



Review article

Trypanosoma cruzi infection in transfusion medicine

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ABSTRACT

Introduction: Infection by *Trypanosoma cruzi* is challenging to blood bank supplies in terms of accurate diagnosis, mostly due to its clinical complexity. Infected individuals may remain asymptomatic for years, albeit they may have circulating parasites potentially transferable to eventual receptors of a transfusion.

Objective: Although risk donors are systematically excluded through a survey, an important residual risk for transmission remains, evidencing the need to implement additional actions for the detection of *T. cruzi* in blood banks.

Method: A review of the scientific literature is presented with the objective of identifying relevant publications on this subject.

Results: We discuss the diagnostic considerations of this chronic infection on transfusion medicine and some recent advances in the processing of blood and derivatives units.

Conclusion: Finally, recommendations are made on how the transmission of *T. cruzi* can be avoided through the implementation of better diagnostic and pathogen control measures at blood banks.

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Introduction

The infection with *Trypanosoma cruzi* is endemic in Latin America, where 6–8 million people are infected, and 100 million people are at risk of becoming infected. Around 15,000 deaths are attributable to Chagas disease (CD) annually.^{1–3} This zoonosis has traditionally affected people living in low-income rural areas, but factors like continuing migration flows

and a long-lasting asymptomatic period may lead to identification of CD in residents of big cities of developed countries, including some places where natural transmission does not occur.⁴ Moreover, CD represents considerable economic costs for endemic developing countries.⁵

In rural regions of Latin America, it is estimated that the vector transmission accounts for approximately 80% of the infections.⁶ In addition to the vector-borne route, *T. cruzi* can be transmitted through the transfusion of blood and its

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components or through solid organ transplantation from infected donors.⁷ Other forms of transmission for this infection may include the congenital infection, the accidental inoculation in laboratory workers, or by the oral route, after the incidental ingestion of food that had been contaminated with the vector's feces.⁸

Historically, between 1975 and 1985, countries that were endemic for CD were classified into three groups, based on the quality of the reported information and the presence of vectors and prevalence of transmission both through vectors and transfusions. Group 1: countries with high prevalence of CD and of *Triatominae*: Venezuela, Honduras, Uruguay, Paraguay, Nicaragua, Argentina, Brazil, Bolivia, and Chile; Group 2: countries with active transmission inside housings and cardiac disorders derived from CD: Colombia, México, and Guatemala, and; Group 3: countries with active transmission within housings, blood banks with infected units and a lack of control programs: Costa Rica, El Salvador, Panama, Peru and Ecuador.^{9,10} Some of these countries have now implemented stringent control measures aimed at the control of transmission of this infection through blood. According to the annual report of the National Network for Blood Transfusions at the Colombian *Instituto Nacional de Salud*, the country has advanced toward eradicating the transmission of *T. cruzi* infection through transfusions, achieving a coverage of 100% in the screening of donated blood units.

The southern cone initiative was a successful regional effort developed in 2001 to interrupt the transmission of *T. cruzi* in Argentina, Brazil, Bolivia, Chile, Paraguay, and Uruguay.¹¹ The initial geographical diagnosis of WHO in 2002 showed that approximately 18 million people had CD, 300,000 new cases appeared per year, 21,000 people died per year, the majority of whom were children, and around 80 million people were at risk of becoming infected.¹² This data is in striking contrast with that reported eight years later when about 8 million people were living with the infection.^{2,3} Such results confirmed that the strategies developed by health institutions are efficient and economically accessible and able to eliminate some species that transmit the infection and control the transmission through transfusions. However, due to a residual risk from donations of people unaware of being infected, pathogen inactivation has been implemented at blood banks.

In 2006, the Pan American Health Organization (PAHO) conducted a study to measure the burden of CD in the Americas. Based on a population of 531,432,850 people, they found that 7,694,500 were globally infected by any route of transmission. Of these, 9365 of the infections were congenitally acquired, 1,065,767 of the infected people were women who were at a potential risk of transmitting the infection by the vertical route (i.e. aged 15–44 years), 37,193,000 people were exposed to endemic areas, and the number of blood donors that tested positive for *T. cruzi* in serology was 5,314,329.¹³

Natural history of disease

The primary infection is asymptomatic in about 70% of the people and occurs most frequently in children. The incubation period is about 14 days and the clinical manifestations, when present, can last for 6–8 weeks. It is characterized by

a high parasitemia and parasite invasion of multiple tissues. During the first 15 days of the infection, a subcutaneous nodule may be observed at the inoculation site, with regional adenitis (inoculation chagoma). In some cases of ocular inoculation, a unilateral palpebral edema may occur (Romana's sign) that can be associated with retro-auricular adenitis. The acute phase can manifest with fever, lymphadenopathy and hepatosplenomegaly. Complications, such as acute fulminant myocarditis or meningoencephalitis, have been described in immunocompromised hosts or after oral infection through contaminated fruits.

