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Threats to blood safety posed by emerging protozoan pathogens

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Introduction

Blood safety strategies designed to prevent the transmission of protozoan pathogens have focused almost exclusively on *Plasmodium* sp., the aetiological agent of malaria. *Trypanosoma cruzi*, the agent of Chagas disease, has received some attention, but only in the endemic countries of Latin America. For the most part, perceptions of the potential risks posed by protozoan pathogens have been slow to change. However, the concept of emerging pathogens has generated a great deal of interest during the past decade, even among practitioners of transfusion medicine. It is now clear that new pathogenic agents continue to emerge due to a variety of factors including immigration patterns, transmission from animals to humans, and microbial adaptation [1]. While the overall blood safety focus has remained on viruses (e.g. West Nile virus, SARS), emerging protozoan pathogens transmissible by blood have received increased attention.

This paper will briefly review two protozoan pathogens that have emerged as blood safety threats. The first agent, *T. cruzi*, has emerged as a blood safety risk in non-endemic countries because of immigration and subsequent changes in donor demographics. The second agent is actually a group of related organsims, all members of the genus *Babesia*. Like many other tick-borne pathogens, the geographical distribution of the *Babesia* has expanded rapidly leading to an increasing number of human infections and transfusion cases. Together these agents present blood safety risks that perhaps have been ignored for too long.

Chagas disease

As already mentioned, Chagas disease or American trypanosomiasis is caused by *T. cruzi* which is endemic to portions of Mexico, Central America and South America. Natural transmission of this parasite to humans occurs following exposure to a haematophagous reduviid bug infected with *T. cruzi*. During the course of a blood meal the bug defecates, passing the infective trypomastigote stage in the faeces. The parasite enters the skin through the bite wound, conjunctiva or other mucosal surface and disseminates via the blood stream to smooth muscle, particularly the heart. In most cases, the ensuing acute disease is relatively mild, lasting only a few weeks. Thereafter, infected persons enter an indeterminate phase of disease characterized by intermittent parasitaemia and elevated antibody titres. Decades later, 20–30% of infected persons will develop chronic disease characterized by cardiac and intestinal complications [2]. Drug treatment options are limited to nifurtimox and benznidazole, but both produce severe side-effects and have limited efficacy.

In addition to natural transmission, *T. cruzi* is also transmitted by blood transfusion. In many endemic countries of South America, interventions designed to interrupt natural transmission of the parasite have been so successful that blood transfusion has become the primary transmission route [3]. Similarly, in non-endemic countries, transmission of *T. cruzi* by blood transfusion is of increasing concern. During the past 30 years, millions of people have emigrated from Latin America to the USA and Canada. It is estimated that up to 100 000 of these people may be infected with *T. cruzi* and thereby represent an extant reservoir population for transmission of the parasite by transfusion [4]. Indeed, seven cases of transfusion-transmitted *T. cruzi* have been reported in the USA (n = 5) and Canada (n = 2), but many more cases likely go unrecognized [5]. Similarly, while no transfusion cases have been reported from Europe to date, increased immigration to Europe from Latin America, particularly through Spain, suggests that transfusion-transmitted *T. cruzi* is also an emerging threat to European blood safety.

Nationwide estimates indicate that approximately 1 in every 25 000 US blood donors is infected with *T. cruzi* and thus at-risk for transmitting the infection to blood recipients. Local seroprevalence rates can be much higher: 1in 9000 Miami donations and 1 in 7500 Los Angeles donations [5]. In Los Angeles, seroprevalence rates increased significantly during the study period, reaching 1 in 5400 during the final year of study. The observed increase was attributable to

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enhanced recruitment of blood donors from the local Hispanic community. This same study also revealed that the rate among directed donors, a population with large numbers of at-risk donors, was 1 in 2400 donations. An earlier study in Los Angeles reported that for selected high-risk populations the rate can approach 1 in 1000 donors [6]. Thus, while seroprevalence rates may vary regionally, infected donors can likely be found throughout the USA at rates that are reflective of the local at-risk population [7]. In Canada and Europe, when and if analogous studies are done in blood donors, similar findings are anticipated. Indeed, two transmission cases have been reported in Canada, while 2% (2/100) of Latin Americans from Berlin were reported to be seropositive for *T. cruzi* [8].

