CHAPTER 52

Transfusion transmission of parasites

Bryan R. Spencer
American Red Cross, Dedham, MA, USA

Summary

Blood recipients in the United States (US) generally face a low risk of being transfused with a component contaminated with parasites. Quantifying the risk often depends on parameters that are unknown or poorly characterized, but estimates have remained stable in recent years at one transmission of parasitic infection per million transfusions.1–2 This round figure obscures divergent trends for some of the agents of highest visibility as well as considerable differences in local risks across the country.

A comprehensive review of 68 pathogens by the AABB’s Transfusion Transmitted Diseases (TTD) Committee3 identified four protozoan parasites among the agents of greatest concern, based on empirically established transmission risk and regulatory/public perception. Human mobility patterns continue to be important factors associated with risk, due to high rates of international travel by US residents, the movement of military personnel, and large migration flows. Increased awareness, more refined risk assessments, and ongoing development of molecular tools and improved diagnostics are helping clarify the risks. For Babesia microti and other Babesia species, recent research suggests that transfusion transmission has been historically underestimated, given that transfusion transmission can easily go undetected, especially when transfused to immunocompetent patients. Implementation of screening for Trypanosoma cruzi, the etiological agent of Chagas disease, has significantly curbed the risk of transmission associated with immigrants from endemic countries in Latin America, while raising questions about the frequency of autochthonous transmission within the US. Transfusion of malaria parasites continues to be a silent, with symptomatic infections more common with advancing age.5 Clinical infections begin 1–6 weeks following tick bite and are frequently nonspecific, presenting with flu-like symptoms including fever, headache, and myalgias. Risk for severe disease is higher in the elderly, the immunocompromised, and the asplenic; complications can include thrombocytopenia, hemolytic anemia, and renal, heart, or respiratory failure.6 The case fatality rate can range from 5% to 10% for B. microti 6 to 42% for B. divergens.7 That nearly all reported cases of B. divergens have occurred in asplenic hosts7 almost certainly contributes to this disparity.

Human babesiosis is an emerging disease both within the US and globally. Since the first case of human babesiosis was recorded in the US in 1966,8 fewer than 2000 cases were reported in the country over the next four decades.9 During that time, the seven states considered “endemic”—Massachusetts, Connecticut, New York, Rhode Island, and New Jersey in the Northeast, and Minnesota and Wisconsin in the Upper Midwest—established their own reporting and surveillance systems. Isolated cases were sporadically identified in other states, sometimes in connection with a transfusion case. In 2009, the Council of State and Territorial Epidemiologists voted to make human babesiosis a nationally notifiable disease, with standardized laboratory, clinical, and epidemiologic criteria developed for diagnosis of tick-borne or transfusion-associated cases. Following implementation in 2011, the number of states adopting the reporting criteria has grown considerably and the number of cases reported has more than doubled the totals from the prior 45 years (see Table 52.1). The seven “endemic” states consistently account for 95% or more of all reported cases, but the number and distribution of locations finding cases outside these states (see Figure 52.1) suggest that the enhanced surveillance capacity may lead to higher numbers in future.

The primary agent responsible for human babesiosis in the US is B. microti. It is transmitted by the black-legged deer tick (Ixodes...
scapularis, previously known as *I. dammini*), the vector of Lyme disease. Heightened awareness and scrutiny, together with increased molecular characterization of patient isolates of *Babesia* parasites, present a complex picture of *Babesia* transmission in nature. *B. microti* is now considered a species complex composed of three distinct clades with identical morphology but partly distinct vertebrate hosts and potentially differing levels of pathogenicity for humans.\(^{15}\) *Babesia duncani*, first recognized in the early 1990s, is morphologically identical to *B. microti* but antigenically and genetically distinct, and has been found in humans, dogs, and wildlife in the Western US.\(^{16}\) *Babesia* sp. MO1 was originally thought to be the primary European parasite *B. divergens*, but it has been shown to be distinct on the basis of genetic sequence difference and in vitro characteristics. All three human cases (in Missouri, Kentucky, and Washington) were in splenectomized patients, and this genotype has also been found in rabbits in Massachusetts and Texas.\(^{17-19}\)

Additional genotypes designated *Babesia* sp. CA-type (CA1–CA4) are morphologically indistinct and serologically cross-reactive with *B. duncani* but are genetically distinct, and have caused severe illness in four patients all of whom lacked their spleen.\(^{16}\) Finally, the first human case in Tennessee, found in an immunocompromised hunter with heavy tick exposure, has been characterized as “genetically distinct” from previously identified zoonotic agents.\(^{20}\) Investigation of the patient’s rural property found *Babesia* sp. MO1 in Eastern cottontail rabbits, but detailed characterization of the patient’s isolate remains unpublished to date.\(^{19-21}\) 

Outside of *B. microti*, very little is known about the geographic distribution, vertebrate reservoirs, tick vectors, or virulence in humans of other *Babesia* species. That nearly all patients are asplenic suggests that most transmission goes undetected. In sum, at least four distinct genotypes of *Babesia* protozoa are known to cause human illness in the US, with very little still known about the risk posed to human health and the blood supply by the newly described species and isolates.

