Inactivation of *Babesia microti* in red blood cells and platelet concentrates

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**BACKGROUND:** With an increasing number of recognized transfusion-transmitted (TT) babesiosis cases, *Babesia microti* is the most frequently TT parasite in the United States. We evaluated the inactivation of *B. microti* in red blood cells (RBCs) prepared in Optisol (AS-5) using amustaline and glutathione (GSH) and in platelet components (PCs) in 100% plasma using amotosalen and low-energy ultraviolet A (UVA) light.

**STUDY DESIGN AND METHODS:** Individual RBCs and apheresis PCs were spiked with *B. microti*-infected hamster RBCs (iRBCs) to a final concentration of 10^6 iRBCs/mL and treated with the respective inactivation systems according to the manufacturer's instruction. Samples were collected before (control) and after (test) each treatment. Dilutions of the control samples to 10^-6 were inoculated into hamsters, while the test samples were inoculated neat or at 10^-1 dilution. At 3 and 5 weeks postinoculation, hamsters were evaluated for *B. microti* infection by microscopic observation of blood smears and 50% infectivity titers (ID_{50}) were determined. Log reduction was calculated as control log ID_{50} minus test log ID_{50}.

**RESULTS:** Parasitemia was detected in hamsters injected with as low as 100,000-fold diluted control samples, while no parasites were detectable in the blood smears of any hamsters receiving neat test samples. Mean log reduction was more than 5 log/mL by amustaline/GSH for RBCs and more than 4.5 log/mL by amotosalen/UVA for PCs.

**CONCLUSION:** *B. microti* was inactivated to the limit of detection in RBCs and PCs after the respective inactivation treatment. Complete inactivation of *B. microti* was achieved in this animal infectivity model, and pathogen reduction treatment inhibited transmission of infection.

In the United States human babesiosis is attributed primarily to infection with *Babesia microti*, a tick-borne intraerythrocytic protozoal parasite endemic to portions of the Northeast and upper Midwest. The clinical manifestations of babesiosis range from subclinical to severe and can lead to death in 5% to 9% of hospitalized patients with 21% of fatalities in immunocompromised patients. During the past five decades, the frequency of reported clinical babesiosis cases has risen. This is in part due to an expansion of the parasite's geographic distribution and increased interaction with humans, but also because of increasing awareness among physicians in endemic areas. Concomitant with the increased recognition of vector-mediated infections, more than 160 cases of transfusion-transmitted babesiosis (TTB) were identified between 1979 and 2009. From January 2010 through

**ABBREVIATIONS:** GSH = glutathione; ID_{50} = 50% infectivity titer; iRBC(s) = *B. microti*-infected hamster red blood cell(s); PC(s) = platelet component(s); TT = transfusion-transmitted; TTB = transfusion-transmitted babesiosis.
December 2016, a total of 70 positive donors have been associated with 67 cases of TTB at the American Red Cross alone. The high number of TTB cases makes babesiosis the most frequently TT disease due to parasites in the United States.

At present, the diagnosis of babesiosis in healthy blood donors relies on detection of antibodies or detection of parasite DNA by polymerase chain reaction (PCR). The lack of blood screening assays is a major barrier to the prevention of TTB. Recently, investigational blood screening assays for the detection of antibodies including arrayed fluorescence immunoassays and enzyme immunoassays, as well as by PCR (included in one investigational protocol), were evaluated for use. However, to date no Food and Drug Administration (FDA)-licensed blood donor screening test is available for the detection of B. microti.

In 2014, the FDA approved a photochemical treatment process utilizing amotosalen and low-energy ultraviolet A (UVA) light (INTERCEPT Blood System, Cerus Corp.), to inactivate pathogens and residual white blood cells in plasma and platelet components (PCs), to reduce the risk of TT infection. A previous study showed this technology inactivated B. microti in PCs suspended in 65% platelet additive solution (PAS), but did not evaluate PCs in 100% plasma. Therefore, evaluation of the ability to inactivate B. microti in PCs manufactured in 100% plasma is important to show the consistency of inactivation for this pathogen in PCs regardless of platelet (PLT) suspension medium. Additionally, since contaminated red blood cells (RBCs) were implicated in almost all documented TTB cases, the evaluation of B. microti inactivation in RBCs is critical. In this study we investigated the inactivation of B. microti in both PCs and RBCs. For PCs in 100% plasma, we used the FDA-approved amotosalen/UVA INTERCEPT Blood System for PLTs, while for RBCs we used the investigational INTERCEPT Blood System for RBCs, which utilizes amustaline and glutathione (GSH).

