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Transfusion of Infectious Agents by Blood Transfusion

Blood transfusion is a lifesaving intervention that has an essential role in patient management within health care systems. It is the responsibility of governments to ensure that safe and sufficient supplies of blood are available and accessible to all patients requiring transfusion. The provision of safe and efficacious blood for transfusion involves a number of processes, including assessment of the suitability of prospective blood donors to donate blood, blood collection, processing, and testing of blood donations, the issue of blood and its transfusion to the patients. Whilst blood transfusion can be lifesaving, there are associated risks, particularly the transmission of blood-borne infections, including human immunodeficiency virus (HIV) (Baggaley, 2006), hepatitis B virus (HBV), and hepatitis C virus (HCV) (Dwyre et al., 2011).

The microbial agents of importance to a blood transfusion services (BTSs) are those that are transmissible by blood transfusion and can cause morbidity and mortality in transfusion recipients. In order to be transmitted by blood transfusion, an infectious agent must be present, in some form, in the donated blood and should have the following characteristics:

- Presence of the agent in one or more components of blood for long periods and in an infectious form.
- Stability at temperatures at which whole blood and blood components are stored.
- Long incubation period before the appearance of clinical signs and symptoms.

- Asymptomatic phase or only mild symptoms in the blood donor, hence not always identifiable during the blood donor selection process.

Any infectious agent meeting all these characteristics can be transmitted by blood transfusion. However, whether transmission actually occurs or not, depends on a number of other factors, particularly on the immune status of the patient and the amount of infectious agent transfused. 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. Many viruses, bacteria, and protozoa can be transmitted by transfusion and new agents that potentially can be transmitted through transfusion continue to emerge (Schmidt et al., 2014).

Markers of Infection

All infections give rise to specific markers that circulate in the bloodstream and which can be used to detect and identify infection and the particular infectious agent. Understanding the biology of infectious agents in general, and particularly the transmissible agents, is very important in determining which markers of infection to screen for. In particular understanding the timing of infection is important in the blood screening process: first, the length of the window period, i.e., the time between infectivity and the first detection of a defined marker of infection; and second, the incubation period, i.e., the time between exposure to infection and the onset of any symptoms of illness. Donors who donate during the window period...
generally pose the greatest threat to blood safety, as despite screening infected donations may not be detectable.

The various markers of infection appear at different times after infection. Each transfusion-transmissible infection (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, in a recently infected individual, the particular screening marker is not yet detectable even though that individual may be infectious. In general, following infection, the nucleic acid of the infectious agent is the first potential screening marker to appear, followed within a few days by antigen, and subsequently by antibody as the immune response to the infectious agent develops.

The extent and range of the screening performed on the blood supply vary greatly from country to country. Sometimes this is simply because of differences in the countries’ needs, but it is sometimes due to financial constraints. As a result, the effectiveness of screening programs also varies. Whatever level of service is provided, however, the main purpose of screening blood is to ensure that the available blood supply is as free as possible from infectious agents by detecting any markers of these infections that may be present before the blood is issued for transfusion.

Not all infectious agents can be detected directly in donated blood. Blood is most often screened for evidence of infection by looking for the presence of specific antibody developed against the infectious agent. Markers of infection can be detected by the presence of the agent itself but, more commonly, by the presence of specific antibodies against the infectious agent. Although the development of antibodies demonstrates the individual’s immune response to the infectious agent and is often considered to reflect immunity to that infectious agent, in the case of many of the TTIs this is not the case, rather it indicates the presence of an infectious agent that may persist indefinitely, sequestered in the body in an active or inactive state, and which if transmitted to another individual may give rise to infection.

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.

**Blood Donor Selection and Screening of Donated Blood for Infectious Agents**

The BTS should assess the potential risks of infectious agents and infections present in its donor population and establish systems for donor selection and donation testing to defer unsuitable blood donors from donation, and to ensure that all donated blood is correctly and appropriately screened for specific TTIs. The key point to remember is that transmission can be avoided in most cases by effective donor selection for assessing donor suitability for blood donation and by screening of donated blood for markers of TTIs. However, at the same time the introduction of biological material from one individual to another is never without risk and there is no such thing as a ‘zero infection risk’; even with effective blood screening there is still a risk (though extremely low) of transmission of infection (Dodd, 2007).