---

**Table 52.1** History of reporting of babesiosis in US before and after it was made a nationally notifiable disease (2011)\(^*\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of states reporting</th>
<th>Number of states with cases</th>
<th>Number of cases reported</th>
<th>Number of cases reported &lt;2000</th>
<th>Number of cases reported &gt;2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966—2010</td>
<td>7</td>
<td>Varies</td>
<td>&lt;2000</td>
<td>159**</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>18</td>
<td>15</td>
<td>1124</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>22</td>
<td>14</td>
<td>911</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>27</td>
<td>22</td>
<td>1762</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>31</td>
<td>20</td>
<td>1571</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) Data from Spencer (2009)\(^{9}\) and CDC (2011, 2012, 2015).\(^{10-13}\)

\(^{**}\) Reported in Herwaldt et al. for 1979–2009.\(^{14}\)

---

**Number of Reported Cases of Babesiosis, by County of Residence, 2013**

*Figure 52.1* Distribution of reported cases of babesiosis in the US in 2013. Image courtesy of US Centers for Disease Control and Prevention. *N* = 1750; county of residence was unknown for 12 of the 1762 patients. Cases are mapped to the patients’ county of residence, which was not necessarily where they became infected. One or more cases were reported by 22 of 27 states that conducted surveillance. Source: US Centers for Disease Control and Prevention (http://www.cdc.gov).
A similar picture of increasing complexity is also emerging in Europe. Reports of human babesiosis are rare, with fewer than 50 human cases reported since the first report in 1957, a fatal case in a splenectomized Yugoslav farmer. Most European cases are attributed to *B. divergens*, a bovine pathogen, with cases reported from several countries in Western Europe, the former Yugoslavia, and the former USSR. Risk for human infection correlates geographically with the presence ofinfected cattle populations and areas infested by the tick vector, *Ixodes ricinus*; little is understood about the role that spleen-intact human populations and silent carriage of *B. divergens* might play in terms of risk to the blood supply. A new variant isolated from asplenic patients in Italy, Austria, and Germany has been designated *B. venatorum*. Also, a single case of autochthonous *B. microti* has been identified in Europe due to this agent, likely by blood transfusion, although entomologically and serologically evidence suggests transmission is much more common than recognized.

Finally, in East Asia, the first case of autochthonous human babesiosis in Japan has been confirmed, due to transfusion-acquired *B. microti*-like infection; asymptomatic *B. microti*-like infection has been documented in Taiwan; and the first case of human babesiosis has been reported from Korea, with the isolated parasite designated KO1 and appearing to be related to *Babesia* species that infect sheep. Dozens of cases have been newly reported from China, in both healthy and immunocompromised populations. Isolated reports from Africa, Australia, and South America reflect the ubiquity of the parasite in vertebrates worldwide. The two most important characteristics of *B. microti* infection driving transfusion risk are the probability that most infections are clinically silent and the ability of immunocompetent persons to carry infection for lengthy periods. There is little direct evidence for the proportion of infections that are asymptomatic, but one recent review suggests that one-half of children and one-fourth of immunocompetent adults have no symptoms with *B. microti* infection. This figure may overstate the clinical attack rate in children, who do not seem to face lower risk of acquiring *Babesia* infection than adults but whose case counts are asymptomatic and population-adjusted incidence rates are much lower than those of persons aged 60 and older. Moreover, a comparison of seropositivity rates of blood donors with symptomatic cases reported to public health departments also supports a high ratio of clinically silent to apparent infections. For example, New London County in southeastern Connecticut reported an average annual case rate of 14 cases per 100,000 population from 2011 to 2013, but serological testing in 8000 blood donors across eight years showed 1.8% with *B. microti* antibodies, a 130-fold difference. A similar comparison of testing performed on islands off the coast of Massachusetts yields 1.4% seropositivity in donors compared to 24 cases per 100,000 population, a 57-fold difference. The ratio of apparent to apparent infections is not estimable from these numbers without also considering the duration of detectable antibody, but available evidence suggests elevated antibody titers lasting 6–12 months, especially in the presence of extended parasitemia. This latter characteristic, of course, is the primary driver of transfusion risk, and early research confirmed the ability of the parasite to persist for several months in untreated individuals. In vitro studies indicate that while cold storage reduces viability, some parasites do survive storage at 4°C and can remain infective for 21 to 31 days. The implications of long-term carriage of *B. microti* are amply demonstrated in a case in Minnesota, where an asymptomatic donor infected recipients from each of four donations over a six-month period.