A large proportion of patients exhibit an acute phase characterized by flu-like symptoms and then enter an asymptomatic phase, which can last for decades without detectable parasitemia (the indeterminate phase of the disease).¹⁴ Identifying this population group is of great public health importance because its members have a high risk of transmission of *T. cruzi* through transfusions, should they become donors at blood banks. In addition, women in the indeterminate phase can transmit the infection by the congenital route. Approximately 30% of patients in the indeterminate phase will develop the chronic form of the disease, which is characterized by a progressive, dilated cardiomyopathy or progressive commitment of the muscular wall of the esophagus or the intestine that can eventually lead to the development of mega viscera.¹⁵

Transmission of the Infection

Vector transmission

Hematophagous *Triatominae* insects are the natural source of the infection, and are present in poor housing conditions. Uruguay, Chile and Brazil, have been declared free of vector transmission. Control measures have been relatively successful in reducing the transmission through vectors, leading to a sustained reduction in the incidence of the infection.¹⁶

Congenital transmission

The prevalence of congenital transmission ranges from 5 to 10%.¹⁷ Over 60% of congenitally infected newborns are asymptomatic or have no specific clinical manifestations.¹⁷ Confirmation of a case involves comparative maternal and child serologies, or polymerase chain reaction (PCR).¹⁸ Detecting infected fertile women is a requirement for preventing congenital CD. Newborns with confirmed infection should be treated with specific antiparasitic therapy immediately after the diagnosis is confirmed, allowing for the prevention of chronic CD.¹⁹

Oral transmission

A person can accidentally ingest vectors (or their feces) carrying the parasite.²⁰ Such cases were first reported in Rio Grande do Sul, Brazil, in 1965. Myocardial biopsies of affected people confirmed a parasite-induced intense myocarditis. Apparently, they had eaten vegetables contaminated with feces from infected marsupials.²¹ This transmission route was

experimentally confirmed in 1982.²² Sporadic outbreaks of the disease by oral transmission has been observed, mostly in Brazil.²³

Transmission by organ transplantation

Infection through kidney transplantation first occurred in the 1980s. Lately, other cases were reported after transplantations of kidney, pancreas, liver, heart and bone marrow.^{24,25} In cases of donor positiveness with a negative receptor, treating the donor is mandatory, and the transplantation is voided. However, if transplantation is indicated due to a life-threatening condition and no other donor is found, then the transplantation can be performed and the receptor should also be treated.²⁶

Accidental transmission

Most laboratory accidents occur due to a lack of trained people handling contaminated samples, lack of protection and biosafety, or wrong handling of equipment and facilities.²⁷ Some accidents have been reported in clinical laboratories during manipulation of the infected blood of patients with CD, while other accidents have occurred in experimental research laboratories.²⁷

Transmission through transfusions

The first description that transmission of *T. cruzi* infection through blood transfusion was made in 1936 by Salvador Mazza in Argentina. This was later confirmed between 1949 and 1952 in Brazil.²⁸ Therefore, a permanent deferral was established for blood donors presenting recurrent fever, Leishmaniasis, Malaria, Trypanosomiasis, “infectious jaundice” or any other disease caused by a blood pathogen.²⁹

The parasite can be detected in the blood of infected persons for years. Hence, transmission can occur through transfusion even if the donation takes place several years after the primary infection. *T. cruzi* can remain alive in the blood components under standard storage conditions (18 days at 4 °C for RBC, 250 days at 22 °C for platelets) and can also be resistant to freezing. Therefore, the infection can be transmitted to receptors of transfused red blood cells (RBCs), platelets, granulocytes, fresh frozen plasma, or cryoprecipitates.³⁰ The type of component transfused and the immune status of the recipient are factors that have an impact on the probability of transmission; in fact, not all patients who receive infected units will become infected. This incomplete infectivity can be in part explained by a reduced parasitemia (less than 1 parasite per 20 mL of blood), as well as the presence of antibodies in the recipient.^{30–32}

Infection through transfusions depends on several factors, including the amount of blood transfused, the burden of parasitemia at the time of the donation, the availability of screening tests, and the prevalence of the infection in the donor population.^{33,34} In Latin America, transfusion is an important route of contagion.³⁵ Around 12–48% of individuals infected through transfusion will develop the disease. Each blood component has a different infectivity potential, and most post-transfusion cases of CD are associated with

receiving platelets, especially in immunosuppressed cancer patients.^{36–38}

In blood banks, the adoption of measures to reduce *T. cruzi* transmission will depend on how prevalent the infection is among the donor population. Thus, in endemic countries, in addition to the screening survey, the universal *T. cruzi* serological screening is mandatory. Although the sensitivity of these tests for this parasitic infection is typically inferior to that of the tests used for detecting other infections, universal screening has significantly changed the risk of transfusion-associated contagion. The residual risk was calculated at about 1: 200,000 transfusions,³⁹ which is still 10–15-fold higher than that of HIV, HBV or HCV.³⁷

