Emerging Pathogens – How Safe is Blood?

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Introduction

Since the HIV-1 blood scandal in the mid-1980s, the main concern of patients before receiving a blood transfusion is the risk of acquiring a transfusion-transmitted infection. Currently in Germany, the residual risk of suffering a transfusion-related HCV or HIV-1 infection is extremely low: approximately 1:1.11 million and 1:4.3 million, respectively [1]. Further reduction of these residual risks with regard to transfusion-transmitted infections is a major goal for transfusion medicine. Next to optimised donor selection programmes, the introduction of nucleic acid amplification technologies (NAT) [2, 3] into blood donor screening has been a major reason for the improvement of blood safety and the reduction of the diagnostic window period to a minimum of 4–6 days for HCV and 6–10 days for HIV-1 [4–6].

With the reduction of the residual transfusion-transmitted risks of the three major transfusion-relevant viruses (HBV, HCV and HIV-1), the activities of transfusion medicine have shifted to reducing the risks posed by bacterial contamination, especially in platelet components [7]. Due to fatal septic reactions after the transfusion of platelet components at the end of their shelf-life (day 5 after donation), the maximum shelf-life of these components was reduced to 4 days in Germany in 2008 [8]. Nevertheless, shelf-life reduction was not able to prevent every case of serious bacterial transmission. In addition, due to new screening strategies with rapid bacterial detection methods, like Bactiflow [9, 10] and 16S and 23S rDNA NAT [11–13], the introduction of pathogen reduction methods [14–18] is a promising option to cover the bacterial contamination risk in the near future.

Other pathogens, like Plasmodium spp. [19], dengue virus [20], Trypanosoma cruzi and Babesia spp., could be transmitted by blood components and become more relevant in their endemic regions as well as to travellers in non-endemic re-
Emerging Pathogens in Blood Components

Emerging Infections

Malaria Infections

Malaria parasites are mainly transmitted by bites from *Anopheles* mosquitoes. Each year, more than 1 million people die from malaria [21, 22]. Approximately 50% are children under 5 years of age. About 90% of all infected people live in Africa. Five pathogens are relevant for human infections: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi* [23]. The most harmful pathogen is *Plasmodium falciparum*. The symptoms of malaria include high recurring-to-periodic fever, chills, dysfuction of the gastrointestinal tract and cramps. Children have a much higher risk of dying from malaria [24].

The lifecycle of *Plasmodium* spp. is separated into two parts: one part is located in the primary hosts (mosquitoes) with sexual reproduction, and a second in hosts like humans with asexual reproduction. After a mosquito bite, sporozoites migrate along blood vessels and infect liver cells (hepatocytes) where asexual reproduction occurs (tissue schizogony). Merozoites release into the blood and are able to infect new red blood cells and also initiate asexual reproduction (blood schizogony). Other merozoites continue to develop into immature gametocytes. These gametocytes are re-transmitted again into mosquitoes, build ookinetes in the mosquito gut and develop zygotes. From the ookinete, new sporozoites will migrate into salivary glands of the mosquito and can infect another host with the next bite. Since only female mosquitoes feed on blood cells, only they are responsible for the transmission of malaria [25].

Aside from transmission by mosquitoes, malaria pathogens can also be transmitted by blood components [26]. Although all blood components should be tested for malaria in endemic countries in sub-Saharan Africa (SSA), most blood components are not tested [27]. This can be explained by several reasons. On the one hand, most malaria tests are not sensitive enough to detect a low level of parasites. On the other hand, some African countries, like Benin, have a prevalence of malaria in blood donors of more than 30% [28]. If all infected blood donors were rejected, the blood supply could not be maintained in these countries.

In Germany, donors travelling to regions at risk for malaria transmission are deferred from donating blood for 6 months after their return. According to the German guidelines, people born in regions endemic for malaria or who have lived permanently in those regions for at least 6 months are deferred from blood donation for 4 years after immigration or return to Germany. After this temporary deferral, the latter are only allowed to donate under the prerequisite that they have tested negative for *Plasmodium* spp. using approved test systems. However, such test systems are currently not available or established in most blood donor services. Therefore, birth or long stays in regions endemic for malaria will normally lead to permanent deferral from blood donation. Against the background that approximately 3.2 billion people live in regions at risk for malaria, it becomes evident that malaria-associated donor deferral is responsible for a large number of lost donors. On the other hand, the existing donor deferral strategy has proven effective in preventing transfusion-associated malaria infections. In total, only 15 cases of transfusion-transmitted malaria have been reported in Germany, with the last case occurring in 1998 [29]. The challenge for countries that are non-endemic for malaria is to reduce the rate of donor deferral due to malaria without compromising the high level of safety for blood products from transfusion-transmitted malaria.