A recent review published by the CDC summarizes 162 transfusion cases in the US from 1979 to 2009. Of these, 159 were due to *B. microti*, most of which occurred in the seven “endemic” states, but another 13% occurred in 21 different states due to interstate movement of blood donors or blood components. The overall mortality rate was 18%, consistent with the advanced age (median age 65) and also the compromised immune status of many recipients, due to asplenia or other morbidity. The median range from transfusion to diagnosis was six weeks, although in some cases it extended over seven months. The overwhelming majority of implicated components were red cells, with a median storage age at time of transfusion of 16 days and four cases where red cells were between 35 and 40 days old. Another three cases were caused by *B. duncani* and occurred in California and Washington. Outside the US, transfusion transmission of *B. microti* has been documented once each in Canada, Germany, and Japan, the only countries besides the US to report transfusion cases of *Babesia*. Only Germany and Japan’s cases reflect autochthonous transmission, however, whereas in Canada the donor acquired infection while on holiday in the United States. Few studies have directly measured the risk for transfusion transmission of *Babesia* parasites. Given the absence of symptoms in healthy individuals, studying paired donor–recipient specimens is the most secure way of estimating the risk in endemic areas. One study estimated that 1/617 units (0.17) of PRBCs might be at risk for transmitting *B. microti* in the state of Connecticut, and that the risk from platelets was estimated as zero. In another Connecticut study, analysis of paired donor–recipient specimens involving chronically transfused patients indicated one possible *B. microti* seroconversion out of nearly 2000 evaluable transfusions. Infec-tivity of different blood components is not easy to determine given that the likelihood both of establishing infection in the recipient and of that infection becoming clinically detected are likely to depend on the dose of parasites, the length of storage, and the recipient’s immune status. In the aforementioned case in Minnesota, one of three recipients of platelets became infected with *B. microti*, whereas three of three surviving recipients of red cells became infected. In another case, out of six individuals transfused with RBCs from an asymptomatic donor, two neonates and one elderly adult became infected, whereas two other neonates and a child remained asymp-tomatic. Lookback studies in Connecticut found that 13% of seropositive or parasitemic donors transmitted infection, but 50% of recipients of red cells from an index donation became infected, compared to only 10% of those receiving red cells from the donor’s prior donation. Investigational testing performed under research protocols in endemic New England states suggests a residual risk of 1 per 20,000–30,000 transfused units. Published numbers at present suggest a frequency of transmission of 1 per million, but the authors note that the 162 recorded cases “undoubtedly represent a fraction of those that occurred.”

Traditional diagnosis of *Babesia* infection relies on microscopic exam of Giemsa-stained blood films. This method, however, requires an experienced microscopist, and a high enough index of clinical suspicion to perform the exam. In US transfusion cases, diagnosis is often made incidentally and not due to clinical suspicion. Immunofluorescent assay (IFA) diagnosis is both sensitive and specific for measuring exposure, but it is too time consuming for mass screening and involves subjectivity on the reader’s part. Automated IFA assays have been employed under investigational protocols with high throughput and strong performance characteristics. Inoculation of blood from suspected human cases into laboratory animals offers both high sensitivity and specificity, but its
utility is limited to research investigation. Real-time polymerase chain reaction (PCR) appears to be highly sensitive and a valuable complement to serological methods.5–8

Human babesiosis has historically been treated with clindamycin and quinine (CQ), but atovaquone with azithromycin has emerged as the first-line recommendation in the US given the fewer collateral effects.7 Treatment with CQ continues to be recommended for severe cases. In severe cases, partial or whole blood exchange transfusion might be indicated, especially for severe infections of *B. divergens.*5

In the absence of a licensed screening assay, prevention of transfusion-transmitted babesiosis currently relies exclusively on a question asking the donor if they have ever had babesiosis. This strategy is insufficient in that only donors whose *Babesia* infection was symptomatic and properly diagnosed will self-report a risk. Because the majority of *B. microti* infections are silent or remain undiagnosed,5 parasitemic donors can escape detection. In the American Red Cross, only about 1 in 20,000 donors in Massachusetts or Connecticut reports a history of babesiosis during health history, showing the low sensitivity of the question.49 Seasonal deferral in endemic areas would adversely impact the blood supply, and would not address the issues of nonresidents who travel to endemic areas and the transfer of blood products from endemic to non-endemic areas.39 The predictive value of self-reported exposure to ticks in relation to serological status has proven low in Wisconsin and Connecticut donors.39 Available evidence indicates that neither serology nor nucleic acid detection alone will be sufficient to effectively mitigate risk.45–47 Cost-effectiveness modeling suggests that screening for *Babesia* will be costly even if limited to the most highly endemic parts of the US, estimated at $5 to 6 million per quality-adjusted life-year.50