**MATERIALS AND METHODS**

**Collection of whole blood and PCs**

RBCs obtained from whole blood collections and single units of apheresis PLTs suspended in 100% plasma were collected by the American Red Cross, Holland Laboratory Research Blood Program, under a human use protocol approved by the American Red Cross Institutional Review Board. Whole blood units were collected from single donors in sets containing CPD and leukoreduced RBCs were prepared using AS-5. PCs were weighed upon receipt, and if necessary the volume was adjusted to approximately 285 mL. A 2-mL sample was removed from the PC and used to determine PLT count and to screen for the presence of antibodies against B. microti by indirect fluorescent antibody testing as previously described.

**B. microti stock preparation**

All hamsters were housed at Bioqual, Inc. animal facility (Rockville, MD) and all related procedures performed were preapproved by the Bioqual Institutional Animal Care and Use Committee. A B. microti-infected colony of Golden Syrian hamsters was established by infecting one animal with cryogenically preserved B. microti-infected hamster RBCs (iRBCs). The parasite was originally isolated from an infected blood donor resident in Connecticut. The sample was injected intraperitoneally into one naïve 4-week-old female hamster (Invigo) and the infection was monitored by blood smears. When the parasitemia reached a minimum of 20%, the hamster was anesthetized before exsanguination via cardiac puncture and the blood was collected into chilled heparin (Fisher Scientific) and used to infect four naïve hamsters. The infection was propagated every 4 or 5 weeks and a new infection was started before each experiment to avoid using infected blood containing parasites with more than four passages in the hamsters. Blood obtained from these infected hamsters was used for the experiments.

**INTERCEPT Blood System for RBCs**

The INTERCEPT Blood System for RBCs includes an amustaline vial, a GSH vial, a trifurcated set with two 0.2-μm filters, and a processing set with three containers: a mixing bag containing a proprietary processing solution, an incubation bag, and a storage bag containing SAG-M (Fig. 1A). An AS-5 RBC unit was spiked with iRBCs, control samples were removed from the unit, serially diluted, and injected into the hamsters. For the inactivation process, GSH was dissolved in saline and delivered to the prepared RBCs in the mixing bag. After the unit was dosed with GSH, amustaline was dissolved in saline and immediately transferred by sterile filtration to the mixing bag of the processing set. The resulting concentrations at the initiation of treatment were 20 mmol/L GSH and 0.2 mmol/L amustaline. After the addition and mixing of GSH and S-303, the RBC unit was transferred to the incubation bag by gravity flow through the integrated tubing. The input RBC bag was detached, and the treated RBC unit was incubated at room temperature (20–25°C) for 3 hours. A sample was removed and used to inoculate the hamsters after appropriate dilutions. The incubation container was allowed to incubate for an additional 15 to 21 hours after withdrawal of the 3-hour sample. The RBC component was then centrifuged to separate the RBCs, and the supernatant was expressed into the mixing bag of the processed RBCs. The sample was injected intraperitoneally into one naïve 4-week-old female hamster (Invigo) and the infection was monitored by blood smears. When the parasitemia reached a minimum of 20%, the hamster was anesthetized before exsanguination via cardiac puncture and the blood was collected into chilled heparin (Fisher Scientific) and used to infect four naïve hamsters. The infection was propagated every 4 or 5 weeks and a new infection was started before each experiment to avoid using infected blood containing parasites with more than four passages in the hamsters. Blood obtained from these infected hamsters was used for the experiments.
Fig. 1. Experimental designs. (A) INTERCEPT Blood System for RBCs. Leukoreduced RBCs were prepared from a freshly collected whole blood and spiked with iRBCs to a final concentration of $10^6$ iRBCs/mL. The positive control (pretreatment) was removed from the spiked unit after mixing and serially diluted in PBS before inoculation into naive hamsters. The entire contaminated component was then treated with the S-303 inactivation system and incubated at room temperature (RT) for 3 hours before a sample was removed (3 hr posttreatment), serially diluted in PBS, and injected into naive hamsters. The treated RBC components were further incubated at RT for up to 24 hours. The RBC component was then centrifuged and the supernatant was expressed and exchanged with storage AS. A second posttreatment sample (24 hr posttreatment) was collected at this stage, diluted in PBS, and injected into naive hamsters. (B) INTERCEPT Blood System for PLTs. PCs collected by apheresis in 100% plasma were spiked with iRBCs ($10^6$ iRBCs/mL) and a control sample (pre-UVA) was removed. Amotosalen was added to the unit by passing the entire PC through the amotosalen container and into the illumination container. The tubing connecting the amotosalen container to the illumination bag was sealed, and the amotosalen container and the original PLT bag were detached. The PC was illuminated with a single 3.0 J/cm$^2$ UVA treatment. After UVA illumination, the illuminated sample (post-UVA) was collected and both samples (pre- and post-UVA) were serially diluted in sterile PBS and injected into naive hamsters. [Color figure can be viewed at wileyonlinelibrary.com]
INTERCEPT Blood System for PLTs
The INTERCEPT Blood System for PCs utilizes a psoralen (amotosalen/S-59) and low energy UVA (Fig. 1B). Amotosalen is a nucleic acid–targeting reagent which, upon UVA illumination, forms covalent adducts with nucleic acid and prevents replication, rendering free or cell-associated pathogens noninfectious. The PC was spiked with iRBCs. Amotosalen was dosed by passing the entire content of the PC through the amotosalen container and into the illumination container. The resulting final amotosalen concentration was approximately 150 μmol/L in the illumination container. A control sample was removed to determine pretreatment infectious B. microti titers. The PC was then illuminated (3 J/cm²). After UVA illumination, a sample was withdrawn from the test unit to determine the postillumination Babesia titers. The control and test samples were serially diluted in sterile phosphate-buffered saline (PBS), transferred to the vivarium, and immediately injected into groups of hamsters. In these studies, the treated PLTs were not exposed to a compound adsorption device, where excess unreacted amotosalen is removed, since this does not impact the extent of pathogen inactivation.