At present, blood bank screening for *T. cruzi* is conducted throughout virtually all of Latin America. However, in the USA, Canada and Europe blood is not screened for antibodies to this parasite despite increasing numbers of at-risk donors. In the USA where the threat is perhaps the greatest, the primary obstacle to blood screening is the absence of a test licensed by the Food and Drug Administration. If and when a test is licensed in the USA, the most likely intervention to protect the blood supply is universal screening of all blood products. Strategies designed to assess risk, either for outright deferral or selective testing, have been shown to lack sensitivity [9,10]. Testing of only first-time donors, while an attractive idea, would likely increase testing errors and would be problematic in the case of donors who travel to endemic areas. Nucleic acid testing would have minimal added value since acute, window period infections are unlikely to occur in non-endemic countries (i.e. USA, Canada, and Europe). Leucoreduction has been shown to incompletely remove the parasite from blood [11], and pathogen inactivation has recently encountered several developmental setbacks. Thus, for those non-endemic countries seeking a rational intervention, universal blood screening appears to be the most promising approach to ensure blood safety.

Babesiosis

Human babesiosis is caused by intraerythrocytic parasites of the genus *Babesia*, with *B. microti* and *B. divergens* the primary agents in the USA and Europe, respectively. Both agents are transmitted by *Ixodes* ticks; *I. scapularis* is the US vector, while *I. ricinus* is the European vector. A variety of other newly described *Babesia*-like agents (e.g. WA-1, MO-1, EU-1) also cause human disease [12,13]. Most people infected with *Babesia* spp. develop an asymptomatic or mild disease that can be characterized by fever, headache, night sweats and myalgia. Immunocompromised persons, including the elderly and asplenic, may experience more severe disease complications including haemolytic anaemia, thrombocytopenia, renal failure and death. Many of these cases are treated with combinations of quinine and clindamycin or atovaquone and azithromycin, and in rare instances exchange transfusions are used to reduce parasitaemia levels [14].

The intracellular niche of *Babesia* spp. provides the parasite with an ideal mechanism for transmission by blood transfusion. During the past 10 years, there have been at least 40–50 reported cases of transfusion-transmitted *B. microti*, but the actual number is probably much higher [15]. All transmission cases have occurred in the USA with the exception of one case in Japan and one in Canada [16,17]. The Canadian case involved a donor who was likely infected during a US visit. Further, despite its initial discovery in 1996, there have already been two reported cases of WA-1 transmission. The relatively high number of transfusion cases is not surprising given the parasite's ability to survive in stored blood products, its seroprevalence rates in endemic areas and transmissibility. Indeed, *B. microti* has been shown to survive at least 35 days in stored red cell units [18]. Seroprevalence studies in blood donors are limited, but rates range from 0·3% to 4·3% for donors in endemic areas of the USA [19–21]. A recent study in Connecticut revealed that the risk of transfusion-transmitted *B. microti* is 1 in 1800 transfused red cell units [22]. Taken together, these factors demonstrate the considerable blood safety risk posed by *B. microti* and related species of *Babesia*.

At this juncture, options for interventions to prevent transfusion-transmitted *Babesia* spp. are extremely limited. Strategies employing risk-factor questions, such as self reported tick bites, have been shown to be unreliable [19]. Since the Babesia are intraerythrocytic, leukoreduction is ineffective and as already discussed, implementation of pathogen inactivation does not appear to be imminent. Options for serologic screening are limited because beyond the standard immunofluorescence assay there are few available options, particularly for a rapid, automated, high throughput test that would be required for today's blood bank. If suitable tests are developed, it is not clear that universal blood screening would be the most cost effective approach since most people infected with *Babesia* sp. clear the infections rapidly. Immunocompromised blood recipients, however, remain susceptible to infection and may benefit from receiving a product that has been tested and shown to be negative for *Babesia* antibodies. A similar approach has been used successfully to prevent the transmission of cytomegalovirus. Active transmission of *Babesia* spp. in North America and Europe indicates that future testing algorithms are also likely to require a NAT component.

Summary

T. cruzi and *Babesia* spp. present two remarkably different stories of how they impact blood safety. *T. cruzi* is of concern in non-endemic areas because of increased immigration. In

contrast, the *Babesia* spp. are truly emerging infectious agents whose endemic range continues to expand. *T. cruzi* causes a life-long infection that is thought to be untreatable, while babesiosis is generally mild and treatable, but can cause severe disease in the immunocompromised. Despite their differences, these two emerging protozoan pathogens represent ongoing threats to blood safety. As for most emerging pathogens, the limited availability of specific and sensitive tests for research and/or blood screening has hindered the implementation of effective control strategies. However, as the geographical distribution of these agents continues to expand and increasing numbers of transfusion cases are recognized, the impact these agents have on blood safety will be increasingly difficult to ignore. Thus, it is not unreasonable to suggest that within the next five years we will see the implementation of new control measures for *T. cruzi* and *Babesia* spp.

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