As with other protozoan infections, pathogen inactivation methods hold promise in reducing the risk from transfusion-transmitted babesiosis. Photocatalytic treatments currently under development indicate parasite reductions of 5 logs in whole blood.51 Equivalent efficacy has been shown in platelets and plasma.52 Market interest in *Babesia*-screened red cell products is not well defined in the United States given the recent, and limited, availability to transfusion services.

**Chagas disease**

Risk for transfusion transmission of *Trypanosoma cruzi* infection has declined considerably in the United States with the widespread implementation of donor screening in 2007. Prior to that, concern had grown from the late 1980s forward with documentation of a small number of transfusion transmissions along with recognition of the potentially large human reservoir population due to the growing Hispanic population in the United States. Endemic in Central and South America and in Mexico, this protozoan hemoflagellate is transmitted in nature by reduvid bugs, or triatomines. These bugs have a tendency to bite on the face (and hence are called *kissing bugs,* but do not directly inject the parasite in their bite. Rather, the insect vector deposits the infective metacyclic forms of the trypanosomes in its feces during or soon after the blood meal, which is rubbed into the wound or transferred to susceptible membranes in the eye or mouth by the sleeping host. Triatomids competent for transmitting *T. cruzi* are widespread in the Americas, including in the United States, where autochthonous transmission occurs.53 The agent is readily transmitted by blood transfusion, solid organ transplantation, and congenital transmission.54 Rare outbreaks from contaminated food or drinks have also been reported.55 Symptoms during the acute phase last four to six weeks and are characterized by mild symptoms, including fever, malaise, and edema of the face, as well as lymphadenopathy and hepatosplenomegaly.56 The fatality rate in the acute phase is usually less than 5%, and many cases go unrecognized. During this period, parasites are readily detectable in peripheral blood.54 The ensuing chronic phase is lifelong, with infections that remain asymptomatic and parasitemia that is low grade and intermittent.56 Ten to 30 years later, 30–40% of carriers will develop serious sequelae involving the cardiac and/or digestive features (megacolon and mega-esophagus). Chagas is estimated to kill about 12,000 people annually, mostly due to cardiac complications.57 Acute stage treatment with benznidazole or nifurtimox leads to cure in 50–80% of cases, but treatment during the chronic phase is less effective at eliminating infection, and therapies for slowing disease progression once asymptomatic are mostly experimental but are under active investigation.56

Public health authorities have achieved considerable success in reducing risk and morbidity from Chagas disease in the last three decades. Whereas in the early 1980s an estimated 17 million residents of Latin America were infected and 100 million lived in areas at risk for transmission, current estimates are roughly eight million infected and 65 million at risk for insect transmission.56 Annual incidence of cases has dropped more sharply, from 700,000 new cases annually to 28,000 or so currently, a 96% decline.56–57 This success began with the Southern Cone Initiative, inaugurated in six South American countries in 1991, which sought to eliminate domestic infection by *Triatoma infestans* (the primary vector in several countries) and to interrupt transfusion transmission through universal donor screening.58 Subsequent efforts were adopted in the remaining regions of Latin America, tailored to the diverse species of vectors and the ecologic conditions found throughout.

The adoption of universal blood screening in Latin American countries has dramatically lowered the risk for transfusion transmission in endemic countries. Whereas in the early to mid-1990s only four of 17 Latin American countries for which data were compiled had achieved universal donor screening, now 20 of 21 have implemented universal testing.57 Estimates within the last 20 years were that nearly 2000 transfusion transmission events might occur annually across the region59 or even within Mexico alone,60 but the adoption of universal screening based on assays of high sensitivity61 suggests a sharply lower risk today.