The acute phase of post-transfusion infection has an incubation period of 20 to 40 days, with a range of 8–120 days. Fever is the most common symptom, and in some cases, the only one. Lymphadenopathy, hepatosplenomegaly, cardiac arrhythmias, and central nervous system (CNS) symptoms may appear in severe cases, while approximately 20% of infected recipients are asymptomatic. Spontaneous recovery can occur after the acute phase, and it may take 6 weeks to 4 months. The disease follows its course to the indeterminate phase,¹³ and 20–30% of patients may develop CD.⁴⁰

Diagnostic tests for *T. cruzi* infection

Diagnosis of *T. cruzi* infection relies on serological or parasitological techniques. The detection of infected individuals coursing the indeterminate phase of the infection pertains to blood banks and is performed largely through serologic tests. Commercially available serological tests include hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay (ELISA), commonly using purified or recombinant antigens.⁴¹

Routine screening of donors is hindered by the low sensitivity and specificity reported for the serological screening methods routinely used. Hence, the PAHO suggested the use of two different serological tests in parallel.^{41,42} The problem arising from this recommendation, in addition to the economic implications for blood banks in terms of the costs of the screening tests, was the frequent presence of inconclusive results from non-specific reactivity tests. In the absence of a gold standard technique, accepted and accessible for serological diagnosis, it was difficult to define the infection status of those samples with inconclusive screening results and, therefore, many units of blood were lost.⁴³ The World Health Organization (WHO) subsequently published a technical note that recommends a single ELISA test, which has an assumed sensitivity close to 99%.¹³

Currently, the most used serological technique in blood banks is ELISA, using either homogenate from the parasite, or preferably, recombinant parasite proteins as antigens. While most manufacturers declare the sensitivity and specificity of their tests to be close to 100%, the routine use of the reagents may reveal some discrepancies, mostly due to factors that depend on the endemicity of the infection and the reagents themselves. Validating novel serologic tests will require a standardized simple method to identify inconclusive infectious states. In general, the panels used to evaluate screening

Table 1 – Sensitivity and specificity of some screening tests used in the diagnosis of *T. cruzi* infection.

Assay	Sensitivity (95%IC)	Specificity (95%IC)	Manufacturer
EIA			
HBK 401 Hemobio Chagas	100 (97.9–100)	99.62 (97.9–100)	Embrabio
Chagas ELISA	97.62 (94.0–99.3)	97.71 (95.1–99.2)	Ebram
Chagatek ELISA	99.4 (96.7–100)	99.24 (97.3–99.9)	Laboratório Lemos
Premier Chagas IgG ELISA Test	94.04 (89.3–97.1)	100 (98.6–100)	Meridian Diagnostics
ELISA test for Chagas	99.4 (91.2–98.1)	99.62 (97.9–100)	BIOSChile
Bioelisas cruzi	98.21 (94.9–99.6)	99.24 (97.3–99.9)	Biolab-Mérieux
Abbott Chagas	99.4 (96.2–100)	98.09 (95.6–99.4)	Abbott Laboratories
EIA Antibodies			
Chagas test IICS, ELISA	97.02 (93.2–99.0)	99.24 (97.3–99.9)	ICC Univ. de Asunción
ELISA test for chagas	98.81 (95.8–99.9)	99.62 (97.9–100)	Wiener lab
Bioelisa Chagas	100 (97.8–100)	99.24 (97.3–99.9)	Biokit
Chagas Hemagen	100 (97.8–100)	96.56 (93.6–98.4)	Hemagen Diagnósticos
Hemagglutination			
Chagas HAI Immunoserum	97.62 (94.0–99.3)	78.62 (77.2–83.4)	Polichaco
Teste Chagas-HAI	88.09 (82.2–92.6)	59.92 (53.7–65.9)	Ebram
Imuno-HAI Chagas	100 (97.2–100)	95.8 (92.6–97.9)	WAMA
Chagas Hemagen HA	92.26 (87.1–95.8)	89.31 (84.9–92.8)	Hemagen Diagnósticos
Hemacruzi	99.4 (96.7–100)	97.33 (94.6–98.9)	Biolab-Mérieux
Particle agglutination assays			
Serodia-Chagas	100 (97.2–100)	97.7 (95.1–99.2)	Fujirebio
ID-Chagas antibody test	97.02 (93.2–99.0)	99.62 (97.9–100)	DiaMed-ID
Rapid tests			
Chagas Stat-Pak	94.08 (89.1–97.3)	95.75 (92.1–98.0)	Chembio Diagnostic Systems
Confirmatory tests			
RIPA	100 (97.8–100)	100 (98.6–100)	University of Iowa
WB	100 (97.8–100)	97.3 (94.6–98.9)	bioMérieux
IB	98.2 (94.9–99.6)	99.6 (97.9–100)	Innogenetics
IF	98.2 (94.9–99.6)	98.0 (96.7–99.8)	bioMérieux