The silver bullet to reduce health-care problems associated with malaria would, of course, be a world-wide vaccination programme [30]. Despite extensive research in this field, a vaccine is currently not available. The gold standard for diagnosing malaria infections is still the direct microscopy of thick blood smear for antigen detection [31]. However, the analytical sensitivity of this technique is highly dependent on the experience of the staff. Rapid antigen detection systems are available but more expensive and potentially less sensitive than microscopy. The most sensitive but also most expensive method is NAT testing. Different commercial assays are available with different analytical sensitivities ranging between 1.27 and 40 copies/ml. NAT is able to detect 4 parasites/ml of blood [32]. However, detection has to be performed on whole blood samples as plasmodia are intracellular parasites.

The possible test strategies for malaria in blood donors may be different for endemic and non-endemic countries. In non-endemic countries, a combination of questioning and deferral, as performed in Germany, is assumed to be the most practical and effective approach. For re-entry of the donors after the deferral period, testing for antibodies or by NAT might be reliable and cost-effective. For countries endemic for malaria, however, the deferral of donors is certainly not an option. Therefore, they should test their blood donors using the highest sensitivity possible, which is given by using NAT. However, routine NAT screening is not widely available in the majority of malaria-endemic countries [33].

Pathogen inactivation could be a good solution in the future, because parasite concentration is moderate. However, the primary target cells are the erythrocytes. Therefore, the development of new pathogen reduction agents is still needed. The Intercept s303 reagent might be a good candidate, but further field trial studies are needed to analyse its inactivation potential [34]. In addition, riboflavin has also been investigated in clinical trials for packed red cell concentrates and whole blood donations [35]. Pathogen reduction methods can
reduce the concentration of *Plasmodium* spp. by 2–4 log periods. Potential changes in climatic conditions within the next decades might aggravate the relevance of malaria and support the development of efficient vaccines, pathogen reduction methods or better screening systems.

**Dengue Virus Infections**

Dengue virus infections pose a major international public health concern [36]. According to the WHO, approximately 2.5 billion people in more than 100 countries are at risk of becoming infected [37, 38]. 50–100 million dengue virus infections occur every year, and approximately 1.25 million people may die due to dengue fever, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Dengue virus maintenance in nature is independent from infected humans [39]. A very recent study suggests that dengue infections are underreported, and the annual infection rates may be even three- to fourfold higher than estimated by the WHO [40]. Dengue fever can therefore be considered the most important mosquito-borne viral disease.

As an arthropod-borne infection, the major transmission pathway occurs by mosquitoes from the *Aedes* genus [41, 42]; however, transmission by blood components or organ transplantations can also occur [43, 44]. The primary vector is *Aedes aegypti*, but other vectors, like *Aedes albopictus* or *Aedes polynesiensis*, are also possible. Female mosquitoes acquire the virus by biting infected humans during the viraemic period and become infective after an extrinsic incubation period of 7–14 days. Subsequently, infected mosquitoes can transmit the virus during every feeding. *Aedes* spp. such as *Aedes vexans* that are generally native in Germany are not capable of transmitting dengue virus [45].

Dengue virus is a single-stranded RNA virus belonging to the *Flaviviridae* family. The mature virion has three structural (core, membrane-associated, and envelope) and seven nonstructural (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5) proteins. There are four serotypes classified according to their immunological properties: DEN-1, DEN-2, DEN-3 and DEN-4.

Laboratory diagnosis can be done using NAT, antibody screening or dengue antigen tests. The diagnostic window period is 3–5 days for IgM antibodies and 2–3 days for NAT [46]. The diagnostic window period for the NS1 antigen test may also be very short [47]. Dengue virus RNA as well as the NS1 antigen are detectable with onset of symptoms [48]. The IgG antibodies are detectable after approximately 9–10 days. Cross-reactivity with other flavivirus infections is possible and can be explained by sharing common antigenic epitopes. Commercial NAT systems for blood donor screening are available with a 95% level of detection of 14.9 copies/ml [49].

Fever is the predominant symptom in adults, whereas young people younger than 15 years old have asymptomatic infections or an undifferentiated febrile illness with maculopapular rash. Dengue fever and DHF are characterized by severe headaches, sudden onset of high fever, haemorrhagic manifestations, thrombocytopenia, and evidence of plasma leakage. DSS has a high mortality rate [50] and often acts as a pathway to disseminated intravenous coagulation. There are no specific anti-viral drugs currently available for dengue; therefore, its management is symptomatic and supportive.

In Germany, 731 total imported cases of dengue fever were reported in 2013 [51]. 75% of these cases were imported from Asia, and 21% came from South and Central America. The last dengue epidemic in continental Europe was reported to have occurred from 1927 to 1928 in Greece. Since then, Europe has been the only populated continent without autochthonous dengue virus infections. However, in 2010, the first cases of autochthonous dengue virus infections were reported from southern France and Croatia [52, 53]. Frank and colleagues [54] reported an outbreak in autumn 2012 in Madeira.

In these countries, *Aedes albopictus* mosquitoes have become domestic and were the implicated vectors in the transmission cases. *Aedes albopictus* has become increasingly established in the European Union. It is assumed that the import of mosquito larvae during the transport of car tyres, in combination with rising average temperatures in Europe due to climate change, are important factors in this process. Today, *Aedes albopictus*, the so-called Asian tiger mosquito, is established in many European countries, such as Greece, Albania, Italy, Croatia, Montenegro, and Spain, and is spreading further. During mosquito monitoring activities in 2011, *Aedes* species were also trapped in the Upper Rhine Valley in Baden-Wuerttemberg [55].

*Aedes albopictus* is not only a very efficient vector for dengue virus but also for numerous other arboviruses, such as the Chikungunya virus. Consequently, if travellers with arboviral infections acquired abroad return to their home regions, in which *Aedes albopictus* has become domestic, there is the risk of causing a local outbreak. Likewise, infected tourists could import infections, as happened during the Chikungunya outbreak in Northern Italy in 2007, which was probably caused by a tourist from India [56].

Although the primary pathway for dengue virus is through the mosquito vector, vertical transmission through intrapartum transmission, nosocomial transmission through needle stick injury, transmissions by organ transplantations, bone marrow transplantation and transfusion of blood components have all occurred [57–59]. Even though the diagnostic window period is assumed to be very short, asymptomatic donors could be the source of such transmissions. In some cases, however, the differentiation between non-mosquito transmission and mosquito-borne infection is difficult in endemic areas where the vector is widespread.

Transfusion-transmitted dengue virus infection has been confirmed in three cases from Hong Kong [60] Singapore [61] and Puerto Rico [44]. As a first step to improve blood safety with regard to dengue virus, many countries implemented a
temporary donor deferral programme for travellers returning from highly endemic areas. These deferral strategies might be helpful if only a few donors will be affected (e.g., less than 1%). If more than 5% of the donor population will be involved, then these options will be ineffective and carry a high risk of unnecessary donor deferral. Donors might not come back, even if the deferral is temporary [62].

Testing for dengue virus is also an option. In the most recent outbreak of dengue fever on Madeira in the Atlantic Ocean, Portuguese authorities implemented blood donor screening by NAT for dengue virus RNA. The percentage of NAT-positive donations differs from region to region; in Puerto Rico it is 1 in 1,000 donations [63, 64]. Additionally, an ELISA test for the NS1-antigen of the dengue virus is available that allows for early detection of an infection. Another approach is the implementation of pathogen reduction methods.

For Germany, however, the main strategy should be the implementation of strict vector control measures, such as insecticide use and reducing potential breeding sites, to avoid the spread of *Aedes* spp. throughout the country.

**Chagas Disease**

Chagas disease, also called American trypanosomiasis, is a tropical parasitic disease caused by the flagellate protozoan *Trypanosoma cruzi* (*Trypanosoma cruzi*). The disease first was described by Dr. Charles Chagas in 1909 [65]. Chagas disease affects approximately 10 million people living in endemic Latin-American countries and approximately 0.4 million people living in non-endemic countries. Each year, 40,000 new infections are registered, about 14,000 infants are born with congenital Chagas disease, and 20,000 deaths are related to trypanosomiasis. The primary wildlife reservoirs for *Trypanosoma cruzi* include opossums, raccoons, armadillos, squirrels, wood rats and mice. The screening of blood donations, solid-organ donors and donors of cells or tissues for *Trypanosoma cruzi* is mandated in all Chagas-endemic countries. Screening can be done using NAT or antibody screening. Most countries in Latin America have implemented blood screening for *Trypanosoma cruzi* antibodies [66].

The prevalence rates vary between countries and from year to year. Schmuniz et al. [67] reported data over a period of 10 years; the highest prevalence was seen in Bolivia, at approximately 10%, and the lowest was in Mexico, with approximately 0.2%. Based on the high prevalence level in some regions, more specific screening tests like NAT might differentiate between infectious and non-infectious donors and blood donations.

Another challenge in blood safety is the high percentage of replacement donors in South America. In Costa Rica, Brazil and Ecuador, approximately 50% of all donors are voluntary unpaid donors; however, in Peru, Chile and Mexico, less than 10% of all donors are voluntary donors. Pathogen inactivation using amotosalen was able to reduce 5.4 log10 TCID50/ml of parasite concentrations in platelets and 5.0 log10 TCID50/ml in plasma concentrates and could be an alternative for platelets and plasma products [68]. The residual risk of transfusion-transmitted infections with *Trypanosoma cruzi* is difficult to determine because neither donor-related nor recipient-related look-back procedures are implemented on a routine basis in endemic countries.

**Transfusion-Transmitted Risk for Infections with Babesia spp.**

*Babesia* spp. are intraerythrocytic protozoan parasites transmitted to animal or human hosts primarily by tick vectors. More than 100 species of *Babesia* have been described worldwide. In Germany, *Ixodes ricinus* is the most important vector for tick-borne diseases in humans and transmits at least *Babesia divergens* and *B. microti* to humans [69]. The first description of *Babesia microti* was reported in 1969 in the USA, with increasing frequency each year. Fatalities in transfusion recipients diagnosed with babesiosis have occurred in the USA within the last few years. Babesiosis is a world-wide disease, with infections reported in France, Germany, Italy, England, Ireland, Spain, Sweden and Switzerland. The overall seroprevalence of *Babesia* spp. was reported by Hunfeld et al. [70] as between 3.6 and 5.4%.

The main transmission pathway is through a bite of infected *Ixodes* ticks. In addition to vector-borne transmission; however, transmission can also occur congenitally and through blood transfusion. The first case of transfusion-transmitted babesiosis (TTB) was reported in 1968 by Fitzpatrick et al. [71] in Ireland. Four months after receiving a blood transfusion, doctors detected *Babesia divergens* in a 48-year-old asplenic male.

A recent report on TTB by the American Red Cross demonstrated that elderly patients are at higher risk of infection by *Babesia* [72]. This might be explained by an age-associated decline in resistance to *Babesia microti*. Esernio-Jenssen et al. [73], New et al. [74] and Sethi et al. [75] reported an infection by *Babesia microti* transmitted transplacentally and perinatally within the third trimester of pregnancy. Transmission by solid-organ transplantations is possible in principle, but no cases have yet been reported. Lux et al. [76] described a babesiosis infection after a heart transplantation in combination with a blood transfusion; however, the origin of the infection in this case is not definitely clear.

Babesiosis shows a wide range of clinical symptoms, from completely asymptomatic to severe, life-threatening illness [77]. The lack of clinical symptoms in many babesiosis infections underlines the challenge for blood transfusions. Infected donors cannot be identified and deferred by clinical signs. Symptoms normally occur after 1–9 weeks post-infection, with fever, headache, chills, drenching sweats, myalgia, malaise and haemolytic anaemia [78]. Patients who suffer from this illness can develop haemodynamic instability, disseminated intravascular coagulation, acute respiratory distress, renal dysfunction, hepatic compromise, myocardial infarction and death.
Table 1. Emerging pathogens overview

<table>
<thead>
<tr>
<th>No.</th>
<th>Pathogen</th>
<th>Definition</th>
<th>Species</th>
<th>Disease</th>
<th>People infected</th>
<th>Infections per year</th>
<th>Deaths per year</th>
<th>Countries</th>
<th>Target cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Plasmodium spp.</td>
<td>parasite</td>
<td>5 species are pathogen for humans</td>
<td>malaria</td>
<td>3 billion (at risk for infections)</td>
<td>243 million</td>
<td>&gt; 1 million</td>
<td>ca. 90% Africa</td>
<td>erythrocytes</td>
</tr>
<tr>
<td>2</td>
<td>dengue virus</td>
<td>virus</td>
<td>4 serotypes</td>
<td>DHF, DSS</td>
<td>2.5 billion</td>
<td>50 million</td>
<td>1.25 million</td>
<td>over 100 countries</td>
<td>monocytes / macrophages fibroblasts</td>
</tr>
<tr>
<td>3</td>
<td>Trypanosoma cruzi</td>
<td>parasite</td>
<td>6 lineages (I–VI)</td>
<td>Chagas disease</td>
<td>10.4 million</td>
<td>40,000</td>
<td>20,000</td>
<td>endemic in Latin-American countries world-wide</td>
<td>erythrocytes</td>
</tr>
<tr>
<td>4</td>
<td>Babesia spp.</td>
<td>parasite</td>
<td>B. microti and B. divergens and others</td>
<td>babesiosis</td>
<td>unknown</td>
<td>&lt;10</td>
<td>unknown</td>
<td>world-wide</td>
<td>erythrocytes</td>
</tr>
</tbody>
</table>

Diagnosis can be performed using three strategies: i) direct identification of Babesia-infected erythrocytes on a peripheral blood smear; ii) detection of antibodies to Babesia spp., and iii) detection of the Babesia genome by NAT. Due to morphological similarities to Plasmodium spp., distinguishing between the two requires highly trained personnel. The indirect immunofluorescent antibody test (IFA) can detect the IgG and IgM antibodies; this test originated in 1978 and represents the up-to-date serological ‘gold standard’ [79]. Testing by NAT represents a more sensitive diagnostic tool, compared to a peripheral blood smear, but negative screening results can also be explained by intermittent parasitaemia during chronic infections.

The current standards issued by the American Association of Blood Banks (AABB) require the indefinite deferral of a blood donor with a history of babesiosis. Testing for Babesia antibodies on an ELA/enzyme-linked immunosorbent assay (ELISA) format would be attractive, but does not yet exist. Therefore, IFA testing for Babesia antibodies represents the current standard. The implementation of blood donor screening by NAT can reduce the diagnostic window period to a minimum, but parasitaemia wanes with time and is difficult to detect after about 2 months [80]. Therefore, NAT is a good screening system for acute infections but less efficient for chronic infections. Pathogen reduction methods using amotosalen or riboflavin could reduce the pathogen content by approximately 5 logs, which might be efficient in the majority of all infections [81, 82]. Other procedures, like leucocyte depletion or irradiation, may have a minimal impact on the prevention of TTB [76, 83].

Discussion

Table 1 summarises the epidemiological data of the emerging pathogens. Malaria and dengue virus are global threats that have infected almost half of the human population and have severe clinical symptoms with high death rate. Other parasite infections, like trypanosomiasis, are currently more relevant for South America.

Detection systems such as antibody tests, antigen tests and NAT systems are available in principle, but have yet to be adopted or combined to achieve a sufficient level of safety. Pathogen reduction systems are good alternatives, with the disadvantage that different target cells or media require the use of different pathogen reduction systems. Currently, three different pathogen reduction technologies are available (table 2).

Photochemical methods like S59/Intercept (Cerus Corporation, Concord, CA, USA) are suitable for plasma products or platelet concentrates or S303 for packed red cells. The chemical agent connects with DNA. After UV-A illumination, an irresistible linkage occurs and prevents any pathogen development.

Photodynamic methods use natural agents like riboflavin/Mirasol PRT (Terumo BCT, Denver, CO, USA). Together with UV-A irradiation, they destroy the DNA in pathogens. These technologies are suitable for plasma, platelets and probably also for packed red cells; this application is in clinical trials [84].

A third technology is based only on illumination with UV-C light in combination with continuously moving blood components on a shaker [18, 85]. Whereas the pathogen reduction capacity of photochemical and photodynamic pathogen reduction systems is approximately 6 log periods, the capacity of the UV-C methods is slightly lower. On the other hand, prevention of any additional agents is an advantage of this system.