Clearly, the risk in the United States and other receiving countries of Latin American immigrants depends on their immigrants’ risk for acquisition of infection extending decades into the past. Recent US census figures estimate that 54 million Hispanics live in the United States, of whom two-thirds are of Mexican origin,52 4.8 million are Central American, and 3.1 million are of South American origin. Roughly one-third of these residents are foreign-born, and 40% of them arrived to the US prior to 1990,62 before the intensification of control programs in endemic countries. This suggests that a very large number of Hispanic immigrants might have been exposed long before entering the US. Current estimates project that 300,000 Hispanic immigrants in the US may be infected with *T. cruzi,*64 Canada and Australia are estimated to have more than 1000 *T. cruzi*-infected immigrants each,65 and Europe between 68,000 and 123,000, nearly entirely undiagnosed.58 Within the US, 55% of Hispanic residents are found in California, Florida, and Texas, and eight states have a Hispanic population of 1 million or greater. Hence, the Hispanic population in the US is concentrated in few states, but risk for transfusion transmission of *T. cruzi* can be found countrywide.62

Until the licensure of a screening test in December 2006, there were seven reported cases of *T. cruzi* transfusion transmission in the
United States and Canada, and five cases of transmission associated with solid organ transplantation. The actual number of transfusion cases was undoubtedly higher, in that all seven cases were detected in immunocompromised patients. Although platelet products were implicated in six of these seven events, robust estimates for infectivity of different blood components were not available until recently. Prior estimates of 20% risk of transmission from a T. cruzi–infected donor were based on studies conducted in endemic countries where transfusion of fresh whole blood is common. Lookback studies based on large numbers suggest that risk of transmission by blood is less than 2% overall, ranging from 0% in PRBCs or plasma to 13% in platelets. A higher inoculum of parasites in platelet concentrates compared to plasma and whole blood might partially explain this difference.

The approach for screening blood donors for T. cruzi is different in countries that are endemic for active transmission than for those where risk derives entirely or nearly so from immigrants from Latin America. As noted above, all but one of 21 endemic countries in the Americas have adopted universal screening. Given that infection is lifelong, seroprevalence and potential risk in blood donors remain elevated for decades longer than achievement of full or partial control of natural transmission. Available data on numbers at risk and prevalence in donors support the current practice of testing all donors at each donation in Latin America. Elsewhere, however, selective testing has become the norm. Canada, France, England, and Japan have all implemented testing, but it is limited to presenting donors with identifiable risk factors relating to own or maternal birth in Latin America or exposure through travel or residence in the region. Donor loss is mitigated, costs are reduced, and the residual risk following testing is vanishingly small.

In the United States, the widespread screening for T. cruzi that followed licensure of the first serological screening test by the US Food and Drug Administration (FDA) provided an abundance of data on the prevalence and distribution of Chagas in the US. Data from the first two years of testing yielded seroprevalence of 1:7000 donors, with 25% of repeat reactive donations confirmed by RIPA (radioimmunoprecipitation assay), a non-FDA-licensed confirmatory assay. On the basis of very strong performance characteristics of the commercial enzyme-linked immunosorbent assay (ELISA) used for screening, together with the very low risk for incident infection in donors with a negatively screened donation, the FDA’s Blood Products Advisory Committee endorsed selective testing for US donors where one negative donation would qualify them going forward, formalized in guidance issued by the FDA in 2010. More recent seroprevalence studies reflect lower prevalence of 1 per 40,000 donors, possibly due to culling of prevalent infections from the donor pool in the earliest years of testing. In areas with high numbers of Hispanic donors, such as Texas, rates may be several-fold higher, such as the 1:6500 confirmed antibody-positive rate in Texas. As of February 14, 2015, the AABB Chagas Biovigilance website indicates 2032 confirmed positive donations in the United States from January 2007 forward, with cases widely distributed but concentrated in California, Florida, Texas, and other states with large Hispanic populations.

An interesting finding triggered by the investigations of seropositive donors in the US and their risk profiles is documentation of a number of presumed autochthonous cases. At least nine of the 11 triatomines species found in the US are competent vectors of T. cruzi, and two dozen or more vertebrate species serve as natural wildlife hosts of the parasite. Although domestically transmitted cases had previously been documented, they were very rare, and the number of cases has now increased from 7 to 23. Hence, unlike in other countries that have embraced selective testing strategies, risk in the US includes that from local transmission in addition to that from migrants. Current estimates suggest a seroprevalence of 1:354,000 donors due to local transmission, but prevalent risk would be mitigated by the testing of all donors at their first donation. The risk for incident infections in humans in the US is unknown, but new evidence suggests that triatomine feeding on humans may be more common than previously thought and that domestic dogs might be the bridge between sylvatic cycles and peridomestic transmission. Developing estimates of risk for autochthonous transmission in the US will help in the management of risk by blood transfusion as well as that from mother to child.

Aside from testing, additional options for risk reduction include donor exclusion, pathogen removal, and pathogen inactivation. Until Canada adopted selective testing of donors with identifiable risk factors, it simply excluded donors on the basis of residence and travel history in endemic areas. Such an approach is not specific and is likely feasible only where such donors constitute a small portion of the donor pool. Leukoreduction filters have been shown to lower the concentration of trypanosomes in blood, but at least one case of transfusion transmission in platelets was from a leukoreduced, and irradiated, product. A variety of photochemical treatment methods in platelets, plasma, and red cell components all show promise in reducing the parasite load by several logs.

