Highlighting Underrecognized Causes of Transfusion Transmitted Infection (TTI): Case of Transfusion Transmitted Babesiosis (TTB)

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Conflicts of Interest

None

Outline

Introduction to Transfusion Transmitted Infection (TTI) and Transfusion Transmitted Babesiosis (TTB)

Evolution in Blood Donor Screening for *Babesia*

Case Presentation of Transfusion Transmitted Babesiosis (TTB)

Challenges of TTB & Future Directions

Transfusion Transmitted Infection (TTI)

Disease agent that can be fatal or life-threatening and is transmissible by blood or blood components

TTIs

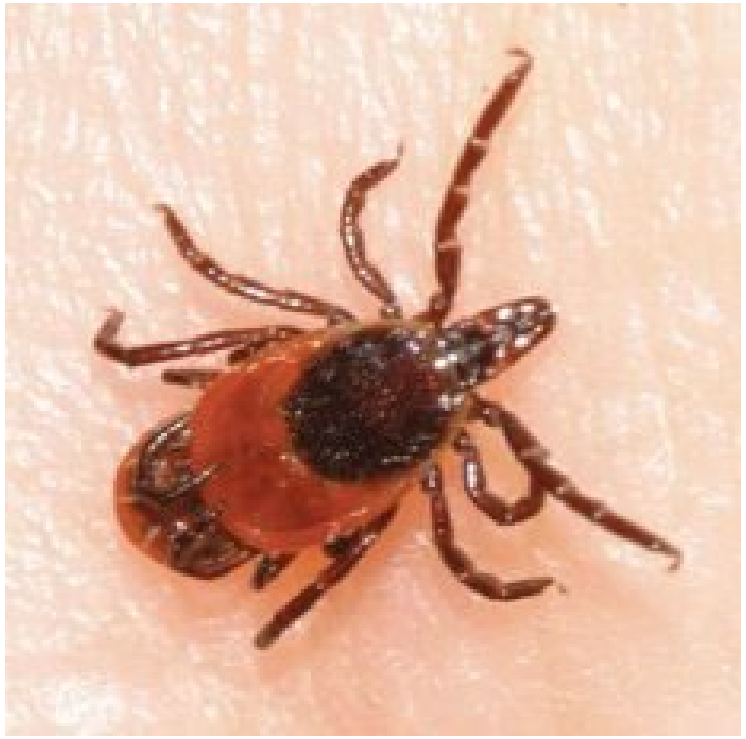
- Bacteria
  - Gram positive bacteria
  - Gram negative bacteria
  - *Anaplasma*
  - *Brucella*
  - *Ehrlichia*
- Parasites
  - *Babesia*
  - *Trypanosoma cruzi*
  - *Leishmania*
  - *Plasmodium*
- Viruses
  - Chikunguyna Virus
  - Dengue Virus
  - Hepatitis Viruses (A, B, C, E)
  - HIV
  - HTLV
  - West Nile Virus
  - Yellow Fever Virus
  - Zika Virus
- Prions

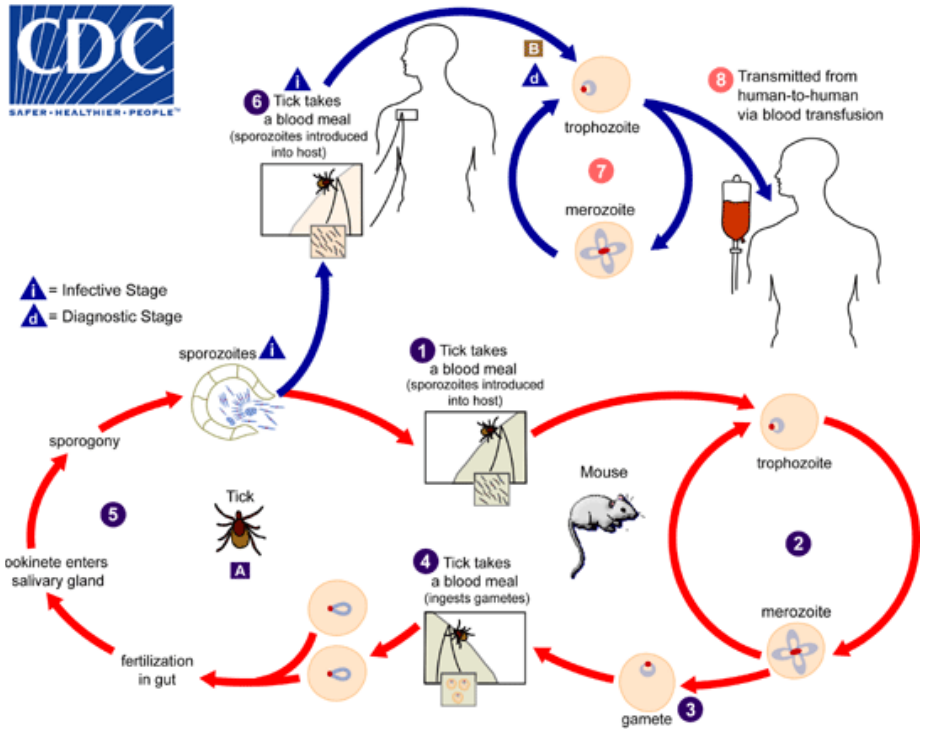
Babesia

Babesia is a genus of tick-borne, intraerythrocytic parasites responsible for a disease known as babesiosis.

