock. Only non-reactive blood and blood components should be released for clinical or manufacturing use.

The various markers of infection appear at different times after infection. Each TTI has one or more window periods, ranging from a few days to months, depending on the infectious agent, the screening marker used and the screening technology employed. During this period, the particular screening marker is not yet detectable in a recently infected individual, even though the individual may be infectious. Nucleic acid, as part of the native infectious agent itself, is the first detectable target to appear, followed within a few days by antigen, and subsequently by antibody as the immune response develops.

One or a combination of markers of infection can be used to detect a particular infection during the screening process. Various assay systems developed for blood screening detect:

- Antibodies that indicate an immune response to the infectious agent
- Antigens that are produced by the infectious agent and indicate the presence of that agent
- Nucleic acid (RNA/DNA) of the infectious agent.

In non-endemic countries, where the blood donor population includes travellers to or migrants from endemic areas, alternative strategies may be required, based on selective blood donor deferral and/or screening tests, if suitable assays are available. Similarly, some infections, such as human cytomegalovirus (CMV), present a risk to certain recipient groups only. In this situation, the selective screening of donations for these specific recipients is normally adopted.

GENERAL RECOMMENDATIONS

To minimize the risk of the transmission of infection through the route of transfusion:

1 All whole blood and apheresis donations should be screened for evidence of the presence of infection prior to the release of blood and blood components for clinical or manufacturing use.

2 All donations should be screened for serological markers of HIV, hepatitis B, hepatitis C and syphilis, following standardized procedures.

3 Screening of donations for other infections, such as those causing malaria or Chagas disease, should be based on local epidemiological evidence.

4 Screening should be performed using highly sensitive and specific assays that have been specifically evaluated and validated for blood screening.

5 Quality-assured screening of all donations using serology should be in place before additional technologies such as nucleic acid testing are considered.

6 Only blood and blood components from donations that are non-reactive in all screening tests for all markers should be released for clinical or manufacturing use.

7 All screen reactive units should be clearly marked, removed from the quarantined stock and stored separately and securely until they are disposed of safely or kept for quality assurance or research purposes, in accordance with national policies.

4.2 TRANSFUSION-TRANSMISSIBLE INFECTIOUS AGENTS FOR WHICH UNIVERSAL SCREENING OF ALL DONATIONS IN ALL COUNTRIES IS RECOMMENDED

Screening for the following four infections that are transmissible by transfusion is recommended as mandatory for the provision of a safe blood supply. These infections can cause chronic disease with possible serious consequences and present the greatest infection risk to recipients of transfusion:

- Human immunodeficiency virus (HIV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- *Treponema pallidum* (syphilis).

Importantly, the risks of infection can be virtually eliminated if the screening of blood donations is performed in a quality-focused way. All efforts should be made to implement universal screening for these four infections by countries in which it is not currently fully in place.

All blood donations should be screened for at least one suitable serological marker for each of these four infections. Screening for additional markers for these infections and for other transfusion-transmissible infectious agents could then be considered, depending on the residual risk, logistics and level of resources available.

4.2.1 Human immunodeficiency virus

Agent

The human immunodeficiency virus (HIV) is a retrovirus, an enveloped RNA virus, which is transmissible by the parenteral route. It is found in blood and other body fluids. Once in the bloodstream, the virus primarily infects and replicates in lymphocytes. The viral nucleic acid persists by integrating into the host cell DNA.

A number of different groups and subtypes (clades) have been identified with some significant antigenic differences; HIV-1 and HIV-2 are the two major distinct virus types and there is significant cross-reactivity between them. HIV-1 is now endemic in many parts of the world, although its incidence and prevalence is low in some regions. HIV-1 group M is responsible for more than 99% of the infections worldwide, whereas the prevalence of HIV-2 is mainly restricted to countries in West Africa and India. Additionally, a few infections with HIV group O and group N have been observed in Africa. The appearance of antibody marks the onset and persistence of infection, but not immunity.

Transmissibility

As HIV can be present in the bloodstream in high concentrations and is stable at the temperatures at which blood and individual blood components are stored, the virus may be present in any donated blood from an HIV-infected individual. Infectivity estimates for the transfusion of infected blood products are much higher (around 95%) than for other modes of HIV transmission owing to the much larger viral dose per exposure than for other routes (*26*).

Screening

The methods used to identify the presence of HIV employ the following screening targets:

- Serological markers:
  - anti-HIV-1, including group O, + anti-HIV-2
  - HIV p24 antigen (p24 Ag)
- Viral nucleic acid: HIV RNA.

The assay should be capable of detecting subtypes specific to the country or region.

Screening donations for both antibody and antigen will identify the vast majority of donations from infected donors (*27*).

anti-HIV-1 + anti HIV-2 and p24 antigen

All screening strategies should employ, at minimum, the detection of antibody because the identification of specific antibody is still the most reliable screening method. They should preferably also employ the detection of antigen. Antibody may be detected approximately three weeks after infection and approximately six days after antigen is first detected (*28*). HIV p24 antigen may appear from 3 to 10 days after viral RNA (*29*), and its detection can further reduce the serological window period by 3 to 7 days before antibody detection.

Screening for anti-HIV has been the basis for blood screening since the mid-1980s and HIV serology is therefore well understood. Although there is cross-reactivity between the main virus types (HIV-1 and HIV-2), it is not sufficient to rely on an HIV-1 specific assay to detect all cases of HIV-2. Since the early 1990s, anti-HIV assays have included specific antigens for both HIV-1 and HIV-2. However, the

use of antibody-only assays has been superseded by the use of combination HIV antigen and antibody assays (combined HIV p24 Ag and anti-HIV-1 + anti-HIV-2), wherever possible. These provide an enhanced level of sensitivity in early infection over antibody-only assays by reducing the serological window period (*30*).

HIV RNA

Viral RNA can be detected approximately 7 to 11 days after infection: i.e. when the results of HIV antigen-antibody assays are negative, but HIV RNA detection is positive (*28*). The detection of HIV RNA can reduce the risk of HIV being transmitted through the transfusion of infected blood donated during the serological window period of antigen and antibody assays.

RECOMMENDATIONS

To minimize the risk of HIV infection through the route of transfusion:

1 Screening should be performed using a highly sensitive and specific **anti-HIV-1 + anti-HIV-2 immunoassay** or **HIV combination antigen-antibody immunoassay** (EIA/CLIA). The assay should be capable of detecting subtypes specific to the country or region.

2 Screening using a highly sensitive and specific **anti-HIV-1 + anti-HIV-2 rapid assay** may be performed in laboratories with small throughput, in remote areas or emergency situations.

4.2.2 Hepatitis B virus

Agent

Hepatitis B virus (HBV) is a member of the hepadnavirus group and is an enveloped DNA virus. HBV is transmissible by the parenteral route and may be found in blood and other body fluids. Once in the bloodstream, the virus travels to the liver where it replicates in hepatocytes.

HBV is endemic globally and hyper-endemic in parts of the world. It is difficult to determine the total number of cases of transfusion-transmitted HBV globally.

Transmissibility

While HBV is present in the bloodstream, the levels of the virus itself are variable. In recently infected individuals, viral DNA is normally present, although not always at high levels. Chronically infected individuals may either be infectious (viral DNA present) or non-infectious (viral DNA absent) and viraemia would generally be expected to be very low or absent entirely. Screening for hepatitis B surface antigen (HBsAg) indicates infection with HBV, but does not in itself distinguish between recent and chronic infections.

The distinction between acute and chronic infection is not relevant to blood screening; all HBsAg positive donations should be considered to be at high risk of transmitting HBV and should not be released for transfusion. Additionally, some studies indicate that even when HBsAg is negative, some individuals may have low levels of detectable viral DNA which will be transmitted by blood and may cause infection in the recipient (*31–32*).

The use of unscreened HBV-infected blood and blood products will result in the transmission of HBV in the vast majority of cases. In general, the earlier

in life that HBV is acquired, the more likely the individual is to develop chronic infection which then has a higher probability of progressing to cirrhosis and hepatocellular carcinoma.

Screening

The serology of HBV is complex. A number of different serological markers develop during the course of infection, including hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). In addition, HBV DNA can be detected in the majority of cases, although in HBsAg negative phases of infection the DNA levels are generally relatively low and the viraemia may be transient.

The methods used to identify the presence of HBV employ the following screening targets:

- Serological markers:
  - Hepatitis B surface antigen
  - Hepatitis B core antibody, in some situations
- Viral nucleic acid: HBV DNA.

Hepatitis B surface antigen

Hepatitis B surface antigen is the prime marker used in blood screening programmes. It normally appears within three weeks after the first appearance of HBV DNA and levels rise rapidly (*31*).

It can thus be detected easily by most of the highly sensitive HBsAg assays available. The presence of HBsAg may indicate current or chronic infection and thus potential infectivity. Most blood transfusion services screen donated blood for HBsAg using sensitive immunoassays. Particle agglutination assays are still available and used in some countries, although they are less sensitive than immunoassays or even simple/rapid assays.

Hepatitis B core antibody

Antibody to hepatitis B core antigen is produced later in acute infection, after the appearance of HBsAg, and marks the start of the immune response to HBV infection. In general, anti-HBc persists for life, irrespective of whether the infection resolves or progresses to chronicity. In the vast majority of cases of hepatitis B, the detection of anti-HBc has limited value as HBsAg is already present. In some cases, however, during the resolution of the infection, HBsAg may decline to below detectable levels. Although anti-HBs usually then appears relatively rapidly, there may be a short period of time prior to its appearance when anti-HBc is the only detectable circulating serological marker of infection, even though the individual may still have low viraemia and would thus be potentially infectious.