Animal inoculation and blood collection
To determine the hamster infectious dose 50% (ID₅₀), 10-fold serial dilutions of the control and test samples collected during both procedures were diluted in PBS and injected intraperitoneally into groups of six animals at 1.5 mL per animal. At 3 weeks postinoculation blood was collected via retroorbital bleeding and used to prepare thin blood smears. Smears were fixed in 100% methanol and stained with acridine orange. The proportion (%) of parasitized RBCs was determined by counting the number of infected cells present per 500 RBCs under a 100× oil immersion objective. Percent parasitemia was also evaluated at 5 weeks postinoculation, when the animals were euthanized and blood was collected by cardiac puncture. For the purpose of calculating the ID₅₀, animals displaying no visible parasitemia were scored as negative and any animal with detectable parasites at any time point were scored as positive.

DNA extraction and PCR
Genomic DNA extraction from hamster whole blood was performed using a commercial kit (Gentra Puregene blood kit, Qiagen), as per the manufacturer’s instructions. Parasite DNA amplification and quantification were performed as previously described. In brief, the reaction was prepared using the universal master mix (TaqMan, Applied Biosystems), and real-time PCR was performed using the thermal cycler (ABI 7500, Applied Biosystems). The number of parasites in collected samples was calculated for each run based on a standard curve present on the plate.

Statistical analysis
Log reduction was calculated by subtracting the log test (ID₅₀) titer from the log control input (ID₅₀) titer. Fifty percent endpoint titers for the untreated control samples (before amotosaline/GSH treatment for RBC and pre-UVA illumination for PC) and the treated samples (3 and 24 hr posttreatment for RBCs and post-UVA illumination for PCs) were calculated using the Reed and Muench method:

\[
\log (ID_{50}) = -\log (\text{dilution of Group 1}) + PD,
\]

where PD is proportionate distribution. For samples in which no viable B. microti was detected, the upper limit of the titer is estimated by assuming that:

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**Fig. 2. Infectivity of stock aliquots.** Blood was collected from highly parasitemic hamsters (≥35% of RBCs parasitized) and serially diluted in PBS. The three highest dilutions were injected into naïve hamsters and the development of parasitemia was monitored up to 5 weeks after injection. The same stock was used to inoculate RBCs and PCs used in the study. Infected animals are shown by solid colors. [Color figure can be viewed at wileyonlinelibrary.com]
Log ID 50

Log reduction was calculated by using $v = 1\text{ mL} (\log /\text{mL})$, as required by the FDA, and using $v = 9\text{ mL}$, where the total tested sample was used (1.5 mL for six hamsters).