Malaria

Human malaria is caused by one of five species of protozoan parasites: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi, the last of which has only recently been described. Malaria is a significant cause of global morbidity and mortality, responsible for an estimated 200 million clinical cases annually and over half a million deaths, and it is especially severe among young children in sub-Saharan Africa. Natural infection with malaria typically occurs through the bite of an infective female Anopheles mosquito. Less frequently, parasites might be transmitted through blood transfusion, organ transplant, parenteral exposure, or mother-to-child transmission. The US recorded an average of three cases of transfusion-associated malaria per year between 1963 and 1989. More recently, there were 13 cases recorded during the 1990s and seven from 2000 to 2012, dropping from about an average of one case per year to one every other year, equivalent to less than 0.05 per million donations. This compares favorably to the historical estimate of 0 to 2 cases per million donations in non-endemic areas, as contrasted with an incidence of 50 cases per million donations in endemic countries.

In malaria-endemic settings, where frequent boosting by infective mosquito bites helps induce and maintain protective immune responses, severe infection is rare for those who survive beyond early childhood. In a non-immune population, such as that in the United States, clinical malaria presents as a febrile illness with paroxysms, possibly at regular intervals, with accompanying flulike symptoms. Complications can include severe anemia, hepatic involvement, cerebral alterations, renal failure, and shock. The case fatality rate for malaria is generally low (less than 1% in developed countries) but can surpass 10% in recipients of blood products.

Once endemic throughout large parts of the country, malaria in the United States is now due almost exclusively to imported
These represented meaningful change from the prior policy: Important clarifications or definitions were added, however, that represented meaningful change from the prior policy:

1 History of malaria within three years;
2 Residence in a malaria-endemic country within three years; and
3 Travel to a malaria-endemic area within one year.

Important clarifications or definitions were added, however, that represented meaningful change from the prior policy:

A malaria-endemic area was now defined as any area with malaria where CDC recommends antimalarial chemoprophylaxis in travelers in The Yellow Book, whereas previously any nonzero risk was considered endemic.

Travel to a malaria-endemic area was now defined as travel of duration between 24 hours and five years, whereas previously even the briefest exposure—including land travel through a risk area—could trigger deferral.

Residence in a malaria-endemic country was now defined as a continuous stay of longer than five years in a country or countries having any malaria-endemic areas.

Donors who meet the definition of a resident in a malaria-endemic country will be deferred for three years following travel to a malaria-endemic country unless they have lived for three continuous years in a non-endemic country.

These first two changes followed published evidence and discussion at Blood Products Advisory Committee meetings that showed a vanishingly small risk for infection with the large majority of donors receiving the one-year travel deferral, but a significant impact on availability equivalent to ~1% of presenting donors. The third change acknowledges the lengthy exposure typically required to acquire partial immunity that allows for asymptomatic carriage, whereas the final change reflects caution against the possibility that partial immunity may be boosted and sustained by return to endemic areas.

Advances in diagnostics have created opportunities for non-endemic countries to implement strategies that lessen the impact of malaria deferrals while minimizing risk of transfusion transmission. In Europe, regulations published by the Council of Europe in 2006 and subsequently updated endorse the use of validated immunological tests to shorten the deferral period of donors with potential malaria risk who test negative: Those donors who have lived for six months or more in a malaria-endemic area are acceptable as blood donors if they test antibody-negative at least four months after their last visit to a malaria area, as opposed to being permanently deferred. Likewise, donors who report a travel history of less than six months in duration to an endemic area may be accepted as blood donors if they test antibody-negative at least four months after their last visit to a malaria area, in contrast to a one-year (no malaria symptoms reported) or three-year deferral (malaria-like symptoms within six months of return from endemic area). Since 2001, England has used an enzyme immunoassay (EIA) based on three recombinant P. falciparum antigens and one P. vivax antigen (all to the erythrocytic merozoite stage) to shorten the deferral period for at-risk donors to six months for those testing negative. Australia also seeks to reinstate deferred donors on the basis of this same test, and a few other countries employ malaria donor-screening tests on a routine basis. Although not all five Plasmodia are screened for in the assay adopted by England, it accounts for the two species causing most cases of transfusion transmission and does appear to have some cross-reactivity with other species.