If anti-HBc screening is introduced for routine use, it would be necessary to distinguish between individuals who are anti-HBc reactive because of previous, resolved, natural HBV infection, and are thus non-infectious, from those who have unresolved HBV infection and are thus potentially infectious. In a population with a high prevalence of infection, the number of blood donors with evidence of natural, resolved infection is likely to be significant, resulting in the potentially unnecessary discard of many blood donations. As the presence of anti-HBs is protective, anti-HBs testing of all anti-HBc reactive donations would therefore be required to distinguish between infectious and non-infectious individuals. In general, a level of anti-HBs at 100 mIU/mL is usually accepted as the

minimum protective level in the context of blood screening; donations that are HBsAg negative, anti-HBc reactive with anti-HBs levels of 100 mIU/mL or more are generally considered to be safe and acceptable for release for clinical or manufacturing use.

Another important consideration is that anti-HBc assays often demonstrate a high level of non-specificity (*33*). This, together with the problems associated with the confirmation of anti-HBc reactivity, often results in a situation where anti-HBc reactivity is identified in the absence of any other markers of HBV infection and where the majority of this reactivity is actually non-specific and does not reflect HBV infection. Thus, although anti-HBc screening may have advantages in some situations, the problems associated with the performance of anti-HBc assays and the complexity of dealing with HBV immune individuals may outweigh any potential benefits.

Alanine aminotransferase

Testing for raised liver alanine aminotransferase (ALT) levels was originally introduced in some countries prior to the identification of hepatitis C and the introduction of HCV screening in an attempt to reduce the incidence of what was then called post-transfusion non-A, non-B hepatitis (PTNANBH) (*34*). ALT is an enzyme found predominantly in the liver. It circulates naturally at low levels in the bloodstream, but is released in high quantities as a result of liver damage; this is often, but not exclusively, due to viral infection.

ALT is a non-specific marker of infection. With the advent of HCV screening, screening for raised ALT levels provides no identifiable benefit in terms of improving blood safety (*35*).

Hepatitis B virus DNA

The detection of HBV DNA further reduces the risk of HBV transmission through the transfusion of infected blood donated during the acute window period: i.e. when the results of HBsAg assays are negative, but HBV DNA is positive (*36*). Low levels of HBV DNA have also been detected in the blood of individuals after the resolution of acute HBV infection and the disappearance of HBsAg or in so-called chronic occult HBV infection (*31–32*).

RECOMMENDATIONS

To minimize the risk of HBV infection through the route of transfusion:

1 Screening should be performed using a highly sensitive and specific **HBsAg immunoassay** (EIA/CLIA).

2 Screening using a highly sensitive and specific **HBsAg rapid assay** or **particle agglutination assay** may be performed in laboratories with small throughput, in remote areas or in emergency situations.

3 Screening for anti-HBc is not recommended as a routine. Countries should determine the need for anti-HBc screening based on the prevalence and incidence of HBV infection.

4 Screening for ALT is not recommended.

4.2.3 Hepatitis C virus

Agent

Hepatitis C virus (HCV) is a member of the flavivirus group and is an enveloped RNA virus. It is transmissible by the parenteral route and may be found in blood and other body fluids. Once in the bloodstream, the virus travels to the liver where it replicates in hepatocytes, resulting in a similar picture to that seen with HBV infection. Seroreversion has been seen in numbers of individuals who have resolved their infections. The loss of circulating antibody may leave no readily detectable evidence of previous infection (*37*).

HCV is endemic in many parts of the world, although in some regions its incidence and prevalence may be low. Several genotypes are identified and are associated with different geographical distributions and some differences in antigenicity and clinical features, including response to treatment with interferon alpha (IFN-α).

Transmissibility

While HCV is present in the bloodstream, the levels of the virus itself are variable. In recently infected individuals, virus is normally present. However, only around 70% of chronically infected individuals are viraemic and the length of time that viraemia persists is not fully understood. Nonetheless, it is expected that most HCV infected donations would contain virus and thus be infectious.

Screening for both HCV antigen and antibody does not in itself distinguish between recent and chronic infection. The distinction is, however, not relevant to the screening of blood for transfusion and all HCV antigen-antibody reactive donations should be considered to be at high risk of transmission of HCV and should not be used for clinical or manufacturing use.

Screening

The methods used to identify the presence of HCV employ the following screening targets:

- Serological markers:
  - — HCV antibody
  - — HCV antigen
- Viral nucleic acid: HCV RNA.

HCV antibody and antigen

HCV antibody becomes detectable approximately 30 to 60 days after infection. Viral antigen normally appears between 0 and 20 days after viral RNA first appears. Antibody is generated and can be detected between 10 and 40 days after antigen is first detected.

The serology of HCV is still not fully understood. Serological screening has been highly effective in significantly reducing the transmission of HCV through the route of transfusion. Until recently, anti-HCV has been the prime serological marker for blood screening programmes. However, HCV antigen can be detected in the peripheral blood earlier than antibody in the course of early infection. HCV antigen assays, both antigen only and combined antigen-antibody, have been commercially available for a number of years. These have been introduced in some countries to improve the overall effectiveness of serological HCV screening (*38*).

Hepatitis C virus RNA

Viral RNA is normally detectable within a few weeks of infection and persists for 6–8 weeks prior to antibody seroconversion (*28*). The detection of HCV RNA may

further reduce the risk of HCV transmission through the transfusion of infected blood donated during the window period of antigen and antibody assays: i.e. when the results of HCV antigen-antibody assays are negative, but HCV RNA is positive (*28*). However, any benefit is dependent upon HCV incidence and the actual number of donations that may be collected in the window period (*38*).

RECOMMENDATIONS

To minimize the risk of HCV infection through the route of transfusion:

1 Screening should be performed using a highly sensitive and specific **HCV antibody immunoassay** or a **combination HCV antigen-antibody immunoassay** (EIA/CLIA). The assay should be capable of detecting genotypes specific to the country or region.

2 Screening using a highly sensitive and specific **HCV antibody rapid assay** may be performed in laboratories with small throughput, in remote areas or emergency situations.

4.2.4 Syphilis

Agent

Syphilis is caused by the bacterium *Treponema pallidum pallidum*. It is transmissible by the parenteral route and may be found in blood and other body fluids. Once in the bloodstream, the bacteria spread throughout the body. A primary lesion, chancre, usually occurs about three weeks after exposure, although the duration may be shorter in cases of transfusion-transmitted infection where the organism enters the bloodstream directly. Syphilis is endemic in many parts of the world.

Transmissibility

While *T. pallidum* may be found in the bloodstream, levels are variable, even in acute primary syphilis, and the bacteraemia is often short-lived. In addition, the treponemes are relatively fragile, in particular being heat-sensitive; storage below +20°C for more than 72 hours results in irreparable damage to the organism such that it is no longer infectious. Thus, although clearly potentially infectious, the risk of transmission through the transfusion of blood and blood components stored below +20°C is very low.

Blood components stored at higher temperatures (above +20°C), such as platelet concentrates, or those not stored at lower temperatures for any length of time, such as blood collected and used within 48 hours, present a significantly higher risk of transmitting syphilis. Thus, although the risk of transmission of syphilis from unscreened donations is variable, the screening test is nonetheless considered essential as most blood transfusion services provide some blood components that are either stored above +20°C or are not stored below +20°C for sufficient time to kill any organisms present.

Screening

The methods used to identify the presence of syphilis employ the following screening targets:

- Non-specific, non-treponemal markers: antibody to lipoidal antigen (reagin)
- Specific treponemal antibodies.

Treponemal serology is relatively complex with different profiles seen at different stages of infection and depending on whether treatment has been given. Infection with the four major types of pathogenic treponemes cannot be distinguished by serological screening because the major immunodominant epitopes are so similar that the antibodies produced are detected by any specific antibody assay for syphilis.

In general, syphilis assays can be divided into specific and non-specific assays; their use depends on whether the purpose of testing is screening or diagnostic testing.

Specific assays

Specific assays commonly used for blood screening are *Treponema pallidum* haemagglutination assays (TPHA) and enzyme immunoassays (EIAs). These detect specific treponemal antibodies and thus identify donations from anyone who has ever been infected with syphilis, whether recently or long in the past, and whether treated or not.

Non-specific assays

Non-specific assays such as Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests identify those individuals who may have been more recently infected. They detect antibodies to cardiolipin or lipoidal antigen (reagin); the plasma levels of these antibodies rise significantly in active infection due to the cellular damage. The use of non-specific assays is of most value in diagnostic testing where it can be used to identify recently infected individuals.

When the incidence and prevalence of syphilis in the blood donor population are high and cannot be reduced through donor selection strategies, it may be necessary to consider screening using a non-treponemal assay (e.g. VDRL or RPR) to identify only the highest-risk donors – those with evidence of recent infections. For routine screening, however, this strategy carries a high risk of false negative results as the sensitivity of these assays is lower than specific assays and the test results may not always be positive, even when the infection is recent.

RECOMMENDATIONS

To minimize the risk of syphilis infection through the route of transfusion:

1 Screening should be performed using a highly sensitive and specific test for treponemal antibodies: either **TPHA** or **enzyme immunoassay**.

2 In populations where there is a high incidence of syphilis, screening should be performed using a non-treponemal assay: **VDRL** or **RPR**.