tests are based on samples with high antibody titers which are used as positive controls. However, the performance of the assay against samples with low antibody titers has not been formally evaluated, slanting the results toward an overestimation of the test sensitivity. ELISA tests based on parasite lysates appear to have better sensitivity, while those produced with recombinant antigens show improved specificity. For blood banks, the priority is the sensitivity of the test, in order to minimize the risk of accepting donations from carriers. The use of a concurrent examination of samples with a technique based on recombinant antigens could help in confirming the infectious status of suspected cases.⁴⁴

One of the most significant problems in the serological diagnosis of *T. cruzi* infection is the absence of a gold standard test. Hence, institutions should opt for various tests using distinct technical principles to confirm the diagnosis in discrepant samples. In this context, the most used complementary test is the indirect immunofluorescence (IFI). Other tests being used are the immunoblot, using trypomastigotes excreted-secreted antigens (TESA),⁴⁵ the radioimmunoprecipitation assay (RIPA) or the Inno-Lia.⁴⁶ These tests have strong limitations due to the frequency of false negative results.^{47,48}

Additional supplementary techniques such as the PCR or blood cultures may be useful in clarifying the diagnosis. However, due to the intermittence or low levels of parasitemia of chronically infected individuals, the efficiency of these tests as confirmatory analysis is limited.⁴⁹ Table 1 summarizes some of the tests that are currently used for the detection of the *T. cruzi* infection.⁵⁰

Prevention of *T. cruzi* transmission through blood transfusions

In addition to systematic serological examination of donors, interventions, such as the leukoreduction, have been effective in experimentally curtailing parasitemia of infected units,⁵¹ yet it was not enough to prevent transmission. Moreover, pathogen reduction or pathogen inactivation showed an effective reduction in the number of parasites (greater than 5 logs), constituting a promising tool for granting better safety to transfusions in endemic countries.^{52–56}

The cost of *T. cruzi* screening for blood banks

The cost of preventing the transfusion of an infected unit represents the cost of detecting the infective status of the donors, using a diagnostic test for each infectious disease in which screening is mandatory in a given country. In Colombia (2017), the cost of the reagents required for the screening of seven infections (HIV, HCV, HBc, HBsAg, Chagas, syphilis and HTLV I/II) was calculated at 10–15 USD. Subsequently, the costs for the screening of 876,311 blood donors (whole blood plus apheresis) in 2017 would have been approximately 8.7–13.1 million dollars.

The overall reactivity in whole blood donors in 2017 was 3.6%, which is approximately equivalent to 30,000 units, and for *T. cruzi* it represented 0.19%, or 1578 units. If the cost per screening and confirmatory test for CD is approximately

150 USD, then the cost of preventing the transfusion of a *T. cruzi*-infected unit was approximately 78,925 USD (830,291 units $\times$ 150 USD/1578 test for *T. cruzi*). In 2017, the serologic test for *T. cruzi* detected 1578 reactive units; if the screening had been omitted by blood banks, it would have meant that nearly 30% of the recipients of these units might have become infected (473 patients); of these, another 30% would have developed CD (142 patients).

For all 2017 blood donors (whole blood plus apheresis units), close to 1.8 million dollars were invested in the screening of *T. cruzi* (876,311 $\times$ 2 USD). As a result, the cost of preventing each potential infection was 3705 USD (1.8 million dollars/473 patients) and the prevention cost of a potential CD case was 12,342 USD (1.8 million dollars/142 patients). This cost is several times less than that which the health system would incur to treat the roughly 142 cases of CD expected from the otherwise potentially infected persons and their complications.

Conclusions

In spite of extensive research on the molecular diagnosis and transmission of the *T. cruzi* infection, it still represents a challenge to blood banks supplies in terms of the accurate diagnosis. This is mostly due to infected individuals remaining asymptomatic for years, despite having circulating parasites potentially transferable to eventual receptors of a transfusion. The success of screening in blood banks has traditionally been determined mostly by strict selection of potential donors. Moreover, due to the disparity of results usually obtained with the use of rapid serological techniques, it is highly advised to adopt molecular techniques such as PCR for the detection of *T. cruzi* in blood banks. Pathogen inactivation techniques, available to be used on cell components,⁵⁷ can be a worthwhile additional measure. Measures aimed at enhancing blood safety should be accompanied by aggressive instructive campaigns to potential donors promoting the responsible donation attitude.

Conflicts of interest

The authors declare no conflicts of interest.

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