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DONOR INFECTIOUS DISEASE TESTING

TRANSFUSION

Risk of transfusion-transmitted *Babesia microti* in Canada

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Abstract

Background: *Babesia microti* has gained a foothold in Canada as tick vectors become established in broader geographic areas. *B. microti* infection is associated with mild or no symptoms in healthy individuals but is transfusion-transmissible and can be fatal in immunocompromised individuals. This is the first estimate of clinically significant transfusion-transmitted babesiosis (TTB) risk in Canada.

Study design and methods: The proportion of *B. microti*-antibody (AB)/nucleic acid amplification test (NAT)-positive whole blood donations was estimated at 5.5% of the proportion of the general population with reported Lyme Disease (also tick-borne) based on US data. Monte Carlo simulation estimated the number and proportion of infectious red cell units for three scenarios: base, localized incidence (risk in Manitoba only), and donor study informed (prevalence from donor data). The model simulated 1,029,800 donations repeated 100,000 times for each.

Results: In the base scenario 0.5 (0.01, 1.75), *B. microti*-NAT-positive donations would be expected per year, with 0.08 (0, 0.38) recipients suffering clinically significant TTB (1 every 12.5 years). In the localized incidence scenario, there were 0.21(0, 0.7) *B. microti*-NAT-positive donations, with 0.04 (0, 0.14) recipient infections (about 1 every 25 years). In the donor study informed scenario, there were 4.6 (0.3, 15.8) *B. microti*-NAT-positive donations expected, and 0.81 (0.05, 3.14) clinically significant TTB cases per year.

Discussion: The likelihood of clinically relevant TTB is low. Testing would have very little utility in Canada at this time. Ongoing pathogen surveillance in tick vectors is important as *B. microti* prevalence appears to be slowly increasing in Canada.

KEYWORDS

Babesia microti, Canada, risk model, transfusion

1 | INTRODUCTION

Babesia microti is an intraerythrocytic protozoan parasite usually transmitted from tick bites to humans. The

Abbreviations: AB/NAT, antibody or nucleic acid test; NAT, nucleic acid test; TTB, transfusion transmitted babesiosis.

infection, babesiosis, is often asymptomatic or characterized by mild flu-like symptoms. *B. microti* can also be transmitted by blood transfusion.[1] As blood recipients are more likely to be immunocompromised, they have a greater chance of more severe complications, even death.[2] In the US, over 200 cases of transfusion-transmitted babesiosis (TTB) were reported prior to implementation of testing and appeared to be increasing.[3,4]

The life cycle of *B. microti* involves the blacklegged tick (*Ixodes scapularis*) vector, and small mammal reservoir hosts, particularly *Peromyscus* spp. mice.[1] The geographic distribution of *B. microti* is believed to be expanding northward from Northeastern USA where most US cases are reported.[5] There are established blacklegged tick populations in southern parts of Canada and *I. scapularis* is expanding its range northward in eastern and central Canada. *Borrelia burgdorferi* (the bacterium responsible for Lyme disease) has been identified in blacklegged ticks in most Canadian provinces.[6,7] Locally acquired Lyme disease cases have been reported in British Columbia, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Newfoundland and Nova Scotia and reported cases have been increasing.[8] *B. microti* positive ticks have also been identified in some of the areas where Lyme disease has been reported, suggesting that there is low-level endemicity in some tick populations that are transmitting *B. burgdorferi*.