RESULTS

The two studies evaluating *B. microti* inactivation in RBCs and PLTs in 100% plasma were performed separately; however, they have several steps in common. In both studies, to verify the viability of the parasite, dilutions of iRBCs spiked in initial component (RBCs or PCs) were injected into hamsters (Fig. 2). Positive control animals were present in all the dilution groups, and the number of infected hamsters was lower in the groups injected with the higher dilution.

Inactivation of *B. microti* in RBCs

Amustaline-GSH treatment of RBCs resulted in effective inactivation of *B. microti* (Table 1). In all four inactivation experiments, *B. microti* was detectable by blood smears in hamsters (between 3/6 and 6/6) injected with as low as 100,000-fold dilution of the positive control sample (15 iRBCs; Table 1). In addition, in one replicate, one of six hamsters injected with the $10^{-6}$ dilution (1.5 iRBCs) of the control sample was also positive. In contrast, none of the hamsters injected with the test samples, either neat or at $10^{-1}$ dilution, were positive by microscopic examination of blood smears.

Selected samples collected during the fourth experiment were also analyzed by real-time PCR (Table 2).

Hamster blood for PCR analysis was collected 5 weeks postinoculation. Genomic DNA was extracted from whole blood samples from three randomly selected hamsters injected with the lowest dilution ($10^{-4}$) of the control and from three hamsters injected with the undiluted sample obtained 3 and 20 hours posttreatment. Real-time PCR analysis detected high levels of parasite DNA in the control hamster blood samples, but no *B. microti* DNA was detectable in the blood of animals injected with the treated test samples. The log reduction of *B. microti* in RBCs treated with the INTERCEPT Blood System for RBCs (Table 3) was more than 5 log/mL when considering the inoculum/mL and more than 5.9 log while considering the total volume tested.
Inactivation of *B. microti* in PCs suspended in 100% plasma

Amotosalen/UVA resulted in effective *B. microti* inactivation (Table 1). Similar to the RBC experiments, *B. microti* was detectable by blood smears in the hamsters injected with as little as the 10⁻⁵ dilution (15 iRBCs) of the untreated positive control sample and in none of the hamsters injected with the amotosalen/UVA treated samples, either undiluted, or at the 10⁻¹ dilution. The mean log reduction for the four replicates, calculated with the same methodology as for RBCs, was more than 4.5 log/mL for the per-milliliter infectivity or more than 5.5 log where considering the total volume tested using the Reed and Muench formula (Table 3).

### DISCUSSION

Community-acquired babesiosis is now classified as a nationally notifiable disease and is also recognized as an emerging pathogenic health risk in several parts of the world. Infections in healthy humans can be asymptomatic. In Europe, reported cases have been attributed mostly to *Babesia divergens* and a few to *Babesia venatorum* (EU1) and *B. microti.* In Asia, *B. microti*-like organisms have caused morbidity in Japan and Taiwan, and in 2007 a new Babesia strain (KO1) has been identified in South Korea. Subsequently, *B. microti* has been identified in southeastern mainland China, and *B. venatorum* has been found to be endemic in northwestern mainland China. Sporadic cases of babesiosis have been reported in Africa, Australia, and South America indicating that the vector and means of infection are present and active in all these regions.

Transfusion services in nonendemic regions of the United States and elsewhere may not consider babesiosis as a potential explanation for symptoms and findings of hemolytic anemia after transfusion of *B. microti*-contaminated blood components although cases of babesiosis have been reported from geographies not considered to be endemic. *B. microti* in the United States was initially restricted to New England, but has subsequently expanded to include much of the northeastern United States. Additionally, studies using vector surveillance have shown that the *Ixodes scapularis* infection rates of *B. microti* and *Borrelia burgdorferi* are similar in some areas where babesiosis and Lyme disease are endemic. The incidence of Lyme disease is greater than that of babesiosis, but the difference may be as small as twofold in areas of the Northeast that are highly endemic for both diseases.