Immunofluorescent antibody tests (IFATs) for malaria antibody detection tend to be sensitive, but have the limitations of being time-consuming and subjective. Direct methods for detection of malaria infection are also available. Most widely used for malaria diagnosis worldwide is Giemsa- or Wright-stained blood films, although their use is not practical for mass screening in non-endemic areas, where labor costs are prohibitive and the expertise is lacking. Assays detecting circulating parasite antigens such as histidine-rich protein 2 (HRP) and lactate dehydrogenase (LDH) offer sensitivity equivalent to microscopy for P. falciparum but are less sensitive for P. vivax below a parasite density of 200 parasites per microliter, still insufficient to prevent transfusion transmission.

A variety of nucleic amplification assays allow for detection of one or more malaria species. Conventional and seminested PCR screening of blood bank samples have detection thresholds on the order of 10^3 parasites/μL. Similar to Babesia infection, malaria transfusion risk cannot fully be mitigated by serologic or nucleic acid detection alone. Although biological outliers, a small proportion of individuals retain low-level infection that lasts for several years, including beyond the exclusion period for prior residents of endemic countries.

With an infectious dose theoretically as low as 1–10 parasites per unit of blood, however, even the most sensitive nucleic acid detection methods cannot reduce the risk to zero. Malaria antibody duration is proportional to length of exposure, however, and is hence an informative complement to direct parasite detection methods for reducing transfusion risk.

Leishmaniasis

Leishmania species are a large group of protozoan parasites with broad distribution worldwide. Leishmania are transmitted in...
nature by the bite of a female phlebotomine sandfly, but can be transmitted in blood components and, rarely, congenitally or sexually. Clinical manifestations can vary widely, ranging from asymptomatic infection to severe illness with visceral, cutaneous, or mucosal involvement. The visceral form (kala-azar) is characterized by fever, wasting, hepatosplenomegaly, and pancytopenia, and if untreated is usually lethal. Cutaneous forms involve progressive skin lesions that become ulcerative, sometimes with mucosal involvement. Although endemic in about 88 countries, the public health burden is hardly uniform. More than 90% of visceral cases appear in Bangladesh, Brazil, India, Nepal, and Sudan, and about 90% of cutaneous leishmaniasis occurs in Afghanistan, Brazil, Peru, Iran, Saudi Arabia, and Syria. The World Health Organization estimates that two million new infections occur annually, about 1.5 million due to cutaneous leishmaniasis (CL) and half a million due to visceral leishmaniasis (VL), and that as many as 12 million people worldwide are infected. The distribution is expanding due to human immigration and deforestation. In endemic areas, the public health risk is considerable, and many countries have implemented targeted donor exclusion to prevent transmission.
survivability of oocysts in nature.\textsuperscript{133} In the United States, the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004 indicated an age-adjusted seroprevalence <10%, with foreign-born residents three times as likely as US-born residents to be antibody-positive, 24.8% to 8.2%.\textsuperscript{134}

Transfusion transmission of toxoplasmosis was reported nearly 40 years ago, in a case where patients with acute leukemia were transfused with leukocytes from donors with chronic myelogenous leukemia.\textsuperscript{135} Despite the scarcity of reports of transfusion transmission, the risk has been well documented in cardiac transplant patients as well as liver and kidney recipients.\textsuperscript{136} Seroreivalence studies in healthy blood donors indicate a broad range of antibody prevalence from 7.4% in Durango, Mexico,\textsuperscript{136} to 75% in northeastern Brazil.\textsuperscript{137} Antibody presence is long-lived and does not necessarily denote infectivity. Unfortunately, little information is available on the long-term kinetics of antibody development and patent parasitemia over long periods of time, and parasite isolation or detection by PCR is rarely useful in immunocompetent patients, except in diagnosis of ocular toxoplasmosis.\textsuperscript{138} Otherwise, parasitemia in healthy individuals seems to be low-grade and intermittent, with low probability of detection. The ability of the parasite to survive 50 days at $4^\circ$C\textsuperscript{139} and the isolated reports of transfusion transmission in the literature both establish an element of risk.

Prevention of transfusion-transmitted toxoplasmosis is not feasible with either donor exclusion or serologic screening. In most places, discarding units from seropositive donors would heavily prejudice blood availability, with unclear indications that positive antibody status of the donor implies risk for parasitemia. In high-prevalence countries, many blood recipients are likely to have been infected. In an immunocompetent recipient, transfusion transmission is likely to go undetected. Given the parasite’s ability to readily invade and replicate in leukocytes,\textsuperscript{139} leukocyte filtration might diminish the risk in similar fashion as with cytomegalovirus. Whether inactivation treatments being evaluated for other protozoa might be of use for Toxoplasma remains unexplored.