**Blood Donor Selection**

The safest blood donors are generally those who donate voluntarily, regularly, and without remuneration – voluntary nonremunerated donors. These donors are highly motivated and generally have the lowest levels of risk, answer donor selection questions most openly and honestly, and because they donate regularly, they are screened regularly, which would quickly identify any infection process. Most BTS therefore strive to recruit a donor base of such voluntary donors as they provide the lowest level of risk. Conversely the use of family replacement and paid donors may result in increased risk of infection and does not encourage regular donation. Although the basis of the donor supply in a number of countries, is not a situation to be encouraged (World Health Organization, 2012).

The assessment of donor suitability for blood donation, prior to acceptance for donation is the first part of the overall screening process. Although part of this process is to identify risks to the donors themselves, a major part is to identify any specific factors that may indicate that the donor has a higher risk of carrying an infection that may then be transmitted through blood transfusion. The safety of blood donations may thus be affected by donors’ risk of exposure to HIV, HBV, HCV, and syphilis and other TTIs via a number of different routes. These primarily include infection early in life, antenatal, perinatal, and other close contact, sexual contact, and percutaneous exposure through high-risk sexual behaviors, and unsafe blood transfusion and injection practices, cosmetic treatments and rituals. Current or previous country of residence, and travel history also need to be considered as there are a number of transmissible agents that are restricted geographically and therefore are not a threat in every donor/donation.

Donors with such identified risks are deferred from donating, either temporarily or permanently depending on their particular risk(s). Although the laboratory screening of donations for evidence of infectious diseases is the process that actually determines whether donations are released for use, donor selection is an essential part of the overall screening process as it identifies and defers ‘unsuitable donors’ before a donation is collected, thus making a significant contribution to ensuring the safety of those donations that are collected.

**Screening of Donated Blood for Infectious Agents**

Screening for TTIs to exclude blood donations at risk of transmitting infections 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 TTI can reduce the risk of transmission to very low levels. However, some infectious agents are found only in certain parts of the world. The blood screening strategies will therefore be different in the endemic and nonendemic regions.
Each BTS or blood bank laboratory should therefore perform laboratory screening of all donations for evidence of infection by the specific infectious agents that are present in the population from which blood donors are recruited. The specifics of the screening process itself will obviously vary depending on the degree of development of a country’s health care system, the numbers of donations being collected and the infectious agents being screened for. In countries with developed health care systems, screening is largely automated using highly sensitive and specific assays performed within highly controlled systems. However, in countries with less well-developed health care systems and lower numbers of donations more manual approaches are used, which nonetheless, if good quality assays are used and standard operating procedures are followed, also provide an effective screening system.

Whichever screening system is used the outcomes are relatively straightforward. Either a donation is negative on screening or it is reactive on one or more of the screening assays performed. A donation may be reactive on the initial screen and, depending on the screening strategy adopted, may be considered to be unsuitable for clinical use at that point. However, many transfusion services follow a strategy that requires any screen reactive donation (initial reactive) to be retested (often in duplicate) using the same assay. If still reactive (repeat reactive) the donation is considered to be unsuitable for use and discarded, but if negative on repeat testing the donation is considered to be screen negative and released for clinical use. Only nonreactive blood and blood components should be issued for transfusion to patients.

Every blood screening program has to face ongoing challenges. Reports of newly identified infections or reemerging infections appear regularly in the scientific literature, including reports of their transmission through the route of transfusion. Examples include variant Creutzfeldt–Jakob disease (Ludlam and Turner, 2005; Wilson et al., 2000), West Nile virus (Stramer, 2007), babesiosis (Cable and Leiby, 2003), and dengue (Teo et al., 2009). 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 and Chikungunya (Liumbruno et al., 2008).

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 reemerging threat to blood safety. BTS 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 health care staff (World Health Organization, 2011).

**Confirmation of Screen Reactive Results**

An essential subsequent activity is the confirmation of all screening reactive results. It is critical that all screening reactivity is properly and fully investigated to determine the true infection status of the donor.

Any screening program will generate reactive results. In the case of blood donation screening, to ensure as high a level of safety as possible, this will result in the discard of the donation, but the status of the donor must then be determined to decide if either the donor is truly infected and must be referred for clinical investigation and management, or, as is often the case with a low risk donor population, if the screening reactivity is nonspecific and the donor is not infected and may still be able to continue to donate.

The confirmatory testing performed must therefore be able to distinguish between true infection and nonspecific reactivity. There are a number of reasons why confirmation is important; first, if a donor is truly infected then clinical intervention may be required for the donor and all contacts of the donor need to be protected and investigated, as appropriate. Second, if a donor is truly infected, it is important to understand the donor’s specific risk(s) and how the donor selection process failed to identify the donor as high risk and defer them. Thirdly, if the screen reactivity is proven to be nonspecific, it may be possible to reinstate the donor and recall for future donations.

The unnecessary loss of donors due to nonspecific screening reactivity is not acceptable; donors are a valuable resource and must be managed effectively. In many cases nonspecific reactivity is transient and also may be assay specific. As most screen reactivity in low risk populations is nonspecific, there is clearly the potential to permanently, and unnecessarily, lose significant numbers of suitable donors if such donors are not managed correctly.

**WHO Recommendation on Screening of Donated Blood for TTI**

The adoption of blood 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 programs have been implemented, the risk of transmission of TTI has been reduced dramatically over the last 20 years.

**Universal Screening of TTIs of All Donations in All Countries**

Screening for the following four infections that are transmissible by transfusion is recommended as mandatory for the provision of a safe blood supply (World Health Organization, 2010). These infections can cause chronic disease with possible serious consequences and present the greatest infection risk to recipients of transfusion:

- human immunodeficiency virus,
- hepatitis B virus,
- hepatitis C virus, and
- 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 infectious
agents. 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.

WHO recommends that, at a minimum, screening of all blood donations should be mandatory for the following infections and using the following markers:

- HIV-1 and HIV-2: screening for either a combination of HIV antigen–antibody or HIV antibodies.
- Hepatitis B: screening for hepatitis B surface antigen (HBsAg).
- Hepatitis C: screening for either a combination of HCV antigen–antibody or HCV antibodies.
- Trypanosoma pallidum (syphilis): screening for specific treponemal antibodies.

The outcomes of the laboratory screening of blood donations remain the final decision point in the release of blood components for clinical use; however, even with the high quality assays and systems now available, the screening process cannot be considered to be totally effective because:

- An infection in donated blood may not be detected due to the collection of the donation during the window period of infection or failure due to assay sensitivity or error.
- A donor may be infected with an infectious agent for which donations are not routinely screened.
- There are some emerging infections for which screening may not be available or effective (Alter et al., 2007; Alter, 2004; Busch and Kleinman, 2003).

**TTIs for Which Universal Screening Is Recommended in Some Countries or for Which Selective Screening Is Recommended**

Infections such as Plasmodium species (malaria), Trypanosoma cruzi (Chagas disease) (Reesink, 2005), and the human T-cell lymphotrophic 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 blood-borne 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 (Kitchen and Chiordini, 2006) and Chagas disease and HTLV.
- In nonendemic 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.

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 program. It should not be implemented until systems are already in place to ensure that all donations are screened for the four major blood-borne infections in a quality-assured manner.

**Summary**

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

1. All blood donations should be screened for evidence of the presence of infection prior to the release of blood and blood components for therapeutic use.
2. Screening of all blood donations should be mandatory for the following infections and using the following markers:
   - HIV-1 and HIV-2: screening for either a combination of HIV antigen–antibody or HIV antibodies.
   - Hepatitis B: screening for HBsAg.
   - Hepatitis C: screening for either a combination of HCV antigen–antibody or HCV antibodies.
   - Syphilis (T. pallidum): screening for specific treponemal antibodies.
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 nonreactive 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.
8. Confirmatory testing of screen reactive donations should be undertaken for donor notification, counseling, and referral for treatment, deferral or recall for future donation, and look-back on previous donations.

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The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

**See also:** Blood Products; Emerging and Reemerging Infectious Diseases; Hepatitis Viruses; Human Immunodeficiency Virus Type-1; Malaria; Prions; Sexually Transmitted Diseases; Transfusion Medicine-Blood Donor Selection, Testing, and Collection; Transfusion-Related Adverse Events; Trypanosomiasis.
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Relevant Website

www.who.int/bloodsafety/en.