Routes of transmission:

- Bite from deer tick (warm months)
- Transfusion (of any RBC containing product)
- Organ transplantation
- Transplacental/congenital





Babesia

Species:

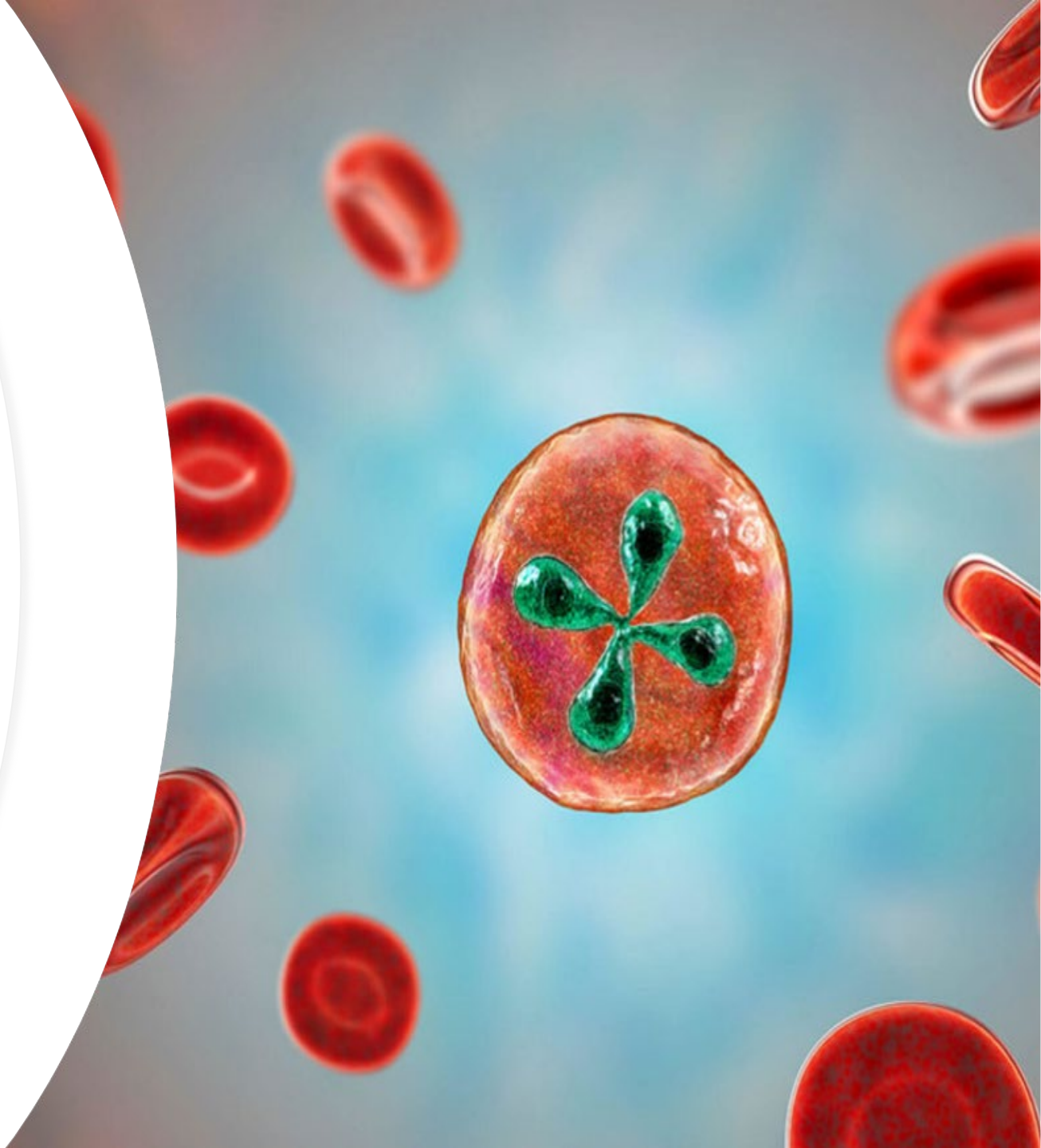
- *Babesia microti* - causes most cases of human babesiosis in northeastern and upper midwestern US; *Ixodes scapularis* vector
- *Babesia duncani* – western US
- *Babesia divergens* – midwestern US, Europe

- *Babesia venatorum*, *Babesia crassa*-like – northeastern China

Transfusion Transmitted Babesiosis (TTB)

- First detected in 1979

- As few as 10-100 parasites needed to cause infection
- Invades RBCs and replicates
- Causes lysis of infected RBCs leading to anemia and production of pro-inflammatory cytokines
- Spleen has important role in clearing parasitemia



TTB

- Primarily associated with RBC units
- Rarely whole blood–derived PLTs
- Potentially stem cell and granulocyte products

- Has not affected:
  - Plasma, apheresis platelets, or cryoprecipitate

- Incubation period for TTB is usually 3-7 weeks but can be as long as 6 months

Risk Factors for TTB

- Extremes in age
- Lack of spleen (splenectomy or functional asplenia)
- Immunosuppression or comorbidities
  - Cancer
  - HIV
  - Immunosuppressive drugs
  - Chronic heart, lung or liver disease

