Editorial Commentary

Blood screening for *Babesia* in the blood supply

Evan M. Bloch[1], Peter J. Krause[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Yale School of Public Health and Yale School of Medicine, New Haven, CT, USA

Correspondence to: Peter J. Krause. Yale School of Public Health and Yale School of Medicine, New Haven, CT, USA. Email: peter.krause@yale.edu.

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In a recent issue of *Transfusion*, Tonnetti *et al.* report findings from their investigation of *Babesia* screening in the United States using a novel nucleic acid test (NAT) ("Transcription-mediated amplification blood donation screening for *Babesia*") (1). This Procleix *Babesia* Assay (Grifols Diagnostic Solutions, USA) detects ribosomal RNA of four *Babesia* species that cause human disease, including *Babesia microti*, *Babesia duncani*, *Babesia divergens*, and *Babesia venatorum*. A large number of blood donation samples (n=176,928) collected from June 2017 to February 2018 were analyzed. NAT reactive samples were confirmed by *B. microti* polymerase chain reaction (PCR) and antibody testing. A total of 61 NAT reactive samples were confirmed as positive (34.5 positive per 100,000 donations), including 35 (57%) confirmed by PCR and 59 (97%) by antibody. Two cases (3%) were NAT reactive but antibody negative because these donors were tested early in infection before antibody was detectable, the window period. As measures of comparison, the prevalence of HIV, hepatitis B and hepatitis C viruses are 1.65, 11.47 and 5.85 per 100,000 donations (2). These findings highlight the high risk that unscreened *Babesia* poses to the US blood supply (3).

Babesia are intraerythrocytic protozoan parasites that are found throughout the world and infect a wide variety of wild and domestic animals, as well as humans. *Babesia* are primarily transmitted by hard bodied (*Ixodid*) ticks but *B. microti*, the most common human pathogen, can also be transmitted through blood transfusion, perinatal transmission, and organ donation (4). The overwhelming majority of babesiosis cases in the US are due to *B. microti*, which is endemic in the Northeast and upper Midwest and causes more than 2,000 reported cases a year. Two other species, *B. duncani* and *B. divergens*, also have been described in the US but fewer than 25 of these cases have been reported to date (4). *B. duncani* is the only other *Babesia* species besides *B. microti* that has been shown to be transmitted through the blood supply but the possibility of transfusion transmitted babesiosis (TTB) due to other *Babesia* species is plausible. *B. microti* cases have been described in Europe and Asia but most reported cases there have been due to *B. divergens* and *B. venatorum*, respectively (5,6). *B. microti* has long been recognized as a leading cause of transfusion-transmitted infection in the US and the number of TTB and tick-transmitted cases are increasing (4,7). This has prompted over a decade of research and development contributing to strategies to mitigate the risk of TTB (7-11).

There have been over 200 reported cases of *B. microti* TTB and three cases of *B. duncani* TTB in the US (11). Babesia is transmissible by any blood product that contains red blood cells. While the majority of cases of TTB have been ascribed to RBC and whole blood products, cases have followed whole blood derived platelets, suggesting that only a few infected red cells are needed to establish competent infection in a transfused host. Tick-borne infection is geographically confined to the Northeast and northern Midwest for *B. microti* and the far West for *B. duncani*. In contrast, blood donors living in non-endemic areas may acquire infection during travel to an endemic area and transmit babesiosis after returning home (7). About a quarter of adults experience asymptomatic infection such that donors are unaware of their infectious status at time of donation (12). *B. microti* may persist in the bloodstream for more than a year following infection (11,13-15).

Furthermore, blood components that are collected in endemic areas may be transported to non-endemic areas. The incubation period for TTB is usually 3 to 7 weeks but may be as long as six months. Blood components can be stored for long periods of time. Tick-borne babesiosis occurs almost exclusively from late Spring to early Fall whereas TTB can occur at any time of year, for reasons stated above, further blurring identification of epidemiological risk factors for infection (4).

Clinically, *Babesia* infection may be mild or subclinical in immunocompetent hosts. By contrast, severe or complicated disease disproportionately affects a large group of vulnerable people, including newborn infants and those over 50; the asplenic; and those with cancer, HIV infection, congestive heart failure, or who are on immunosuppressive drugs (4). Severe anemia, coupled with over-representation of these vulnerable patient groups in the transfused population, likely accounts for the high mortality rate of TTB (~20%) (7). The first case of TTB was reported in 1981 and the numerous reports that followed highlighted the need for preventive measures (7,16). Several blood donor screening studies were initiated and demonstrated that screening could effectively reduce the incidence of TTB (8,10,11). In 2019, the US Federal Drug Administration (FDA) published their most recent recommendations to mitigate risk of TTB. Strategies include screening with NAT using an FDA approved molecular test in 14 states and Washington DC where 97% of the TTB cases have been reported (17). The recommendation also includes pathogen reduction using an FDA approved technology. Currently, there is one licensed pathogen reduction technology for use, albeit in plasma and platelets that have low to absent risk of *Babesia* transmission (17).

Three molecular assays are currently FDA approved for blood donor screening in the US. Two of the assays, the Procleix TMA assay (Grifols Diagnostics Solutions, USA) and the Cobas Polymerase Chain Reaction (PCR) (Roche, Roche Diagnostics, USA), are able to identify four major species that cause human disease (*B. microti*, *B. divergens*, *B. venatorum* and *B. duncani*). The Procleix TMA assay used in the Tonnetti study is highly sensitive (limit of detection of 2–3 parasites per mL) and specific (1). The assay is approved for individual and pooled donor testing; the latter being advantageous for high throughput blood donor screening.

Initial interest in antibody-based tests has waned, in part due to the potential for unnecessary donor loss in endemic areas because of the poor correlation between seroreactivity and active infection. By contrast, molecular (RNA/DNA) positivity is a better—albeit imperfect—correlate of active parasitemia. Molecular assays are able to detect pre-seroconversion window period infections, as occurred in the Tonnetti study, although these are very uncommon (1 in 88,464 donations). *Babesia* DNA clearance has been demonstrated in 86% of donors at one year of follow-up and in 96% of untreated *Babesia*-infected patients by two years post infection, allowing for re-entry of NAT positive donors after 2 to 3 years of negative testing (13). In contrast, less 10% of donors serorevert at 1 year and antibody reactivity can persist for several years, risking loss from the donor pool when antibody-based tests are used to qualify donors (11). The index study supports blood donor screening using molecular assays. Nonetheless, in an industry that is already under financial strain (18), *Babesia* screening is not without cost, as had been projected ahead of its mandatory adoption (19-21).

Although babesiosis has been reported throughout the world, studies of TTB with characterization of transfusion risk outside of the US are few (4). In Australia, a study of 7,000 blood donors yielded no confirmed cases (22). Similarly, a serosurvey of 13,993 donors at selected high risk sites in Canada showed none to be positive for antibodies to *B. microti* (23). In China, 13 of 1,000 (1.3%) donors were low titer seroreactive for *B. microti* by indirect fluorescent antibody testing, although the authors acknowledged limitations of their study and recommended follow-up investigation (24). Finally, in a serosurvey of 988 blood donors in the Tyrol region of Austria, 2.1% were positive for IgG antibodies against the *B. divergens* complex and 0.6% were positive against *B. microti* (25).

In summary, the study by Tonnetti el al. lends support for regional molecular screening of *Babesia* as outlined in the FDA recommendations (17). As risk of TTB in the US wanes, the opportunity for wider (i.e., global) *Babesia* surveillance should not be overlooked because TTB due to *B. microti* (and possibly other *Babesia* species) may be found to be increasingly problematic. High performance diagnostic tools that have been developed for donor screening in the US can then be used to reduce the burden of TTB throughout the world.

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