Most US cases of babesiosis now occur in nine states, seven of which are located in the Northeast (Maine, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey) and two in the upper Midwest (Minnesota, Wisconsin). However, the geographic distribution of community-acquired human infection has expanded with cases of babesiosis now reported throughout

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**TABLE 3. Inactivation of *B. microti***

<table>
<thead>
<tr>
<th>RBCs</th>
<th>Log titers (ID₅₀/mL)*</th>
<th>Posttreatment</th>
<th>Posttreatment log reduction†</th>
<th>Posttreatment log reduction/mL‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment 3 hr 24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replicate 1</td>
<td>4.8 &lt;-1.0 &lt;-1.0</td>
<td>&gt;5.8 &gt;5.8</td>
<td>&gt;4.8 &gt;4.8</td>
<td></td>
</tr>
<tr>
<td>Replicate 2</td>
<td>5.0 &lt;-1.0 &lt;-1.0</td>
<td>&gt;5.9 &gt;5.9</td>
<td>&gt;5.0 &gt;5.0</td>
<td></td>
</tr>
<tr>
<td>Replicate 3</td>
<td>4.8 &lt;-1.0 &lt;-1.0</td>
<td>&gt;5.8 &gt;5.8</td>
<td>&gt;4.8 &gt;4.8</td>
<td></td>
</tr>
<tr>
<td>Replicate 4</td>
<td>5.2 &lt;-1.0 &lt;-1.0</td>
<td>&gt;6.2 &gt;6.2</td>
<td>&gt;5.2 &gt;5.2</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD§</td>
<td>5.0 ± 0.2 &lt;-1.0 &lt;-1.0</td>
<td>&gt;5.9 ± 0.2 &gt;5.9 ± 0.2</td>
<td>&gt;5.0 ± 0.2 &gt;5.0 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCs</th>
<th>Log titers (ID₅₀/mL)*</th>
<th>Post-UVA</th>
<th>Post-UVA Log reduction†</th>
<th>Post-UVA Log reduction/mL‡</th>
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<tbody>
<tr>
<td></td>
<td>Pretreatment 3 hr 24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replicate 1</td>
<td>4.5 ± 0.2 &lt;-1.0</td>
<td>&gt;5.5 ± 0.1</td>
<td>&gt;4.5 ± 0.2</td>
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<tr>
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<td>&gt;5.5</td>
<td>&gt;4.6</td>
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</tr>
<tr>
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<tr>
<td>Replicate 4</td>
<td>4.6 &lt;-1.0 &lt;-1.0</td>
<td>&gt;5.5</td>
<td>&gt;4.6</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD§</td>
<td>4.5 ± 0.2 &lt;-1.0</td>
<td>&gt;5.5 ± 0.2 &gt;5.5 ± 0.2</td>
<td>&gt;5.0 ± 0.2 &gt;5.0 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

* Volume injected per hamster was 1.5 mL. For nonparasitemic samples, the upper limit of the titer was estimated by assuming that log (ID₅₀) = log (1/v), where v is the volume of sample injected (1.5 mL × 6 hamsters or 9 mL).
† Log reduction is calculated as log (control Tᵢ / test Tᵢ) where titers are expressed as 10x ID₅₀/mL. Log reductions were determined from numbers that were not rounded.
‡ Log reduction is calculated using the input titer as the limit of detection.
§ Means and SD were determined from numbers that were not rounded.
the Northeast United States ranging from Maine to Maryland. Travelers represent an additional concern as blood donors resident in nonendemic areas may unwittingly acquire the infection while visiting an endemic area. In May 2015, the FDA’s Blood Products Advisory Committee recommended year-round, nationwide antibody screening along with PCR in endemic states (not defined by the committee). However, there is a concern that this approach would result in the needless deferral of high numbers of serologic false-positive reactive donors and those with resolved infections. Recent studies reporting the results of investigational blood donation screening for \textit{B. microti} suggest that testing limited to endemic areas could reduce the risk of TTB without imposing a substantial financial burden on hospitals and blood banks. However, FDA-licensed blood donation screening tests are not yet available. In addition, most of the tests in development only recognize \textit{B. microti}, which although responsible for the majority of the TTB, is not the only \textit{Babesia} species accountable for human infections in the United States. For all these reasons, pathogen reduction treatment of RBCs and PCs represents a viable alternative to reduce the risk of TTB.