Based on different natural pathogen concentrations, the risk analysis for these methods changes. UV-C will be less efficient for pathogens like dengue virus, which can reach high virus concentration of 10^9 copies/ml. But for parasites like trypanosomiasis or bacteria it could be a good option.

A challenge for the next decade is to develop new reagents suitable for whole-blood inactivation to prevent known and
0.19% were repeat reactive by transcription-mediated amplification testing. Therefore, blood donor screening for dengue virus by NAT will be relevant in endemic areas.

A study by Tonnetti et al. [87] demonstrated that 42 out of 2,150 blood donors were positive for Babesia antibodies and 1 was also NAT positive. Although the geographic distribution of positive blood donors did not completely overlap with the distribution of the reported clinical cases, a regional screening strategy can be one tool to improve blood safety. Johnson et al. [88] identified several NAT-positive, antibody-negative blood donors, which underlines the request for genomic screening systems. Leiby et al. [89] reported long-term parasitaemia of T. cruzi in seropositive US blood donors. Since 2006, an FDA-licensed antibody assay is available. Testing US donors is important and life-saving for recipients as well as donors. However, commercial FDA-licensed or CE-licensed systems are still lacking. The medical field eagerly awaits the advent of an efficient blood donor screening system.

Next to the implementation of new modern screening methods – like NAT - and pathogen reduction methods, it is important to establish general blood safety procedures, like utilising voluntary, unpaid donors, leucocyte depletion or diversion of the first few millilitres globally to implement equal safety standards for all donors and patients in the world.

The risk analysis for these four pathogens, especially for a non-endemic country like Germany, should consider the risk for asymptomatic infectious donors within and outside of the diagnostic window period. For malaria, Chagas disease and dengue virus infections, a donor deferral strategy will be sufficient at the moment in Germany because infections from all of these pathogens are rare in Germany, and efficient commercial screening systems are not available. Nevertheless, blood donor services should be on alert and might develop screening methods for those pathogens because the climatic environment as well as the donor population can change over time. Blood donor screening for babesiosis infections could be relevant for Germany, with a high seroprevalence of 3–5%, but efficient screening systems are still missing.

The experience in the USA will be different. As reported by Leiby et al. [86], in the USA more than 540,000 blood donations were lost by the deferral strategy. However, the majority of the transfusion-transmitted malaria cases were not based on these travellers. Stramer et al. [44] reported on the screening of 10,508 blood donors in Puerto Rico for dengue virus. A total of unknown pathogens efficiently. For trypanosomiasis as well as for babesiosis, an inactivation capacity of 4–6 log periods will be efficient. For Plasmodium spp.– which must be inactivated in red cells or whole blood – and for dengue virus, the natural pathogen concentration can be higher than the capacity of the pathogen reduction methods. Therefore, a combination between donor deferral, blood donor screening and pathogen reduction is recommended.

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**Disclosure Statement**

The authors declared no conflicts of interest.

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**Table 2. Methods to improve blood safety**

<table>
<thead>
<tr>
<th>No.</th>
<th>Pathogen</th>
<th>Screening systems</th>
<th>Pathogen reduction methods</th>
<th>Donor deferral</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>antigen antibodies</td>
<td>other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plasmodium spp.</td>
<td>RDT available, DWP 1–2 weeks</td>
<td>microscopy, DWP 1–2 weeks</td>
<td>s303, riboflavin</td>
<td>for non-endemic countries possible</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>available, DWP 3–4 weeks</td>
<td></td>
<td>s59, UV-C, riboflavin</td>
<td>Germany 28 days</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>available, DWP 2–3 weeks preferred, DWP 2–3 weeks</td>
<td>only for acute infections, DWP 1 week</td>
<td>s59, riboflavin</td>
<td>for non-endemic countries possible</td>
</tr>
<tr>
<td>4</td>
<td>Babesia spp.</td>
<td>not available</td>
<td>microscopy, DWP 1–2 weeks</td>
<td>s303, riboflavin</td>
<td>for people with acute or post babesiosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not possible</td>
</tr>
</tbody>
</table>

DWP = Diagnostic window period; RDT = rapid diagnostic test.
References


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Transfus Med Hemother 2014;41:10–17