Table 1: Summary of screening markers, assays and recommendations for the four mandatory transfusion-transmissible infections

Virus	Screening marker*	Assay	Recommendation	Comments
HIV	Anti-HIV (1,2,O)	Immunoassay: ■ EIA ■ CLIA	Recommended	■ Essential for effective HIV screening; screening for HIV antibody is recommended as minimum standard for blood safety ■ Currently the most efficacious assays are combination antigen-antibody assays ■ Specific detection of antibodies to both HIV-1 and HIV-2 is essential
	Anti-HIV (1,2,O)	Immunoassay: ■ Rapid ■ Particle agglutination	May be used in special situations	
	HIV p24 antigen	Immunoassay: ■ EIA ■ CLIA	Recommended only if part of combination antigen-antibody assay	■ First serological marker of HIV infection ■ A valuable target for donation screening although viral antigen is neutralized by antibody ■ Screening for HIV antigen only is not appropriate as levels fall as specific antibody levels rise ■ HIV antigen may be detected at the same time or very soon after first detection of HIV RNA ■ Currently the most sensitive HIV serological assays combine detection of both antigen (p24 antigen) and antibody (anti-HIV-1 and -2). These assays are considered to be the most effective for the serological screening of donations
	HIV RNA	Nucleic acid amplification technology	Evaluate increased safety vs costs and logistics	■ First circulating marker of HIV infection but the window between the detection of HIV RNA and HIV p24 antigen may be short ■ Screening for HIV RNA has been implemented in a number of countries ■ Value of RNA screening is related to serological screening performed and incidence of infection in donors

Virus	Screening marker*	Assay	Recommendation	Comments
Hepatitis B	HBsAg	Immunoassay: ■ EIA ■ CLIA	Recommended	■ First serological marker of HBV infection ■ Significant quantities of HBsAg produced and released into circulation, the majority not associated with viral nucleic acid ■ Essential for effective HBV screening; screening for HBsAg recommended as minimum standard for blood safety
		Immunoassay ■ Rapid ■ Particle agglutination	May be used in special situations	
	Anti-HBc	Immunoassay: ■ EIA ■ CLIA	Not recommended, especially in countries with high HBV prevalence	■ Used as an additional marker in some countries to identify resolving infections when HBsAg has declined below detectable levels but HBV DNA may still be present. ■ May be the only circulating marker of infection at that point ■ Assays may lack specificity and specific confirmation is not available ■ Anti-HBs levels should be determined for all anti-HBc reactive donations to identify resolved infections ■ Accepted in many countries that donations that are both anti-HBc reactive and have an anti-HBs level >100 mIU/mL are suitable for clinical use
	Alanine amino-transferase	Biochemical assay	Not recommended	
	HBV DNA	Nucleic acid amplification technology	Evaluate increased safety vs costs and logistics	■ First circulating marker of HBV infection, but with limited usefulness in blood screening unless individual donation testing is performed ■ Virus is generally low-titre and the window between the detection of HBV DNA and HBsAg is generally very short

Virus	Screening marker*	Assay	Recommendation	Comments
Hepatitis C	Anti-HCV	Immunoassay: ■ EIA ■ CLIA	Recommended	■ Currently the most commonly used serological marker of HCV infection ■ Appears in response to infection, but window period from first appearance of viral RNA may be relatively long ■ Screening for HCV antibody recommended as minimum standard for blood safety
		Rapid	May be used in special situations	
	HCV antigen	Immunoassay: ■ EIA ■ CLIA	Recommended only if part of combination antigen-antibody assay	■ First serological marker of HCV infection ■ A valuable target for donation screening although viral antigen is neutralized by antibody ■ Screening for HCV antigen only is not appropriate as levels fall as specific antibody levels rise ■ HCV antigen may be detected at the same time or very soon after first detection of HCV RNA ■ Very limited assay availability ■ The most sensitive HCV serological assays combine detection of both antigen and antibody. These assays are considered to be the most effective for the serological screening of donations although currently only a limited number of assays are commercially available
	HCV RNA	Nucleic acid amplification technology	Evaluate increased safety versus costs and logistics	■ First circulating marker of HCV infection but the window between the detection of HCV RNA and HCV antigen may be short ■ Screening for HCV RNA has been implemented in a number of countries, primarily for the safety of plasma for fractionation ■ Value of RNA screening is related to serological screening performed and incidence of infection in donors

Virus	Screening marker*	Assay	Recommendation	Comments
Syphilis	Antibody to *Treponema pallidum*	■ Particle agglutination (TPHA) ■ Immunoassay (EIA)	Recommended	■ First specific serological marker of syphilis infection ■ Essential for effective syphilis screening; screening for specific treponemal antibody recommended as minimum standard for blood safety
	Antibody to lipoidal antigen (reagin)	■ VDRL ■ RPR	Consider when high incidence of syphilis	■ First serological marker of syphilis infection ■ Do not detect syphilis specific antibody ■ Lack sensitivity and specificity

Note

* Markers of infection that are potential screening targets

4.3 TRANSFUSION-TRANSMISSIBLE INFECTIONS FOR WHICH UNIVERSAL SCREENING IS RECOMMENDED IN SOME COUNTRIES OR FOR WHICH SELECTIVE SCREENING IS RECOMMENDED

Infections such as malaria, Chagas disease and the human T-cell lymphotropic viruses I/II (HTLV) may present a greater risk in certain regions and countries, even though there is not the same level of risk across the world. Each country should assess whether any bloodborne infections in addition to HIV, HBV, HCV and syphilis also pose a significant threat to the safety of the blood supply owing to their biology, incidence and/or prevalence in the general population and the subsequent risk of the presence of this infection in blood donors:

- In endemic areas, specific risks include the transmission of malaria, Chagas disease and HTLV
- In non-endemic areas, specific risks are posed by the donation of blood by individuals who have lived in or visited areas that are endemic for malaria, Chagas disease or HTLV
- Specific recipient groups are at risk from the transmission of certain infections such as human cytomegalovirus (CMV).

Reliable epidemiological data are needed to assess the specific risks of transmission by transfusion and of resultant disease. Screening for other TTIs should be considered when there is clear evidence that the safety of the blood supply would be significantly compromised without their inclusion in the screening programme. It should not be implemented until systems are already in place to ensure that all donations are screened for the four major bloodborne infections in a quality-assured manner.

The following issues require consideration before the introduction of screening for TTIs in addition to HIV, HBV, HCV and syphilis:

- Is the infectious agent readily transmissible through the transfusion of infected blood or blood products?
- Could the infection result in severe morbidity or mortality in recipients?
- Is the infection widespread or endemic to the country or region?
- Can blood donors at risk of the specific infection be identified and deferred through the donor selection process?
- Is the infectious agent identifiable by blood screening?
- Is an effective screening assay readily available that can specifically identify infected donations?
- What are the benefits of screening for an additional TTI in relation to resource and logistics requirements?
- What might be the impact on the blood supply if such a test is introduced?
- Are confirmatory assays available to distinguish between true and false positive results?

If indeed considered to be a risk, the specific target marker(s) of the infection then needs to be identified, the appropriate screening strategy and algorithm developed and suitable assays sought.

4.3.1 Malaria

Agent

Malaria is caused by parasites of the *Plasmodium* species. There are four main types that infect humans: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Malaria is primarily transmitted to humans through the bite of the female anopheles mosquito.

Although always of concern in endemic countries, malaria is increasingly also a matter of concern to blood transfusion services in non-endemic countries. Significant numbers of blood donors from non-endemic countries travel regularly in malarial areas and there is wide migration from endemic areas to non-endemic areas where migrants may then become donors. Malaria is gradually spreading into non-endemic areas or regions where it had previously been eradicated.

Transmissibility

Although primarily transmitted by mosquitoes, malaria is readily transmitted by blood transfusion through donations collected from asymptomatic, parasitaemic donors. The parasite is released into the bloodstream during its lifecycle and will therefore be present in blood donated by infected individuals. The parasites are stable in plasma and whole blood for at least 18 days when stored at +4°C and for extended periods in frozen state.

Screening

There are a number of potential targets for malaria screening and the selection of screening method may depend on whether it is endemic in the country or not. The methods used to identify the presence of malaria employ the following screening targets:

- Direct detection of parasite by thick film
- Serological markers:
  - — Antibody
  - — Antigen.

Endemic countries

In endemic countries, direct detection of parasite by thick film is often used to identify parasitaemic donations. However, the technique is time-consuming, highly operator-dependent and prone to error. Consequently there is a risk that this approach will not detect lower levels of parasitaemia where transmission may still occur.

High quality, sensitive malaria antigen assays are now readily available and may be better able to identify parasitaemic donations, including those with much lower levels of parasites than are reliably detectable by thick film (*39*). However, in endemic countries, if screening is even considered, screening strategies are generally complex, combining specific criteria for donor selection and deferral, based on the season, geography and availability of anti-malarial prophylaxis, with laboratory-based screening.

Non-endemic countries

In non-endemic countries, the detection of specific antibody is effective for the screening of donations from individuals identified to be at risk of transmitting malaria. In virtually all cases, the deferral of risk individuals for a period of six months from the date of the last potential exposure combined with malarial antibody testing will prevent the transmission of malaria (*39*).

RECOMMENDATIONS

Endemic countries

To prevent malaria infection through the route of transfusion in endemic countries:

1 Donor selection criteria should be developed to identify and collect blood from donors at the lowest risk of infection, both during the malaria season and during the rest of the year.

2 Donor selection and deferral strategies should be implemented to identify those donors with a current history of malaria or a specific identifiable exposure risk, such as travel to malarious areas. These donors should be deferred for a period defined by the country.

3 Donor selection and deferral strategies should be developed to identify donors with a history of current malarial infection and defer them for a period of six months after symptoms or treatment have ceased.

OR

All donations should be screened for parasitaemia using thick blood films or for evidence of malarial antigen using a highly sensitive **enzyme immunoassay**.

4 Transfusion should be followed by the administration of appropriate and effective malarial prophylaxis to all recipients or at least to those recipients at risk of significant disease as a result of transfusion-transmitted malaria.

Non-endemic countries

To prevent malaria infection through the route of transfusion in non-endemic countries:

1 Donor selection and deferral strategies should be implemented to identify those donors with a current history of malaria or a specific identifiable exposure risk, such as travel to malarious areas. These donors should be deferred for a period defined by the country.

2 If screening tests are available:

(a) All donors with a history of malaria should be temporarily deferred until six months after symptoms or treatment have ceased and then may be re-instated as donors if there is no evidence of malarial antibody using a highly sensitive **enzyme immunoassay**.

(b) All donors with an identified malaria exposure risk should be temporarily deferred for a period of six months from their last return from a malarious area and then may be re-instated as donors if there is no evidence of malarial antibody using a highly sensitive **enzyme immunoassay**.

4.3.2 Chagas disease

Agent

Chagas disease is caused by the parasite *Trypanosoma cruzi*. Chagas disease is transmitted primarily when the parasite contained in droppings of an infected bug enters the bloodstream through the bite of the primary host, a reduvid bug. However, it can also be transmitted from human to human through the parenteral route by the transfusion of blood or transplantation of tissues from an infected individual.

Chagas disease is geographically restricted and endemic only in Central and South America and parts of Mexico. It is estimated that up to 30% of infected adults die from the chronic effects of Chagas disease in some areas. Up to 20% of infected individuals remain asymptomatic for long periods.

Effective vector control is an important factor in the reduction of the risk of Chagas disease. This has the effect of reducing the disease burden in the population and so reducing the incidence of infections in blood donors. Vector control has proved to be effective in a number of countries in Central and South America, in some resulting in the eradication of all cases of insect-borne infection. Some Latin American countries have eliminated incident cases of primary infection, although a reservoir of infected individuals still remains in the population.

Transmissibility

Although primarily transmitted by an insect vector, Chagas disease is readily transmitted by the transfusion of blood donated by asymptomatic parasitaemic donors. The parasite is released into the bloodstream during its lifecycle and will therefore be present in donated blood from infected individuals. The parasites are stable in plasma and whole blood for at least 30 days when stored at +4°C and for extended periods in frozen state.

Chagas disease is a major concern in endemic countries. It is also of concern to blood transfusion services in some non-endemic countries to which significant numbers of blood donors migrate from regions where Chagas disease is still endemic or where donors travel regularly to endemic areas. Sporadic primary infections have been reported in the southernmost states of the USA. Although not a global problem, many countries have to deal with blood donors who have travelled in Central and South America and therefore need to develop strategies to address this problem.

Screening

Screening for Chagas disease involves the detection of anti-*T. cruzi* in the donated blood. There are a number of sensitive and reliable assays available and the serology of *T. cruzi* is well understood (*40*). In addition, there are antigen detection assays, nucleic acid amplification technology and even xenodiagnosis, although this is clearly not suitable for blood screening.

RECOMMENDATIONS

Endemic countries

To prevent the transmission of Chagas disease through the route of transfusion in endemic countries:

1 Screening should be performed using a highly sensitive **Chagas antibody enzyme immunoassay**.

Non-endemic countries

To prevent the transmission of Chagas disease through the route of transfusion in non-endemic countries:

1 All donors with a history of Chagas disease should be permanently deferred.

2 If screening tests for Chagas disease are not available, all donors with an identified risk of Chagas disease should be identified and permanently deferred.

3 If screening tests for Chagas disease are available, all donors with an identified risk of Chagas disease should initially be deferred for six months since their last return from an endemic area. Their subsequent donations should then be screened for evidence of infection using a highly sensitive **Chagas antibody enzyme immunoassay**.

4.3.3 Human T-cell lymphotropic viruses I/II

Agent

The human T-cell lymphotropic (or leukaemia) viruses I/II (HTLV) are enveloped, single-stranded RNA retroviruses. HTLV is transmitted by the parenteral route and may be found in blood, normally in lymphocytes, and in other body fluids. It is generally not found in plasma or cell-free body fluids.

HTLV is endemic in parts of the world but, in some regions, its incidence and prevalence are low or it may be totally absent. HTLV-I and HTLV-II are two very similar but distinct viruses which are generally considered together because of their similarities. The specific differences include their geographical distribution and clinical disease association. HTLV has a high prevalence in some groups of injecting drug users.

Transmissibility

While HTLV is present in the bloodstream, the levels of the virus itself are variable. In recently infected individuals, virus may be found free in the plasma. Subsequently, free virus is rarely found, the virus being present in the T-lymphocytes. The infectivity of blood and products is reduced but not removed by leucodepletion. As infection is considered to persist for life, screening for anti-HTLV identifies donations that may transmit HTLV but does not in itself indicate the timescale of an infection. However, there is evidence that the pathogenicity of transfusion-transmitted HTLV is low, except in severely immunodeficient recipients (*41–43*).

HTLV is always of concern in endemic countries as well as to blood transfusion services in a number of non-endemic countries. There is significant migration from endemic areas to non-endemic areas where migrants may then become blood donors. In addition, a low level of incident infection may be introduced into a non-endemic country through migration, and the infection may spread horizontally into the non-migrant population or vertically to the children of migrants that were conceived in the non-endemic country.

Screening

HTLV screening involves the detection of specific antibody to both HTLV-I and HTLV-II. Although there is cross-reactivity between HTLV-I and II in a similar way to HIV-1/2, it is incomplete; cross-reactivity to HTLV-I cannot be relied on to

detect all cases of HTLV-II. Antibody levels are generally high and, even though the response may vary, antibodies generally persist at a detectable level for life following resolution of the initial acute infection. Combined anti-HTLV-I and -II assays are effective in identifying potentially infectious donations.

RECOMMENDATIONS

To prevent the transmission of HTLV-I/II through the route of transfusion:

1 In countries in which HTLV is endemic, decisions on introducing screening for HTLV-I and -II should take into consideration the impact on the blood supply.

2 When implemented, screening for specific anti-HTLV-I/II should be performed using a highly sensitive **HTLV-I/II antibody enzyme immunoassay**.

3 Countries in which HTLV is non-endemic should consider screening for evidence of HTLV-I and -II infection prior to the release of blood and blood components for clinical use.

4.3.4 Human cytomegalovirus

Agent

Human cytomegalovirus (CMV) is a herpesvirus, an enveloped DNA virus. CMV is transmitted by the parenteral route and may be found in blood and other body fluids. It is endemic in many parts of the world, although in some regions its incidence and prevalence have declined in recent years as living standards have improved.

Transmissibility

HCMV circulates in the leucocytes and free in plasma during active infection. It subsequently persists latently in leucocytes as well as in other non-circulating body cells and may be released into the bloodstream following reactivation of latent virus. It is thus readily transmitted by blood transfusion, although transmission is generally a concern only when transfusing immunocompromised individuals.

As leucocytes are one of the sites of latency of CMV, pre-storage leucodepletion has been proposed as an additional means of minimizing the risk of CMV transmission. However, while some studies have demonstrated that leucodepletion is just as effective as anti-CMV screening, these have been conducted in populations with a low incidence of CMV infection (*44–45*). In addition, this approach has only been possible where the decision had already been made to introduce leucodepletion for other reasons.

In populations with a higher incidence of CMV, there is a correspondingly higher risk of blood being donated by viraemic individuals. In such cases, leucodepletion will not prevent transmission. Thus, for the majority of countries, anti-CMV screening is still central to the prevention of post-transfusion CMV.

Screening

CMV screening involves the detection of specific antibody to CMV. Antibody levels are generally high and, even though titres may vary, antibodies generally persist at a detectable level for life following resolution of the initial infection.

RECOMMENDATIONS

To prevent the transmission of human CMV infection through the route of transfusion:

1 CMV-screened whole blood and blood components are not required for immunocompetent individuals.

2 All whole blood and apheresis donations intended for transfusion to immunosuppressed individuals, neonates and pregnant women should be screened for evidence of CMV infection prior to the release of blood and blood components for clinical use.

3 Screening should be performed using a highly sensitive **CMV total antibody enzyme immunoassay**.

4 Only CMV antibody negative donations should be used for the transfusion of immunosuppressed individuals.

OR

5 In the absence of screening, selective leucodepletion may be considered.

4.4 EMERGING AND RE-EMERGING INFECTIONS

Every blood screening programme has to face ongoing challenges. Reports of newly identified infections or re-emerging infections appear regularly in the scientific literature, including reports of their transmission through the route of transfusion. Examples include variant Creutzfeldt Jakob disease, West Nile virus, babesiosis, dengue and chikungunya. There are also infections for which there is a theoretical risk of transmission, but where no cases of transmission have yet been identified or proven, such as severe acute respiratory syndrome (SARS).

While it is likely that new infections will be identified that may be transmissible through transfusion, a cautious and measured response is needed to any apparent new or re-emerging threat to blood safety. Blood transfusion services should develop contingency plans that ensure surveillance for emerging infections, assessment of their transmissibility by transfusion and the actual likelihood of transmission, the diseases associated with transmission, and action to be taken in the event of increasing incidence of infection, including to pandemic level. These plans should also address the potential effects of infection on donors and donor sufficiency, potential recipients, BTS staff and other healthcare staff (*46*).

Before any consideration is given to introducing screening for a new infection, some important factors need to be taken into account.

1 Universal screening for HIV, hepatitis B, hepatitis C and syphilis should be in place throughout the country and screening should be applied effectively and consistently in accordance with national standards. Disparities in the standards and quality of screening across a country should be resolved before consideration is given to the introduction of screening for any additional infections.

2 The actual threat to blood safety should be properly evaluated. The incidence and prevalence of the new infection in the general, blood donor and patient populations should be determined. The disease

process associated with the infection needs to be understood, together with its potential impact on the population as a whole and the impact of its transmission by transfusion.

3 An appropriate screening assay or assays must be available. The technology should be compatible with the current screening strategy and programme, and the resources should be available to implement it. In addition, the ability to confirm reactive results obtained on blood screening should be taken into consideration.

RECOMMENDATIONS

1 Laboratory screening for any potential or known transfusion-transmissible infection, other than for the four mandatory infections, should be considered only if:
   - There is a proven risk of transmission of infection to recipients
   - The transmission carries a significant disease risk
   - An appropriate screening assay is available.

2 Blood screening programmes should include strategies for confirmatory testing and blood donor management.

3 When there is a *proven* risk of transfusion-associated transmission but no appropriate screening assays are available, donor selection criteria **should** be developed to identify and defer potentially infected donors for an appropriate period of time.

4 When there is a *theoretical* risk of transfusion-associated transmission and no appropriate screening assays are available, donor selection criteria **may** be developed to identify and defer potentially infected donors for an appropriate period of time.

4.5 CLINICALLY INSIGNIFICANT TRANSFUSION-TRANSMISSIBLE INFECTIONS

A number of clinically insignificant infections may, on rare occasions, be transmitted by transfusion. These include:

1 Infections that are not normally transmitted parenterally, but may be transmitted if the blood donor is infected and has a high level of the infectious agent in the bloodstream at the time of donation: e.g. hepatitis A virus (HAV).

2 Infections that, in theory, can be transmitted, but which are transmitted only very rarely at a significantly lower level than the prevalence or incidence of the infection in the population: e.g. parvovirus B19.

3 Infections that may be transmitted more frequently, but which then do not give rise to any clinical disease in the recipient: e.g. TT virus.

Routine screening for such infections is generally not practical or cost-effective. The screening tests available, if any, may not be appropriate for blood screening, often being designed primarily to aid the diagnosis of infection in symptomatic individuals. In these situations, the donor selection process is a significant factor in the exclusion of those donors who might harbour these infections in order to prevent them from entering the blood supply.

5 Blood screening, quarantine and release

5.1 BLOOD SCREENING PROCESS

The screening of donated blood and the quarantine of blood and blood components represent critical processes that should be followed to ensure that blood units are safe. Based on the screening results, they should either be released for clinical or manufacturing use or be discarded. Laboratory screening for TTIs should be performed on blood samples collected at the time of donation. All tests on blood samples should be performed and recorded in accordance with standardized procedures in laboratories that are properly equipped to undertake them.

All blood samples, donations and components should be correctly labelled to ensure correct identification throughout the screening process. The BTS should also have appropriate, validated systems for linking all test results to the correct donations and donors so that donors' records can be reviewed each time they come to donate. These systems will ensure that the correct results are allocated to each donation and prevent errors resulting in the transfusion of an unsafe unit.

Laboratory staff should always adhere to the national screening strategy, algorithm and standardized procedures when conducting the tests and analysing the results. The performance of laboratory tests in a quality environment with competent staff and a functional documentation system will minimize the risk of analytical and transcription errors, particularly false negative results.

The objective of blood screening is to detect markers of infection in order to prevent the release of infected blood and blood components for clinical use. Blood screening strategies are designed to assure the safety of blood units, but should not be used for notifying blood donors of reactive test results. The appropriate confirmatory testing strategy for blood donor management should be applied before notifying donors of their infectivity status (see Section 6). The results of all tests performed for infection markers for TTIs and blood group serology should be evaluated when making final decisions on the release of blood units for therapeutic use.

5.2 APPROACHES TO BLOOD SCREENING

Two approaches to blood screening are recommended for blood safety, depending on whether or not an effective quality system has been established in the laboratory in which the testing is carried out (see Section 7). These options represent the processes recommended for screening blood for each TTI in laboratories where:

1 Quality systems are weak or have not yet been established.

OR

2 Effective quality systems are in place.

The assay selected for blood screening should be **highly sensitive** and specific. The aim is to detect all possibly infected donations while minimizing wastage due to false positive results. Donations that yield **reactive** or **indeterminate** test results should be discarded using methods in accordance with standard safety precautions (*47*).

Option 1: In laboratories *without* well-established quality systems

1 Use a single assay (A) and test each blood sample singly in accordance with standard operating procedures. The assay should have been validated for the specific TTI.

2 Collate and analyse the results of the assay. If a result is non-reactive (A–), the blood unit can be released for clinical use.

3 If a blood sample is initially reactive for a TTI (A+), immediately segregate and then **discard** the blood donation and all blood components derived from it.

Note: The decision not to use the reactive donation is taken on the basis of one test. However, to exclude technical error and any possibility of mix-up of samples at any stage, the test on an initially reactive donation may be repeated in duplicate, either using the same sample or a sample from the tubing attached to the blood donation, and using the same assay.

If any discrepancy in the results is identified, a thorough investigation should be undertaken and corrective actions taken to prevent the release of an unsafe unit of blood.

Option 2: In laboratories with established quality systems

1 Use a single assay (A) and test each blood sample singly in accordance with standard operating procedures. The assay should have been validated for the specific TTI.

2 Collate and analyse the results of the assays. If a result is non-reactive (A–), the blood unit can be released for clinical use.

3 If a blood sample is initially reactive for a TTI (A+), immediately segregate the blood donation and all blood components derived from it.

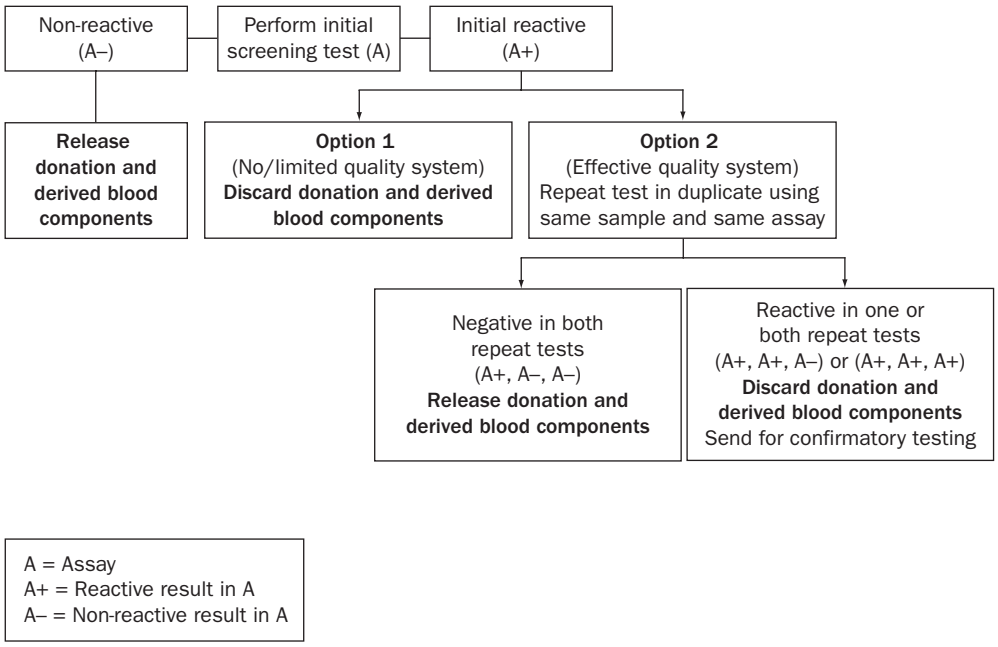
4 **Repeat test** in duplicate, from the same sample and using the same assay.

5 Analyse the results of the repeat tests:

- If both repeat tests are non-reactive (A+, A–, A–), the initial result could be due to false reactivity or technical error and the donation can be released for clinical use
- If one or both of the repeat tests are reactive (A+, A+, A–)/ (A+, A+, A+) immediately segregate and then **discard** the blood donation and all blood components derived from it. Send the sample for confirmatory testing.

The algorithm shown in Figure 1 shows the decision points on whether the blood and blood components should be released or discarded, based on the screening results, and whether confirmatory testing should be performed for blood donor management and epidemiological monitoring (see Section 6).

Figure 1: Algorithm for blood screening



5.3 POOLING FOR SEROLOGICAL ASSAYS

The pooling of samples before testing has been the subject of debate for some years. It has been considered to be a cost-saving measure, but any cost savings have to be balanced against the risk of failing to detect a positive donation. This is likely in some assays where sensitivity is compromised in diluted sample. In a pooled sample each individual sample is diluted. There is also a high risk of errors being made as a result of poor quality procedures during the preparation of the pool and when recording individual samples in each pool. An additional complication is the resolution of pools that test positive and the subsequent delay in releasing the units that comprise the pool. The pooling of samples for serology testing is therefore not recommended for a blood screening programme.

5.4 SEQUENTIAL SCREENING

Blood transfusion services routinely screen for TTI markers (HIV antigen-antibody, HBsAg, anti-HCV and syphilis) at the same time. The main reason for this is to reduce the time needed for screening so that the blood or blood components, especially labile components such as platelets, can be released in a timely manner. Initially reactive donations are segregated and quarantined. Depending on the algorithm used by the laboratory, the donation is then either discarded or repeat testing is performed.

Some laboratories may use sequential screening by initially testing for one or two infection markers. If a reactive result is obtained, no further testing is performed on this donation. The screening strategy for determining the test or tests that are undertaken first will be influenced by the prevalence of infections in the blood donor population. Sequential screening is sometimes used in countries where the prevalence of one TTI is higher than others; for instance, HBsAg might be screened for first when the prevalence of hepatitis B is higher than the prevalence of HIV and HCV. In this situation, only HBsAg negative donations would then be

tested for HIV antigen-antibody, anti-HCV and syphilis. No tests for these viral markers would be performed on the donations that test reactive on the HBsAg screening test. Thus there is potential for cost savings, especially if the more expensive assays do not need to be performed on donations that have already tested positive for HBsAg.

While sequential testing may be perceived to have economic benefits, the potential cost savings need to be balanced against factors such as the increased turnaround time for results and increased staff costs owing to longer shifts. It may result in delays in screening and releasing blood and blood components, leading to poor blood stocks, especially if there are chronic shortages. Another disadvantage of this strategy is that donors with co-infections (i.e. with more than one infection) will not be identified and cannot, therefore, be notified and counselled about these additional infections as part of the duty of care towards blood donors. Sequential testing could also increase the possibility of mix-ups and errors owing to frequent handling of blood samples, donations or the components derived from them. In centres with limited or no quality systems, this might lead to an increased risk of untested or unsafe units being transfused. The opportunity to study the epidemiological profile of infections in donors will also be lost. Sequential screening is therefore not recommended for a blood screening programme.