Clinical Presentation of TTB

Immunocompetent host

- *Asymptomatic* (25%)
- Mild, flu-like illness

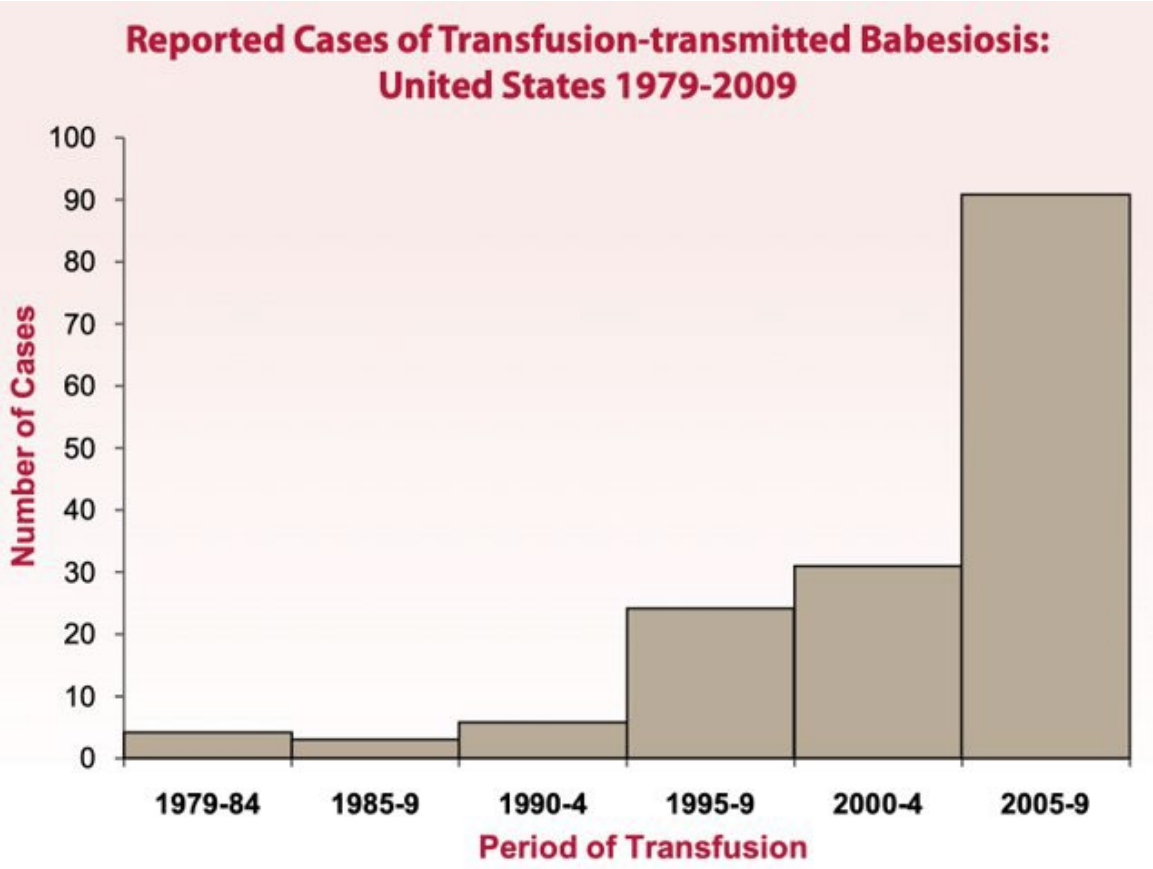
Persistent asymptomatic infection >1 year common

Immunocompromised host

- Acute respiratory distress syndrome
- Disseminated intravascular coagulopathy
- Congestive heart failure
- Renal failure
- Liver failure
- Coma

Mortality rates of TTB are *~20%*.

Impact on Blood Supply



From 1979–2009, 159 transfusion-related *Babesia microti* cases were identified, most (77%) from 2000 to 2009. Adapted from a graph published in the *Annals of Internal Medicine* in 2011.

Probably underestimates actual number of transfusion-associated cases because:

- disease is clinically silent in most healthy adults who are bulk of blood donors
- absence of licensed test (at that time)

https://www.cdc.gov/parasites/babesiosis/US_blood_supply.html

Over 250 cases of TTB have been reported in the US.

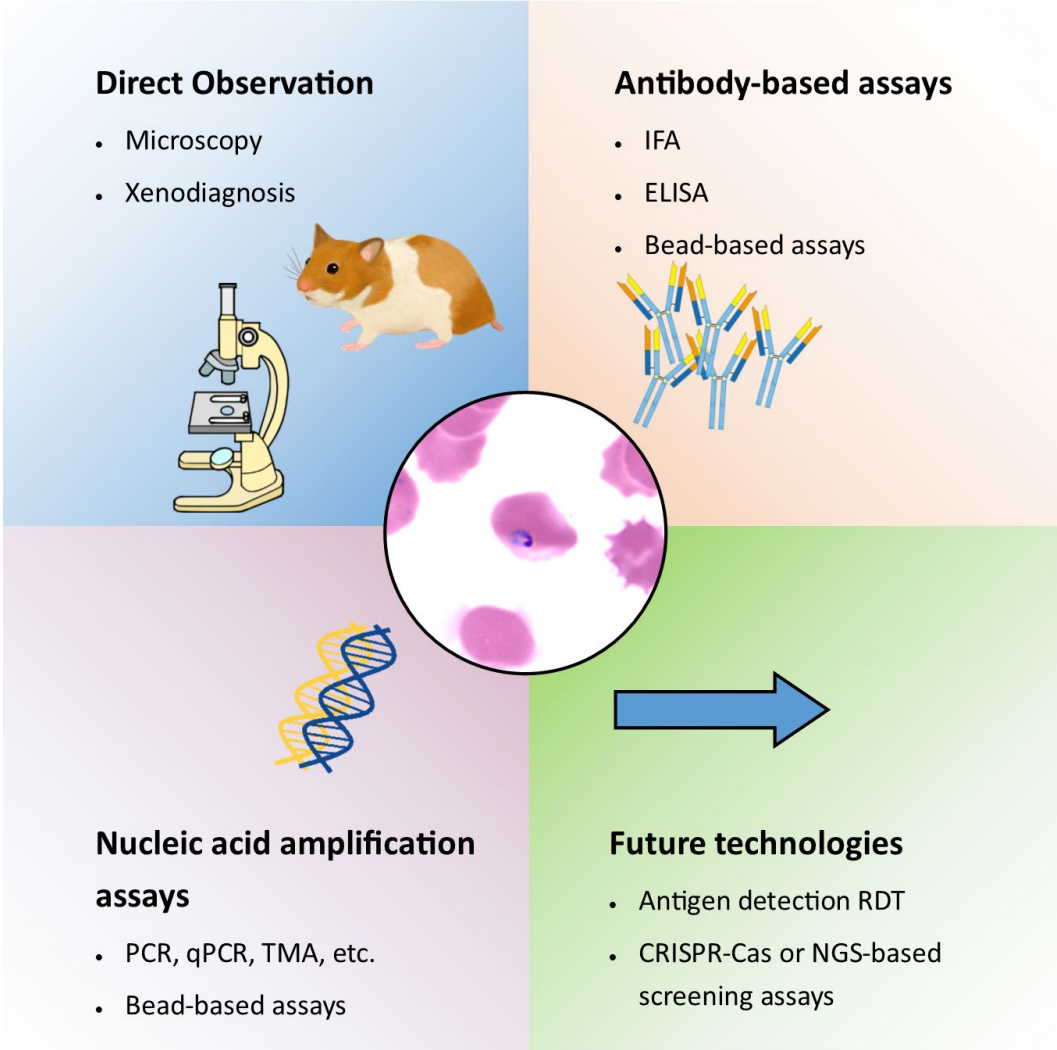
In the period from 2005 to 2010, 3.6% (11/307) of transfusion-related deaths reported to the FDA were attributed to TTB.

Babesia was designated as a nationally-notifiable disease (as defined by the CDC) in 2011 and has long been recognized as a major risk to the US blood supply.

Babesia Risk Mitigation

- Donor Screening, Blood Testing and Pathogen Inactivation
- Donor Deferral and Lookback Process
- Physician and Recipient Education

Babesia Donor Screening



Meredith S, Oakley M, Kumar S. Technologies for Detection of *Babesia microti*: Advances and Challenges. *Pathogens*. 2021; 10(12):1563

Blood Donor Screening

- Donor History Questionnaire (DHQ)
  - history of having had babesiosis (clinical or lab test)– permanently deferred
  - anemic, febrile, or not feeling well on day of donation – temporary deferral

- Shortcomings:
  - Relies on donor response
    - Asymptomatic - infection can be clinically silent!
    - Symptomatic - can remain infectious long after symptoms have resolved
  - Excludes prospective donors who may no longer be infectious and reduces blood supply

Blood Donor Screening

- On March 6, 2018, FDA licensed two independent assays for screening donors for *B. microti:*
  - *Babesia microti* Arrayed Fluorescent Immunoassay (AFIA) for detection of *B. microti*-specific antibodies
  - *Babesia microti* NAT for detection *B. microti* DNA
- Manufacturer notified FDA of the permanent discontinuance of both donor screening tests in November 2018.
- **On January 24, 2019, FDA licensed a NAT assay** for use in whole blood specimens for use in screening donors.

Current Blood Donor Screening

Blood donor screening for *Babesia* in states deemed at high risk of transmission (FDA recommendations 2019):

- **Screening:**

  NAT testing of blood donors for *Babesia*

  OR

  FDA-approved **pathogen reduction** technology

- Policy was confined to **14 US states and the District of Columbia** given that 95% of TTB cases had been reported in those areas:

  Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin

Current Blood Donor Screening

- In states where testing is not required, FDA recommends donor centers revise their DHQ to ask prospective donors if they have “ever had a positive test result for *Babesia*.”

- When testing or PRT is performed, may discontinue asking donors questions about a history of babesiosis.

Babesia Molecular (NAT) testing

Molecular FDA approved assays:

1. Procleix TMA assay – highly sensitive (limit of detection 2-3 parasites per mL)
2. Cobas PCR

Both detect ribosomal RNA of 4 *Babesia* species:

- *B. microti*
- *B. duncani*
- *B. divergens*
- *B. venatorum*

Babesia Testing

Molecular Testing:

Detect pre-seroconversion window period infections

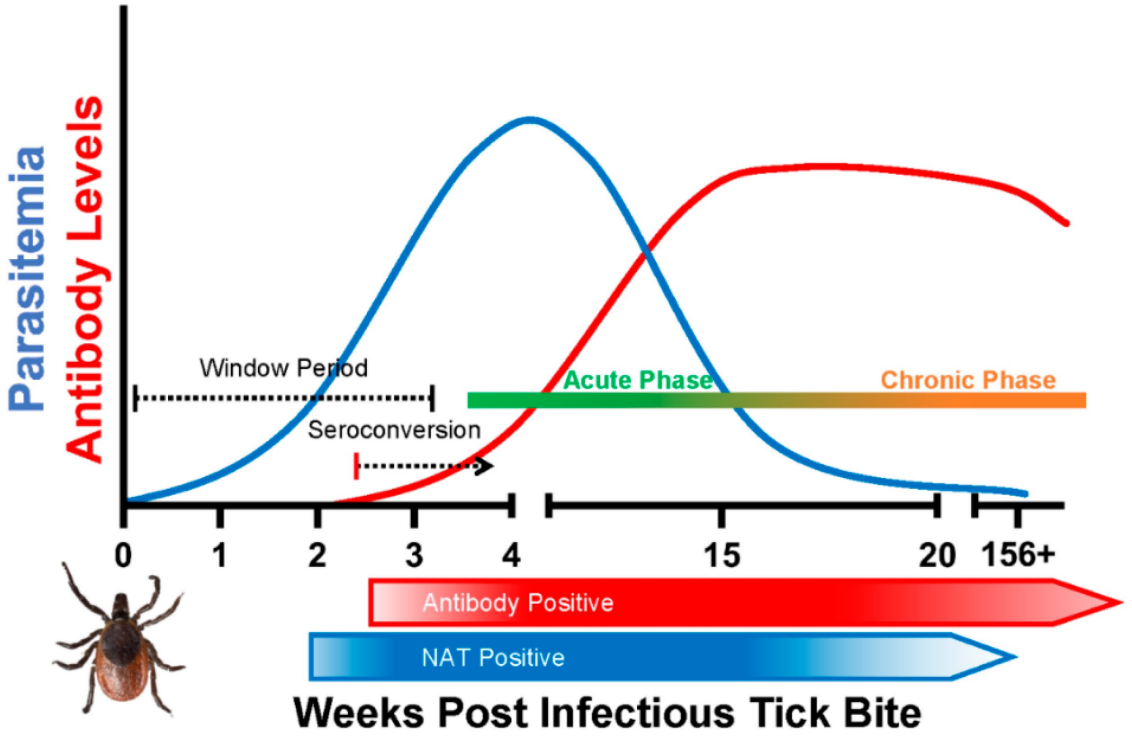
Allow for re-entry of NAT positive donors after 2 years of negative testing

- *Babesia* DNA clearance in 86% of donors at 1 year and in 95% of donors at 2 years

Serology Testing:

Fails to detect patients in window period

Antibody reactivity can persist for several years leading to loss of donors



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Pathogen Inactivation

- Increases availability of blood components
- Reduces donor restrictions
- Improves safety
- Limits costs associated with infectious disease testing and irradiation

Pathogen inactivation methods

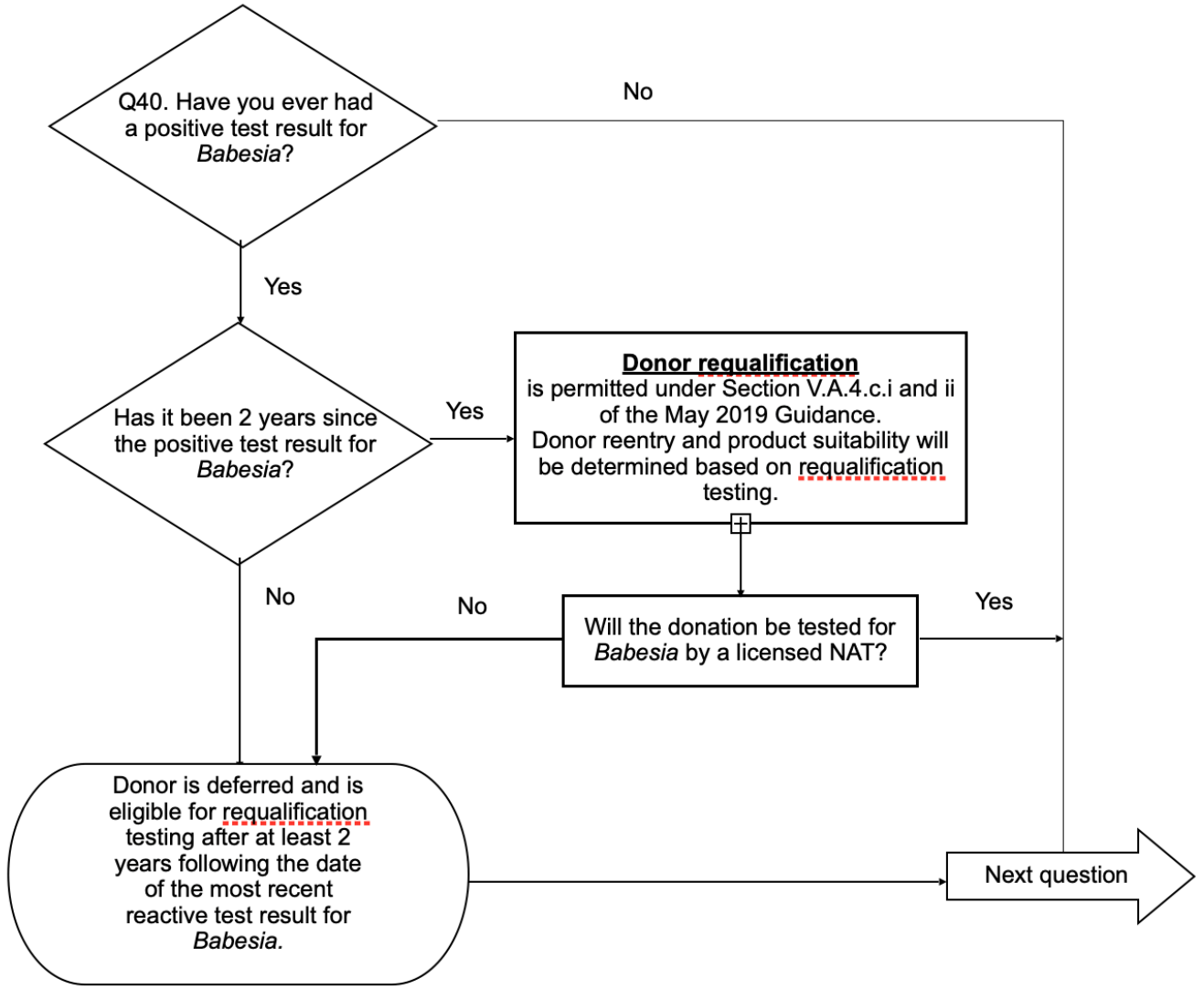
Method	Used for	Comments	Licensure
Solvent/detergent treatment	Plasma	▪ Damages lipid membranes ▪ Destroys lipid-enveloped viruses (HIV, HCV, HBV, HTLV, EBV, CMV) ▪ Does not inactivate non-enveloped viruses (HAV, HEV, parvovirus B19) ▪ Used in "Octaplas" system	▪ CE marked ▪ FDA approved
Amotosalen + UVA light	Cryoprecipitate; plasma; platelets	▪ Crosslinks DNA, preventing replication ▪ Used in "INTERCEPT" systems	▪ CE marked ▪ FDA approved
Riboflavin + UV light	Cryoprecipitate; plasma; platelets; whole blood	▪ Oxidizes guanine nucleotides in DNA, preventing replication ▪ Used in "Mirasol" systems	▪ CE marked
Methylene blue + visible light	Cryoprecipitate; plasma	▪ Inactivates lipid-enveloped viruses ▪ May reduce concentrations of some clotting factors ▪ Used in "THERAFLEX" systems	▪ CE marked
UV light alone	Platelets	▪ Damages DNA, preventing replication ▪ Used in "THERAFLEX" systems	▪ CE marked

Donor Deferral

When the donor

- reports a history of a positive test for *Babesia,* or
- was previously deferred for a positive test for *Babesia*, or
- tests reactive for *Babesia*

you must defer the donor for at least 2 years from the date of the most recent positive test result.



Lookback Process

- Identify all cellular blood components previously collected from donor in 12 months prior to date of reactive index donation.
  - May also consider in-date cellular components (e.g., frozen RBC components) collected more than 12 months prior to reactive index donation
- Quarantine components
- Notify if components distributed/transfused

Case Report

Objective

We describe the clinical and laboratory investigation of transfusion-transmitted babesiosis (TTB) attributed to RBCs collected in a non-endemic state.

Methods

Recipient:

- Clinical and laboratory investigation was performed.

Donor:

- Donor lookback investigation was initiated with blood supplier.
- RBCs transfused in 6 months preceding symptomatic infection were included, and 65 extended antigen matched RBC units were investigated.

Results - Recipient

30-year-old man with sickle cell disease complicated by alloimmunization and cerebrovascular disease on chronic automated red cell exchange regimen since childhood, transfused ~10 RBC units every 3 to 4 weeks.

Approximately 2 months after a red cell exchange, he presented to an outside ED with fever, neck pain, and photophobia.

Vital signs: T 38.3 degrees Celsius, HR 89 beats/min, RR 18 breaths/min, BP 117/75 mm Hg, O2 sat 99% on room air.	CBC: WBC count 5.8 K/cu mm, Hgb 10.8 g/dL (baseline 11-12 g/dL), Hct 33.1%, and platelet count 241 K/cu mm.	SARS-CoV-2: negative.	CSF testing and head imaging were unrevealing.	In setting of negative workup for meningitis, he was discharged.

Two days later, the patient continued to feel unwell and presented with **persistent fevers, chills, headache, fatigue and loss of appetite**.

- Patient was **febrile** with a maximum temperature of 39.8 degrees Celsius, otherwise hemodynamically stable.
- CBC: WBC count 5.22 K/cu mm, Hgb 10.4 g/dL, hct 32.6%, and platelet count 194 K/cu mm.
- Viral panel negative
  - SARS-CoV-2
  - CMV
  - HIV
  - HAV, HBV, HCV
- Bacterial cultures of peripheral blood, urine, and stool showed no growth.
- Serologic testing negative
  - *Borrelia burgdorferi*
  - West Nile virus
  - Brucella
  - *Treponema pallidum*
  - Epstein-Barr Virus serology positive for IgG antibodies but not IgM antibodies.
  - SARS CoV2 IgG antibodies identified (patient had been vaccinated).
  - *Ehrlichia chaffeensis* IgG antibody titer 1:64 (reference range <1:64) and *Ehrlichia chaffeensis* IgM antibody titer <1:20 (reference range <1:20).
  - *Anaplasma phagocytophilum* IgG titer <1:64 (reference range <1:64) and ***Anaplasma phagocytophilum IgM*** **antibody titer 1:40 (reference range <1:20).**
  - Assay for *Plasmodium* antigens negative.

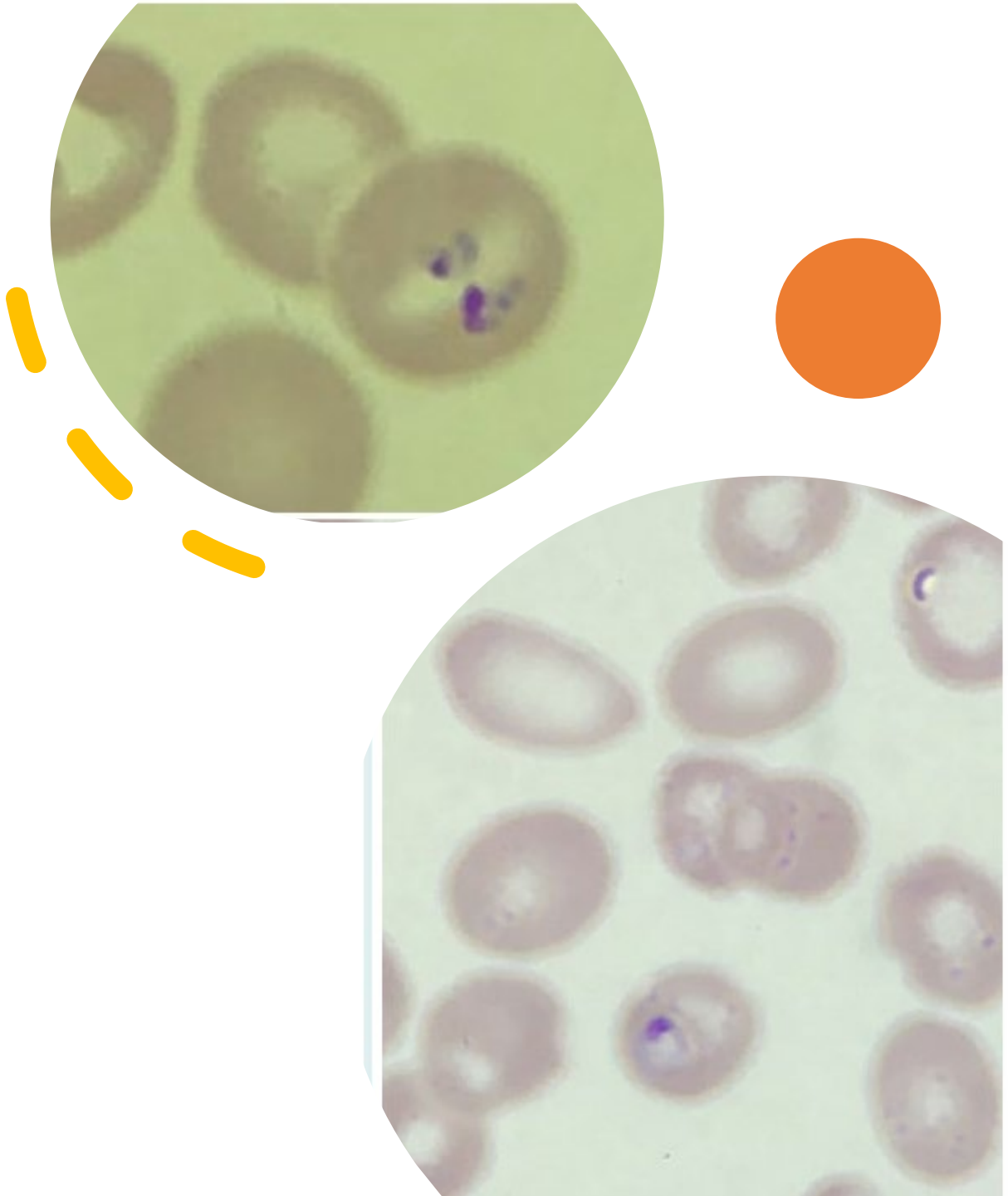
Intra-erythrocytic inclusions were identified on a peripheral blood smear (<**0.5% parasitemia** based on a representative 1000-cell count).

***Babesia microti* IgM and IgG titers were positive** to >1:320 and 1:1,024

The patient was started on azithromycin and atovaquone therapy with resolution of symptoms.

***Babesia microti* DNA was detected** by NAT.

The recipient lived in Maryland (endemic) but had no risk factors for tick borne acquisition of the infection.



Results - Donor

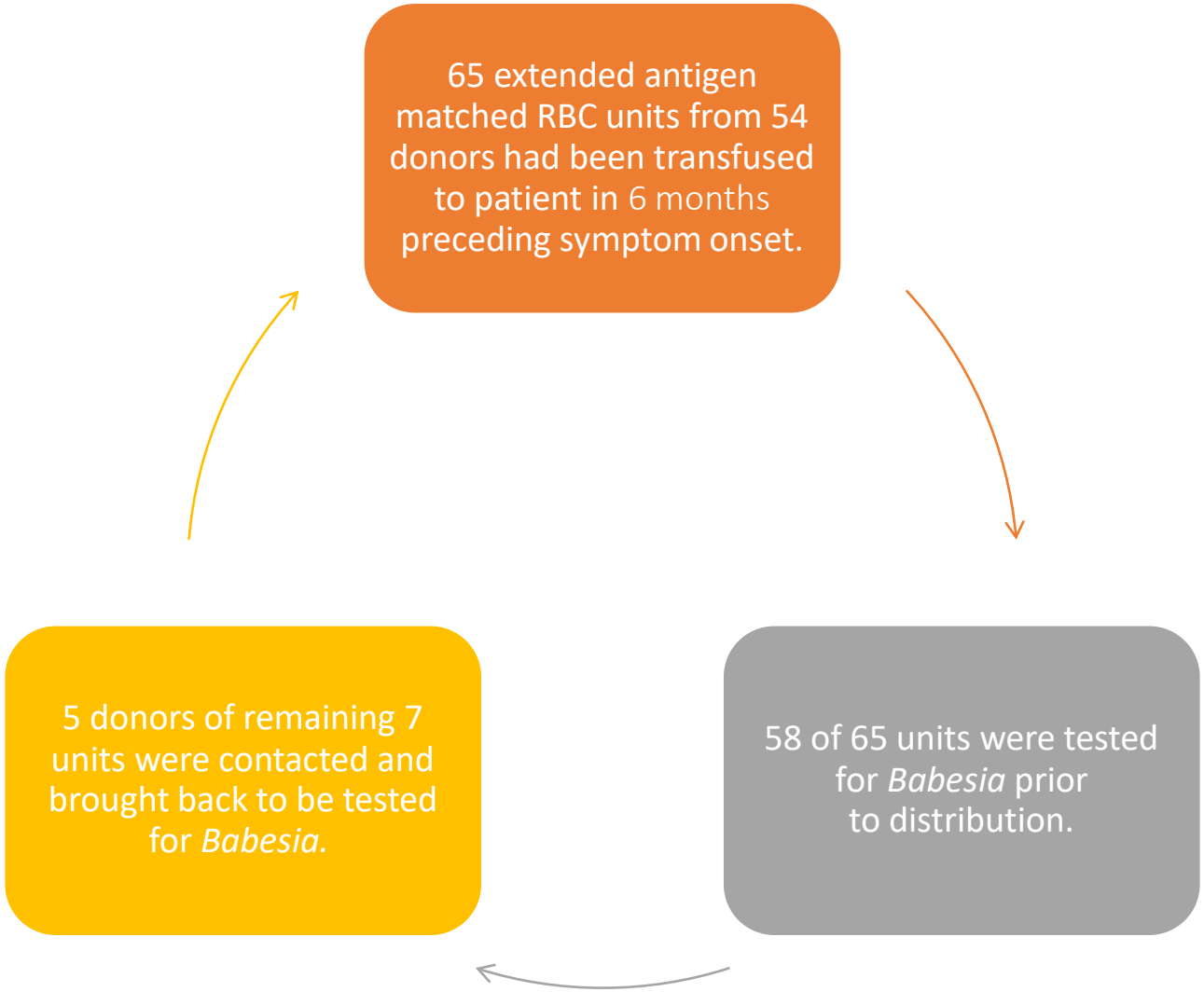


Table 1. Characteristics of 5 donors whose units did not undergo *Babesia* testing prior to distribution of RBCs

DONOR	STATE WHERE UNIT COLLECTED	BABESIA IFA	BABESIA NAT
Donor 1	Ohio	Positive	Negative
Donor 2, 3, 4, 5	Washington, Oklahoma, Indiana, Utah	Negative (4)	Negative (3), Unable to be performed (1)

Seropositive donor had not had any symptoms of babesiosis; the donor lived in Ohio and reported being very active over the past year, including hiking and camping in several states (Ohio, Tennessee, and North Carolina).

Donor had donated both before as well as after the index donation.

No other cases of TTB were ascribed to other donations from the implicated donor.

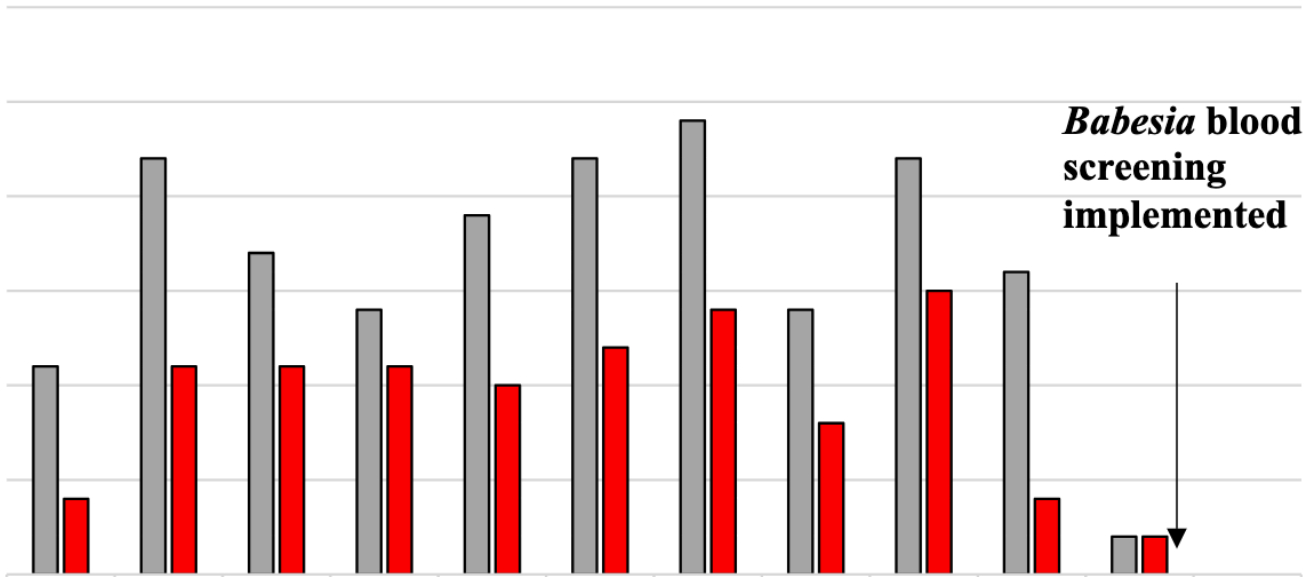
Overview of Managing TTB

- Review patient clinical history – natural acquisition vs transfusion transmission
  - Test pre-transfusion specimens if available
- Contact blood supplier and test donor(s) for *Babesia*
- Perform lookback, destroy remaining blood products from donor and in prior months
- Defer donor from donating

Proposed Strategies

- Regional *Babesia* antibody/NAT testing
- Risk-targeted testing
- Seasonal testing

Benefit of Screening & Testing



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Cases opened	11	22	17	14	19	22	24	14	22	16	2	0
# Positive donors	4	11	11	11	10	12	14	8	15	4	2	0

FIGURE 4 Cases of TTB investigated by the ARC, and the number of cases with identified positive donors since 2010. The two cases identified in 2020 were collected before blood screening implementation, and the involved donations were not screened for *Babesia*

Tonnetti L, Dodd RY, Foster G, Stramer SL. Babesia blood testing: the first-year experience. Transfusion. 2022 Jan;62(1):135-142.

Challenges of TTB

Residual risk of TTB outside of endemic areas underscores need for vigilance.

- TTB occurs in both endemic and non-endemic areas year-round.
  - Individuals who donate blood travel between endemic and non-endemic areas.
  - Blood is shipped across the country between endemic and non-endemic areas.

Challenges of TTB

Patients with sickle cell disease are disproportionately at risk of TTB and severe or even fatal sequelae.

- Patients are typically asplenic, anemic, and have a high burden of comorbid disease, rendering them in need of transfusion and susceptible to severe infection.
- They are frequently multiply-transfused with RBCs, often in large volumes (red cell exchange procedures).

Challenges of TTB

Alloimmunization complicates procurement of compatible blood for transfusion.

- Our patient's requirement for extended antigen matched RBC units necessitated broadening the search for RBC units in states where blood donor testing for *Babesia* is not routinely performed.

Challenges of TTB

Frequent transfusion may also **obscure or delay presentation**.

- Our patient underwent an exchange in September 2021, which could have reduced the level of parasitemia, thus delaying the onset of symptoms (October 2021).

Future Directions

- Continue to track TTI/TTB with state and local health departments; re-evaluate which areas at highest risk
- Monitor for emerging strains of *Babesia* that may cause human disease
- Continue to improve prevention strategies and donor screening for babesiosis

HEALTH

What is Babesiosis? A rare tick-borne disease is on the rise in the Northeast

March 17, 2023 · 2:54 PM ET

By Emily Olson

Conclusion

Babesia is the most common cause of transfusion transmitted infection (TTI) with advancements in blood donor screening to detect infection.

Our case demonstrates that the US blood supply is still vulnerable to *Babesia* **in both endemic and non-endemic areas** and poses a greater risk for immunosuppressed patients.

Acknowledgements

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Questions?