In 2013, the first endemic, community-acquired case of *B. microti* infection was reported in Canada (i.e. in Manitoba).[9] In 2013, 13,992 blood donations in regions of Canada proximal to known Babesia endemic areas in the US were tested for antibody to *B. microti*. No positive cases were identified.[10] In 2018, 50,752 donations from Canadian blood donors were tested for *B. microti* using a nucleic acid amplification test (NAT); one positive donor was identified in South East Manitoba. An additional 14,758 donor specimens that were initially negative by molecular testing were also tested for *B. microti* antibodies and if positive, were tested with confirmatory antibody methods. One of 14,758 molecular test-negative donor specimens was confirmed to be antibody positive for *B. microti*; the donation was unlikely to be infectious because no nucleic acid could be detected. Another 3/14,758 donor specimens were antibody reactive but possibly false-reactive. All four donations were from Southwestern Ontario.[11] In 2019, a donor reported a symptomatic *B. microti* infection postdonation.[12] The red blood cells had been transfused but the recipient tested negative by both nucleic acid and serology assays. These data suggest low-level *B. microti* prevalence in Canada.

In 2018, the FDA released a draft guidance document (finalized in May, 2019) mandating testing of blood donations for *B. microti* infection in endemic US states.[13] While a Health Canada approved donor screening assay for blood donations is not currently available in Canada, one could be approved if needed. With a potential for *B. microti* infections in Canadian blood donors, we sought to estimate the risk of acquiring clinically relevant *B. microti* infection by blood transfusion in Canada.

2 | METHODS

2.1 | The model

A schematic diagram of the model is shown in Figure 1. First, the expected number and percentage of donors with *B. microti* infection in 1 year were estimated. Then a Monte Carlo simulation was employed to estimate the number and proportion of red cell units from *B. microti*-NAT-positive donors likely to transmit a clinically relevant infection to a transfusion recipient.

2.2 | Estimating the number of expected *B. microti*-positive donors

Given the low prevalence of infection in studies of blood donors in Canada, the number of *B. microti* AB/NAT-positive donors was estimated using a proxy for tick exposure: cases of Lyme disease in the general population. The number of cases of Lyme disease was extracted from published reports by the Public Health Agency of Canada by 13 regions.[8] The low frequency of Lyme disease cases in many regions led to the combination of multiple years of data (2016–2019 in Quebec, 2012 to 2015 other provinces). A general linear model with region, year, and their interaction terms was used to estimate the number of cases in provinces other than Quebec in 2016–2019. Proportions of the general population with Lyme disease by region were estimated as the number of reported cases divided by the number of the population multiplied by 10 to correct for under-reporting.[14,15] It is unlikely that this level of under-reporting of Lyme disease cases occurs in Canada (where approximately one third of cases are reported: Ogden et al. 2019)[16] but this was chosen to err on the side of caution.

The number of whole blood donors was multiplied by the proportion of the general population reported to have acquired Lyme disease in the corresponding regions to provide an estimate of the number and percent of donors with Lyme disease in 2019. To estimate the percentage of donors with *B. microti* infection in 2019, these numbers were multiplied by 5.5%, the same as that reported in the US for community-acquired cases (see Figure 1 and Table 1).[17,18]

Although *B. microti* is transmitted by the same tick vectors as *B. burgdorferi* (the agent of Lyme disease), the ecology is different, and the geographic range of