Pathogen reduction treatment has the potential to inactivate a wide array of pathogens demonstrated to be transmitted by blood, including those agents for which blood is not tested. Treatment of PCs and plasma with amotosalen/UVA was licensed by the FDA in 2014 to reduce the risk of TT infections. Inactivation of \textit{B. microti} has been demonstrated previously in plasma and PCs suspended in 65% PAS and 35% plasma by the use of amotosalen and UVA and in plasma, PLTs, and whole blood with riboflavin and broad-spectrum UV light. Since technology to culture \textit{B. microti} in vitro is not available, these studies were performed by spiking the selected component with iRBCs, treating the respective component with the pathogen reduction treatment, and inoculating naive hamsters to measure residual infectivity titers. In this study, we spiked full RBC units in AS and PCs manufactured in 100% plasma to an approximate final concentration of 10^6 iRBCs/mL and achieved inactivation of the parasite to below the limit of detection after treatment with amostaline/GSH and amotosalen/UVA, respectively. To assess the relevance of these results, two key parameters are necessary: 1) the mean number of parasites present in the blood of infected donors (to ensure an initial load falling within the range of a human infection) and 2) the limit of detection of parasites in infected hamsters to ensure that all the surviving parasites were detected.

A repository of blood donor samples screened using investigational tests reported parasite loads ranging from 40 to 13,000 parasites/mL in infected blood donors. In another study, the same investigational assay was used for prospective screening of a larger number of donors under IND in which 76 DNA-positive donors were identified (67 antibody-positive and nine antibody-negative). The parasite loads ranged from 5 \times 10^6 to 3 \times 10^6 parasite DNA copies/mL. In our study, we spiked the RBC units to a final concentration of 10^6 iRBCs/mL. However, it is important to note that each infected RBC often contains several parasites, as demonstrated by microscopic observation of hamster-infected blood used to spike the units under study (Fig. 3). As a consequence, the actual number of parasites introduced into the initial components was a minimum of two or three times the number of iRBCs, thus within the highest concentration of parasites detected in the blood of an infected blood donor. In another study, the median parasite load in blood donors was reported as 480 parasites/mL, suggesting that the parasitemia in asymptomatic donors is usually quite low.

We investigated the detection limits of the \textit{B. microti} infectivity model in hamsters by inoculating the animals with serial dilutions of contaminated components. Injection of as few as 15 iRBCs resulted in hamsters with detectable parasitemia in all eight experiments. In
addition, in one instance, one hamster was parasitemic after receiving a 1.5-iRBC inoculum. Similar results were also obtained in a previous study where 10 iRBCs infected three of five inoculated hamsters, suggesting that the hamster model provides a very sensitive infectivity model. In contrast, a recent study investigated the immune response to *B. microti* in Rhesus macaques using a transfusion transmission model and found that 25,000 *B. microti* parasites resulted in an infection.36

Regardless of animal models, the minimum infectious dose of *Babesia* that can infect humans remains unknown. *B. microti*-positive blood donations with a known parasite load identified through blood screening were not transfused into recipients, and prior lookback studies do not provide sufficient information to correlate the minimum amount of parasitemia required to induce TTB.37

Our data demonstrate the efficacy of pathogen reduction with amotosalen/UVA and amustaline/GSH for *B. microti* within the range of parasites observed in blood donor PCs suspended in 100% plasma and in RBCs. Combined with prior studies showing the inactivation of the parasite in plasma and in PCs suspended in 65% PAS using the same model, these experiments demonstrate robust inactivation of *B. microti* in these blood components using these pathogen reduction technologies. Licensed pathogen reduction systems can therefore be a valuable resource in mitigating the risk of TT infections from recognized pathogens, as well as emerging infectious agents for which immediate testing may not be available.

**REFERENCES**


B. MICROTI INACTIVATION IN RBCs AND PLTs