5.5 BLOOD SCREENING AND DIAGNOSTIC TESTING

In general, there is no difference between screening and diagnostic assays themselves; the differences lie in the reasons for the testing, the population being tested, the interpretation of the results and the subsequent actions. The screening algorithms used and the focus of quality systems may also differ as blood screening is product-related and diagnostic testing is not.

Microbiological screening of blood is performed on donations from apparently healthy, asymptomatic donors to rule out the presence of infections and assure safe blood for transfusion. Diagnostic testing is performed as part of a clinical investigation to pursue a diagnosis of infection either as a result of signs and symptoms in an individual or a specific or identifiable risk of infection.

Blood screening involves a single test with the resultant action, such as the release or discard of the donation arising from that single test alone, even though an initially reactive result may be followed by repeat testing. Diagnostic testing often involves additional testing over a period of time either to pursue the diagnosis in early infections or to follow-up or monitor infection. A single test result alone is not relied upon to determine infection or subsequent actions.

Diagnostic samples are high-risk samples as they are generally taken from symptomatic patients; they should not be mixed with blood samples from blood donors. In hospital-based blood services, diagnostic testing facilities should be separate from those used for blood screening.

5.6 EMERGENCY SCREENING

In emergency situations in which blood and blood components are needed urgently, but are not readily available from blood inventory, screening with rapid/simple single-use assays could be used to obtain results quickly and enable blood to be released for clinical use in consultation with the prescribing clinician.

Wherever possible, however, the blood sample should be retested as soon as possible using an EIA or another assay used routinely for blood screening in the laboratory in order to check the validity of the test results. Any discrepant results should immediately be investigated further and corrective action taken, including communication with the clinician who has prescribed the blood. Countries should work towards systems that avoid these situations.

5.7 SCREENING PLASMA FOR FRACTIONATION

In blood transfusion services where plasma is collected for fractionation, either as recovered plasma (whole blood) or as source plasma (apheresis), the screening requirements and algorithm adopted may be different from those needed for blood donations for clinical use. Plasma for fractionation may require additional screening tests, depending on its source and the regulatory requirements applied to the fractionation facility. Such requirements may be national or international, depending on the location, ownership, nature and scale of the facility.

5.8 PRE-DONATION TESTING

The testing of blood donors for TTIs before they donate blood (pre-donation testing) is the subject of debate. It is sometimes considered to be a cost-saving measure, particularly in high-prevalence situations. However, pre-donation testing of the donor does not ascertain the infectious status of the donation and will need to be followed by tests on the blood sample collected during the blood donation process. Pre-donation testing may lead to a wastage of resources and increased screening costs unless prevalence is extremely high. It increases the time taken for a donor to donate blood, causing undue inconvenience to donors, and also the risk of discrimination and stigmatization. The practice of pre-donation testing could undermine the long-term development of a sustainable blood donor programme based on well-selected voluntary non-remunerated blood donors who donate regularly.

All screening of blood donations for TTIs should be carried out only on samples taken during the donation process and in a quality controlled environment. In an effective national blood screening programme, pre-donation testing of blood donors has limited applicability. In settings where the prevalence of an infection is very high and donor selection would not be effective in reducing prevalence in first-time donors, pre-donation testing may be useful as an interim strategy while building a stable pool of regular voluntary non-remunerated donors.

5.9 QUARANTINE OF BLOOD AND BLOOD COMPONENTS PRIOR TO RELEASE OR DISCARD

A quarantine system should be in place for the physical segregation of all unscreened donations and their blood components until screening for infection markers has been completed and the suitability of donations for therapeutic use has been determined. A system should be in place to ensure that screened and unscreened units are stored in separate blood storage equipment to prevent the issue of unscreened units. All reactive or positive donations and all components derived from these donations should be labelled “Not for transfusion” and segregated for discard or non-clinical use.

The BTS should ensure that separate blood storage equipment is clearly designated for:

- Unscreened units
- Reactive/positive units
- Unresolved/indeterminate units
- Units suitable for clinical use: i.e. available blood stock.

There should be a fully documented system that identifies the current location and eventual fate of all blood and blood components, whether destined for clinical use or disposal. The BTS should also have documented policies and procedures to deal with the emergency release of blood components prior to all screening being completed.

Reactive or positive units of blood or plasma are valuable resources for quality control samples and panels, evaluations and validations, and for research purposes. Blood screening laboratories can provide blood or plasma to be used as reagents to institutions involved in research or to quality assessment schemes for the production of proficiency panels.

5.10 RELEASE OF BLOOD AND BLOOD COMPONENTS

Only blood and blood components from donations that are non-reactive for all markers screened for should be released for clinical or manufacturing use. When all the required blood screening tests have been performed, the results have been checked and any other required checks have been made, formal release procedures can be undertaken to release quarantined units and physically move the released blood stock from one location to another. The BTS should have appropriate systems for labelling the blood and blood components as ready for clinical use. The label on each blood unit should contain the relevant details of the donation and the tests carried out on the donation. When this has been carried out, the screening process is considered to be complete.

All reactive units should be removed from the quarantined stock and stored separately and securely until further handling.

5.11 LONG-TERM STORAGE OF DONATION SERUM/PLASMA SAMPLES

The long-term archiving of donation serum/plasma samples can be very useful for a BTS in facilitating the investigation of adverse transfusion events and transfusion-transmitted infections or the evaluation of new screening assays or reagents. However, archiving should be considered only if adequate and suitable resources are available, including sufficient space and efficient paper-based or software-based warehousing systems to manage sample retrieval.

A number of crucial issues should be considered before building a sample archive. These include:

- System for the identification and history of each sample in the archive related to its use and length of time of storage
- Type of storage containers required
- Specified temperature at which samples are to be stored
- Volume of samples to be archived
- Criteria and documentation of the reasons for the recovery of an archive sample.

6 Confirmatory testing and blood donor management

6.1 CONFIRMATORY TESTING STRATEGIES

Confirmatory testing for TTIs is carried out for different purposes from those for blood screening. While the purpose of screening donated blood is to ensure the microbial safety of the blood supply, confirmatory testing is performed to confirm the infectious status of donors deferred on the basis of repeat reactive screening tests, allowing the appropriate action then to be taken. It is also used to obtain accurate epidemiological data on infections in the blood donor population.

Effective confirmation requires appropriate and well-designed confirmatory strategies for each TTI, including the selection of assays and algorithms for the analysis and interpretation of results (*48*). Special equipment and advanced training are also required. Confirmatory testing should be undertaken by a reference laboratory unless considerable expertise and resources are available within the BTS itself. It is important, however, that the laboratory recognizes the difference between diagnostic testing and blood screening and that this is reflected in its confirmatory strategy. All quality requirements pertaining to screening assays apply equally to confirmatory assays.

The algorithm shown in Figure 2 represents the minimum processes recommended for blood donor management and epidemiological monitoring based on initial screening and confirmatory testing. It relates to blood screening strategy 2 for laboratories where effective quality systems are in place. The algorithm shows the decision points on whether the donor should be accepted, deferred or referred, based on the results of confirmatory testing, but may not be sufficient on its own for the true infectious status of the donor to be confirmed.

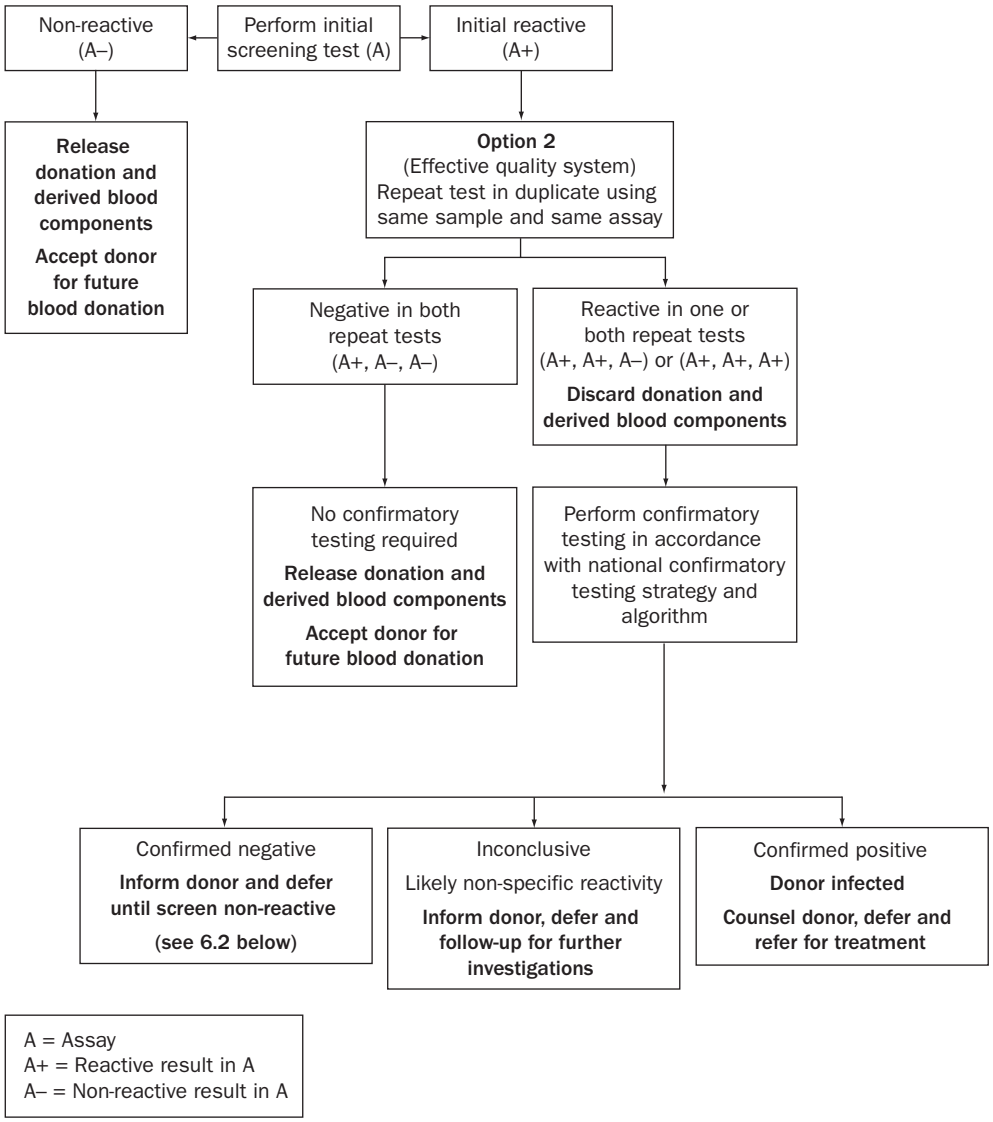
6.2 INTERPRETATION AND USE OF CONFIRMATORY RESULTS

Confirmatory testing is primarily concerned with the status of the donor and the subsequent action to be taken. Donations that are repeat reactive may be confirmed as being of negative, inconclusive or positive status:

- A negative conclusion on confirmatory testing indicates that the donor is not infected with the specific infection. However, a donor showing repeat reactive results on screening and negative results on confirmatory testing should be counselled and temporarily deferred until screen non-reactive on follow-up. The donor can then be accepted for future donations.
- An inconclusive outcome is usually due to non-specific reactivity not related to the presence of the infectious agent. The donor should be counselled, deferred for blood donation and followed-up for further investigations.
- A positive conclusion confirms that the donor is infected and should be deferred from future blood donation, counselled and referred for appropriate medical care.

In low incidence or prevalence countries, a significant proportion of blood donors whose donations give reactive screening results are not truly infected. A considerable number of donors may be lost due to deferral resulting from

Figure 2: Algorithm for blood donor management based on screening and confirmatory testing



non-specific reactivity, especially if a test is not highly specific. Most screening assays currently available from the major international diagnostics companies are of high quality with good sensitivity and specificity, but to ensure high sensitivity there is still some trade-off of specificity. Thus non-specific reactivity needs to be identified and the donors handled appropriately. In addition, truly infected donors need to be identified, counselled and referred for medical care. The confirmatory process also has an important role to play in public health as the close contacts of infected donors need to be protected from the transmission of infection.

Confirmatory testing is an essential component of look-back for ascertaining the true infectious status of the donor and recipients of previous donations. It also provides further benefit to the BTS in the epidemiological monitoring of infection rates in blood donors, thus contributing to a better understanding of donor behaviour and assessment of risk. Knowing and understanding confirmed infection rates in blood donors helps to ensure that donor selection, donor deferral and blood screening strategies are up-to-date and effective.

6.3 MANAGING BLOOD DONORS

The management of blood donors is an essential part of the activities of every blood transfusion service. Donors are the source of the blood and blood components that are processed and released for clinical or manufacturing use. Accordingly, they should be managed in a way that ensures high standards of care and assures them of the concern of the BTS for their health and well-being.

Blood screening and confirmatory testing enable the identification of infected donors or donors with non-specific reactivity or inconclusive results. Even if only limited facilities are available, the blood transfusion service has a duty of care to donors, their families and the general population to ensure that infected individuals are referred for appropriate counselling, treatment and further management as they may infect other individuals if they are not aware of their status. The BTS and relevant authorities should have a clear policy and systems for communicating with these donors and informing them of their status in order to minimize any risk of further transmission. Donors who test negative for TTIs should be encouraged to donate regularly and lead low-risk lifestyles.

6.3.1 Deferral of blood donors

Confirmed positive donors

Donors who are confirmed positive should be deferred from blood donation, notified of their infection status, counselled and referred for clinical management as soon as possible.

Repeat reactive but confirmed negative donors

The handling of repeat reactive donors with non-specific reactivity is a critical part of a screening programme because the selection of suitable screening assays and the use of an appropriate screening algorithm can minimize the unnecessary deferral of donors and loss of donations. Donors showing repeated reactive results on screening and negative results on confirmatory testing should be reassured, counselled and temporarily deferred until non-reactive on follow-up using the same screening assay or a different assay. If negative, they can again be accepted as blood donors.

Inconclusive donors

Donors with inconclusive results present challenges to blood transfusion services and screening laboratories as their management is less clear than with confirmed positive or confirmed negative donors. It is important to decide whether they can be retained on the donor panel or are to be deferred. It is advisable to defer inconclusive donors temporarily, usually for up to six months, explaining the reasons for their deferral. If screen non-reactive and confirmed negative on follow-up, they can be accepted as blood donors in the future.

6.3.2 Post-donation counselling

Informing donors that they are confirmed positive for an infection clearly poses sensitive issues and donors need to be counselled on the results and the actions that should subsequently be taken. Where feasible, the BTS should appoint specialist donor counselling staff and provide referrals to agencies that provide further counselling, treatment and care. If applicable, the BTS should request the donors' own physicians to communicate with them.

Informing donors of non-specific reactivity is highly problematical and should be undertaken with care because this reactivity often varies and usually does not have any impact on the actual health of the individuals. Clear policies on the handling

of non-specifically reactive donors are essential. The permanent deferral of these donors is sometimes considered to be unnecessary, but may be unavoidable unless policies and procedures are in place that recognize variable non-specific reactivity and facilitate the appropriate management of such donors.

Post-donation counselling of donors can provide information on the possible routes of infection and the effectiveness of donor education and donor selection criteria, including why the donor decided to donate, whether they already knew they were infected and whether donor education materials give sufficient information about risk behaviour. This kind of information aids in understanding patterns of infection in "healthy" individuals and can be used to ensure that donor information and education materials are clear and unambiguous. It can also be used to improve donor selection criteria and the donor selection process.

7 Quality systems in blood screening

7.1 THE ELEMENTS OF QUALITY SYSTEMS

Quality systems are crucial for the overall effectiveness of all aspects of the screening programme and in assuring the quality, safety and efficacy of all blood and blood products (*49*). Key elements of a quality system for blood screening include organizational management, quality standards, documentation, traceability, training, assessment and maintenance and calibration. All screening tests should be performed in accordance with defined quality requirements, and all blood donations and blood components prepared from them should be handled appropriately before, during and after laboratory testing. It is the responsibility of the blood transfusion service as well as individual laboratories to implement these standards consistently.

A quality system in a laboratory defines all processes and procedures that should be put in place to ensure effective blood screening. Its implementation minimizes errors and ensures that:

- Appropriate tests are performed on the correct samples
- Accurate results are obtained
- Only screen non-reactive blood and blood components are released for transfusion or manufacturing use
- Screened blood and blood components are available in the blood inventory at all times.

Errors often result from a combination of factors, with the original error being compounded by inadequate checking procedures in the laboratory. Table 2 shows the scope of a laboratory quality system.

7.2 ORGANIZATIONAL MANAGEMENT

The support of senior management is required for developing a quality policy and quality system in each screening facility. A quality manager should be designated in all facilities in which screening is performed. Management should ensure that responsibility, authority, accountability and job descriptions are clearly defined and communicated within the organization. Laboratory managers should review the quality system at planned intervals, including:

- Outcomes of internal and external audits performed
- Non-conformances and follow-up
- Preventive and corrective actions performed in the event of non-conformance
- Staff competency results and error management
- Analysis of quality control results and trends
- Failed runs and retest rates
- Analysis of internal and external quality assessment results and recommendations
- Safe disposal of bio-hazardous waste.

Table 2: Quality systems in the laboratory

General principles	All aspects of policy, management and operations are covered by the quality system
Standards	Standards for blood screening are defined and all screening is performed to these standards
Staffing	There is a sufficient number of staff members with individual job descriptions, appropriate training and periodic assessment of competency
Infrastructure and facilities	Infrastructure and facilities are appropriate for screening activities, enabling work to proceed in a logical sequence
Contract management	Contracts are specifically written for all critical externally supplied goods and services
Assays	Assays are evaluated and validated for use in blood screening
Equipment	Equipment is validated for blood screening before use and is correctly calibrated and used; a regular maintenance and servicing schedule, with records, is implemented by trained operators in accordance with manufacturers' instructions
Procedures	Tests are performed, controlled and documented in accordance with standardized procedures to ensure consistency
Labelling	All blood donations, components and samples are correctly labelled to ensure correct identification throughout the screening process and linkage of results from the individual blood donation to the donor
Documentation	Documentation system is maintained for all significant areas of the service, with specifications, standardized procedures and records for each activity; documentation should be easy to review for changes and accessible to all relevant members of staff
Storage	All donations, blood components, blood samples, test kits and reagents are stored in suitable equipment in which defined storage temperatures and conditions are strictly maintained, monitored and recorded
Quarantine and release	Safe and secure quarantine system is maintained with full documentation of each donation or unit
Errors	Errors and incidents are recorded and corrective and preventive action is taken
Health and safety	Systems are in place to ensure compliance with safety, health and environmental requirements
Assessment	The quality system is assessed to monitor laboratory performance
Inspections, audits and improvements	Pertain to all areas of the screening process and are carried out regularly, using approved procedures
Nonconformance	Encompasses risks or anomalies, whether real, potential or perceived, deviations, complaints, recall and corrective and preventive actions

Management should assess the need for changes to the quality system when deficiencies and opportunities for improvement are identified. Management reviews should specify the actions and resources required to improve the effectiveness of the quality system.

7.3 STANDARDS FOR QUALITY SYSTEMS

Blood screening laboratories should have appropriate quality standards, based on national standards, to ensure process control and valid results. Globally recognized international standards could also be adopted by BTSs to ensure that there is a consistent approach to quality throughout all their activities and to assure the overall safety and efficacy of the blood and blood products prepared for therapeutic use. The standards should take into account relevant existing legislation or other national requirements.

7.4 DOCUMENTATION

A complete set of appropriate documents, including the quality policy, quality manual and standard operating procedures, forms and datasheets should be developed and kept up-to-date. These documents should be used to guide every process, procedure and task to ensure consistency, traceability and accuracy. All processes carried out by the laboratory should be documented and the records kept for traceability. Records include test results, quality control results, batches of test kits and expiry dates. Completed testing forms provide the records of the screening process. There should be a document management system in place for the safe storage, retrieval, archiving and disposal of documents. This system should also ensure confidentiality of records.

The records of donors whose test results are reactive, inconclusive or positive should be marked or flagged to prevent further donations or for further action to be taken, such as follow-up for further investigation or recall for future donations.

7.5 TRACEABILITY

Traceability is a critical part of the quality system in a blood transfusion service. All activities and actions associated with the handling, testing and processing of each donation should be recorded completely and fully linked to the donation, the donor, the fate of the donation and the patient. A fully documented audit trail should be available to demonstrate that each donation has, in fact, been tested and handled correctly and that all test results are valid. To provide this evidence, records and other documents should be stored for a defined period of time; this should be determined nationally in accordance with any relevant existing legislation or other national requirements.

7.6 TRAINING

All staff should be fully trained to perform blood screening to the required standards. Initial and ongoing training should be provided to ensure that the knowledge and competence needed are maintained and further developed, including the ability to perform basic troubleshooting if problems are encountered. Formal training programmes for laboratory managers and technical staff should be established

and reviewed at appropriate intervals. The WHO distance learning materials, *Safe Blood and Blood Products*, provide a useful basis for training, particularly the Introductory Module: *Guidelines and Principles for Safe Blood Transfusion Practice* (*50*) and Module 2: *Screening for HIV and Other Infectious Agents* (*51*).

All training should be conducted in accordance with a national training plan and curricula should be reviewed regularly. Staff should be assessed on a regular basis on their knowledge of policies and their competency in the performance of procedures. Accurate training and competency assessment records should be maintained for each member of staff which will also be useful in assessing ongoing training requirements.

7.7 ASSESSMENT

Ongoing monitoring and assessment, using appropriate parameters, are integral parts of a quality system. In a blood screening programme, assessment may be at two broad levels: at national levels to assess the effectiveness of the programme and individual facility level to assess the effectiveness of blood screening. Data generated at national level can be used to assess the achievement of expected outcomes and to collect information on national indicators. For example, the percentage of donated blood units screened for TTIs in a quality-assured manner is one of the key blood safety indicators used by WHO (*52*) and the United National General Assembly Special Session on HIV/AIDS (*53*).

At the screening facility level, the control of assay performance is the first step in ensuring reproducibility and reliability. Laboratories should record daily quality control data and analyse these data for trends so that any corrective action required can be taken early to maintain the optimum performance of the screening process.

All activities in screening laboratories should be reviewed on a regular basis through self-inspection and internal and external audits. Assessments should pertain to all areas of the screening process and should be carried out using approved procedures to identify areas for improvement and demonstrate that quality systems are being implemented adequately.

For objective assessment of laboratory performance, each laboratory should also participate in external quality assessment (EQA) in which sets of samples for testing are provided regularly by an external laboratory. The results are then submitted back to the external laboratory. Analysis of these results provides useful information on the performance of assays, as well as of each laboratory participating in EQA.

A national haemovigilance system should also be established which includes monitoring, investigation and reporting of TTIs in donors and patients.

7.8 MAINTENANCE AND CALIBRATION

A preventive maintenance programme is essential to ensure that equipment is well-maintained and any potential problems are detected and corrected prior to the machine's breakdown and subsequent downtime. All equipment used for blood screening should be maintained and calibrated regularly and correctly. In general terms, maintenance can be divided into:

- Maintenance performed by users
- Maintenance requiring professional service personnel.

For each item of equipment, daily records should be kept of all the work performed from start-up to shut-down. Daily user maintenance and preventive maintenance, at appropriate intervals, should be carried out in accordance with the manufacturer's instructions. All maintenance activities should be planned and completed on schedule and should be fully recorded. Error records should also be maintained for all equipment.

All equipment and instruments that measure specific parameters should be calibrated and validated at set intervals, in accordance with a planned schedule, to ensure that it provides reliable results. Records should be maintained of all calibration. Only equipment and instruments that have been calibrated to perform volumetric procedures should be used in procedures requiring the aspiration and dispensing of a specified volume.

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Glossary

Apheresis: Procedure that involves withdrawal of blood, ex vivo separation and collection of a desired component (e.g. red cells, plasma or platelets) and reinfusion of the other components.

Audit: Systematic, independent and documented examination to determine whether activities comply with a planned and agreed quality system.

Blood centre: A facility which carries out all or part of the activities for donor recruitment, blood collection (whole blood and, in some cases, apheresis), testing for transfusion-transmissible infections and blood groups, processing into blood components, storage, distribution to hospital blood banks within a defined region, compatibility testing, issue of blood and blood components for clinical use and liaison with clinical services. Blood centres may be stand-alone or hospital-based. The following should NOT be categorized as blood centres:

- Mobile or fixed blood collection sites/rooms which are operated as part of a blood centre
- Hospital blood banks which only store, check compatibility and issue screened blood.

Blood cold chain: The storage and transportation of blood and blood products at the appropriate temperature and conditions from the point of collection to the point of use – "from vein to vein".

Blood donors

- *Voluntary non-remunerated blood donor*: A person who donates blood (and plasma or cellular components) of his/her own free will and receives no payment for it, either in the form of cash, or in kind which could be considered a substitute for money.
- *Family/replacement blood donor*: A person who gives a replacement unit of blood only when a family member or friend requires transfusion.
- *Paid "donor"*: A person who provides blood for money or other form of payment.

Blood product: Any therapeutic substance derived from human blood, including whole blood, labile blood components and plasma-derived medicinal products.

Blood transfusion services (BTS): A generic term to describe blood centres and other facilities that are involved in the provision of blood for transfusion where there is no National Blood Transfusion Service.

Calibration: The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or system, or values represented by a material measure, and the corresponding known values of a reference standard.

Characteristic: Distinguishing feature – ISO 9000 (2000).

Compliance: Meeting required standards.

Conformity: Fulfilment of a requirement – ISO 9000 (2000).

Consistency: Doing the same thing time after time, which makes the outcome more predictable and reduces variations in products and processes.

Correction: Remedial action taken to rectify a non-compliance or other situation in which an error has occurred.

Corrective action: Action taken to eliminate the cause of a detected nonconformity or other undesirable situation – ISO 9000 (2000).

Cross-reactivity: When an antibody recognizes not only its corresponding specific antigen, but also other antigens that may have certain similarities.

Documentation: Written policies, instructions and records involved in providing a product or service.

Effectiveness: Measure of the extent to which planned activities are realized and planned results achieved – ISO 9000 (2000).

Error: An incident where the quality system has failed.

Evaluation: The specific selection process to determine the suitability of a procedure or material (e.g. assay, reagent, equipment).

External quality assessment (EQA): The external assessment of a laboratory's performance using samples of known, but undisclosed, content and comparison with the performance of other laboratories.

External quality assessment scheme (EQAS): A recognized scheme for organizing EQA. This can be a local scheme or organized at national, regional or international levels.

Haemovigilance: A set of surveillance procedures for the monitoring, reporting and investigation of adverse events (reactions and incidents, including near-misses) covering the whole transfusion chain, from the collection of blood and its components to the follow-up of recipients, intended to collect and assess information and to prevent their occurrence or recurrence.

Hospital blood bank: A laboratory or part of a laboratory within a hospital which receives and stores supplies of screened whole blood and blood components from a blood centre. The hospital blood bank performs compatibility testing and issues blood and blood components for clinical use within the hospital. It may be called a hospital transfusion laboratory.

Incidence of infection: The proportion of a defined population becoming newly infected by an infectious agent within a specific period of time.

Infrastructure: System of permanent facilities and equipment of an organization – ISO 9000 (2000).

Inspection: Conformity evaluation by observation and judgement accompanied, as appropriate, by measurement, testing or gauging – ISO 9000 (2000).

ISO: International Organisation for Standardisation.

Monitoring: On-going collection and analysis of information about an activity to assess progress.

National blood transfusion service (NBTS): The organization with statutory national responsibility for the provision of blood for transfusion, and liaison with clinical services. The NBTS coordinates all activities concerned with blood donor recruitment and the collection, testing, processing, storage and distribution of blood and blood products, the clinical use of blood and surveillance of adverse transfusion events. Activities are carried out within a network of national/regional/provincial blood centres and hospital blood banks.

Non-compliance: Not meeting required standards.

Prequalification of assays: A process designed to ensure that assays meet global standards of quality, safety and efficacy. Prequalification consists of a transparent, scientifically sound assessment, which includes dossier review, consistency testing or performance evaluation and site visits to manufacturers.

Prevalence of infection: The proportion of a defined population that are infected with an infectious agent at any particular time.

Preventive action: Action taken to prevent the recurrence of potential non-conformity, defect or other cause of error.

Quality control samples: Well-characterized samples, individual or pooled, that are where possible calibrated against international standards and are diluted in an appropriate matrix.

Screening algorithm: A sequence of steps in the blood screening process to determine the suitability of each unit of donated blood and its components for clinical or manufacturing use. A blood screening algorithm specifies the actual tests to be used and, based on each test result, directs the user to the next step.

Standard operating procedure (SOP): Local written instructions for the performance of a specific procedure in a standardized manner.

Transfusion-transmissible infection: An infection that is potentially capable of being transmitted by blood transfusion.

Validation: Confirmation and provision of objective evidence that the requirements for a specific intended use or application have been fulfilled.

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