**Microfilariasis**

Filarial worms are arthropod-borne macroparasites that can be caused by a number of different organisms. *Wuchereria bancrofti* and *Brugia* spp. cause lymphatic filariasis; *Loa loa*, *Onchocerca volvulus*, and *Mansonella streptocerca* cause nonlymphatic, subcutaneous filariasis; and *Mansonella ozzardi* and *Mansonella perstans* cause nonlymphatic infections of different body cavities and are typically asymptomatic or mild.\textsuperscript{3} The filariases occur in more than 80 countries, and the health and socioeconomic burdens from lymphatic filariasis and *O. volvulus* are particularly severe, with an estimated prevalence of 120 million and 37 million infections, respectively.\textsuperscript{140} These organisms share similar life cycles and are all transmitted by hematophagous arthropods. In each, adult female worms produce larvae called microfilaria, which for most species circulate in the bloodstream, sometimes with periodicity timed to their primary vector’s feeding habits. The microfilaria are the infective form for insects, but when transmitted by transmision they are incapable of propagating further.\textsuperscript{141}

The lymphatic forms of filariasis, which cause elephantiasis, have been targeted by the World Health Organization as potentially eradicable, primarily by eliminating the human reservoir of microfilaria that infect the mosquito vectors through repeated mass administration of curative drugs.\textsuperscript{140} Results from low- to moderate-prevalence areas in Egypt\textsuperscript{142} and from moderate- to high-prevalence parts of Papua New Guinea\textsuperscript{143} indicate dramatic success in lowering human infections and even, surprisingly, reversing the pathology associated with infection.

There is little published information on the risk for transfusion transmission of filariasis. In most endemic areas, the risk for vector-acquired infection would be orders of magnitude greater than that from transmission for the average individual, given the relative degree of exposure to infective insect vectors and the limited rate of blood transfusion. However, limited studies from Nigeria have shown prevalence of microfilaria of 3.5% with *Loa loa*,\textsuperscript{144} 15.6% with *M. perstans* and 1.3% with *L. loa*;\textsuperscript{145} and 1.3% with unspecified microfilaria.\textsuperscript{146} There has been at least one report of an American blood donor being found with microfilaria.\textsuperscript{141} Isolated case reports of transfusion transmission exist from Italy\textsuperscript{147} and India,\textsuperscript{148} in both cases indicating that the outcome in blood recipients might often be no more severe than mild allergic reaction response to microfilarial antigens. The microfilaria of both *W. bancrofti*\textsuperscript{149} and *L. loa*\textsuperscript{150} survive routine storage conditions for blood. Those from *M. ozzardi*\textsuperscript{151} and from *B. malayi* and *W. bancrofti*\textsuperscript{152} have been successfully recovered following cryopreservation in research laboratories. Given the modest clinical consequences even with direct transfusion, most countries appear to consider the risk to blood recipients too small to merit donor or component screening.

**Summary**

The current risk for transfusion transmission of parasites in the United States is not high, but it is likely greater than the prevailing estimate of one per million units. Until the recent licensure of a screening assay, it appears probable that hundreds of individuals donated annually while infected with *T. cruzi*, the result of demographic changes in the United States and its donor population. Although that implies potentially several cases of transfusion transmission annually, the adoption of testing for all donors at least once has brought the incident risk to near-zero.

Silent infection in semi-immune donors constitutes at least some risk for malaria transmission in blood products in the absence of serological and nucleic acid screening, but recent years have seen an average of one case every other year. Meanwhile, most presenting donors hold very small risk from travel exposure, and the three-year deferral for prior residency has high (even if imperfect) efficacy. Both serological and direct detection assays can contribute to enhanced safety against these and other parasitic agents. Briefly effective methods such as pathogen removal or inactivation also appear promising.

Perceived risk for *Babesia* species in blood is growing and represents the most commonly transmitted parasite in the United States. A recent review indicates growing recognition of transfusion-associated cases, and surveillance data following its publication document a frequency of roughly one per million transfusions. Undoubtedly, though, many cases remain undetected. The combination of asymptomatic infection in healthy donors, the lack of a licensed screening assay, and the mobility of both people and blood products altogether imply risks that are higher and geographically less circumscribed than appreciated.

Other parasites with wide global distribution are rarely documented as transfusion transmitted. *Leishmania* parasites frequently produce asymptomatic infection, but malaria travel exclusion policies interrupt risk from some donors while the adoption of universal leukoreduction in many countries further reduces the risk.
Toxoplasma gondii is a common infection worldwide, but parasitemia is not commonly found except in immunocompromised patients, who are not part of the donor population. Microfilaria of different species can be transmitted in blood products, but as a self-limiting infection producing allergic reaction is considered of modest clinical consequence. In sum, the potential for transfusion transmission exists from other parasites that cause human illness, but they are generally not considered significant enough to merit specific interventions.

**Key references**

A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion