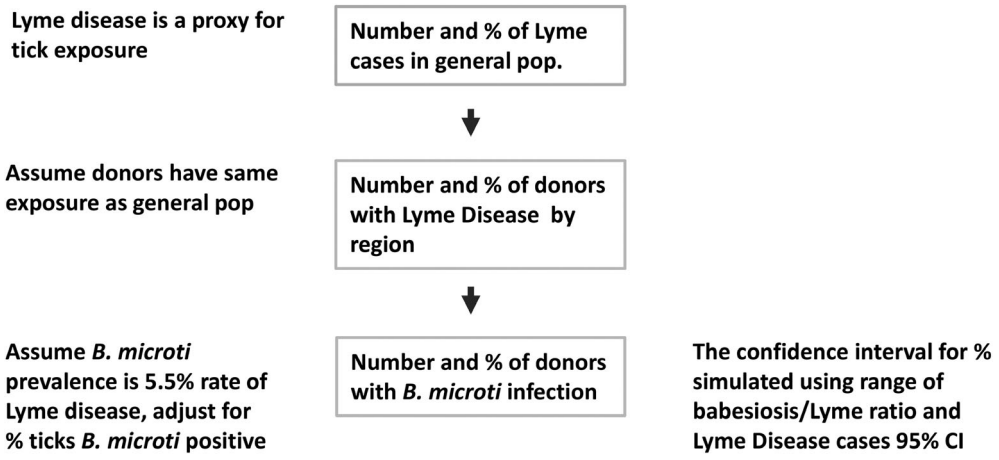
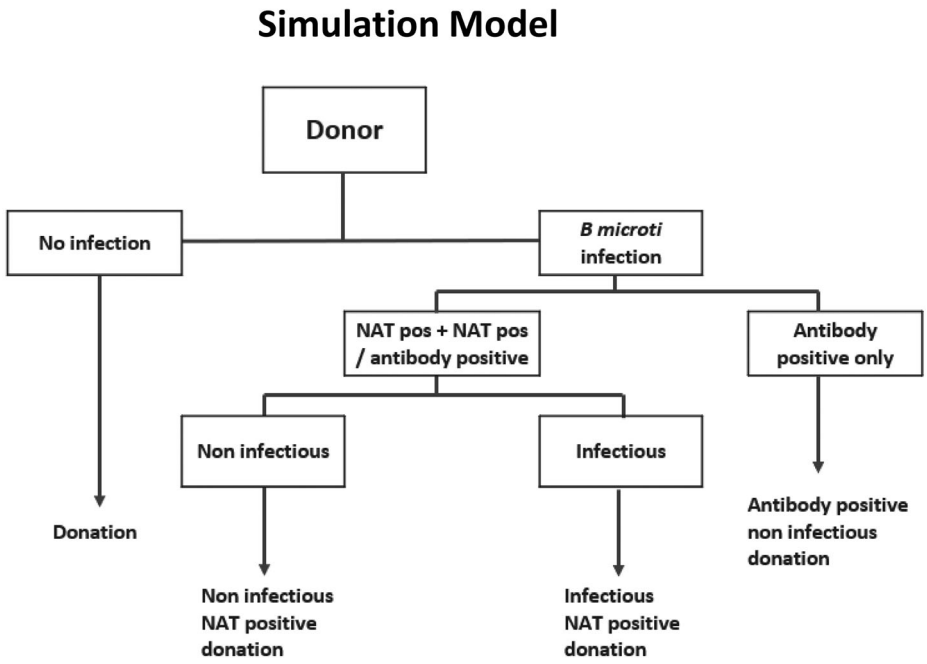


FIGURE 1 Process for estimating number and percentage of donors with *Babesia microti* infection



B. burgdorferi in Canada is likely to be greater than that for *B. microti*. As active tick surveillance of these geographic ranges is limited in scope, correction factors based on expert opinion were applied (for details see Table 1).[19] The 95% confidence intervals were simulated using the range of babesiosis/Lyme disease from different US states, and Poisson 95% confidence intervals for Lyme disease cases.

2.3 | Monte Carlo simulation

Monte Carlo simulation was carried out for 1,029,800 red cell units (the number of units in 1 year). The simulation of units was carried out separately from each geographic region, and because prevalence was very low repeated 1000 times, thus 102,980,000 units. To estimate 95% confidence intervals, the simulation was repeated 1000 times, thus the total number of units simulated was 102,980,000,000. Three random numbers from binomial distributions were generated to determine if a red cell unit was *B. microti* positive (antibody or NAT), NAT positive and if the recipient was infected. The total estimated number of infected units per year was calculated for each region. The proportion of units from *B. microti*-infected donors that were NAT positive (with or without antibody) or antibody positive was estimated as described by Goodell et al.[20,21] The proportion of NAT-positive red cell units that would result in an infection if transfused was estimated from two studies in the US as described by Goodell et al. (see Table 1).[20-22] The proportions of *B. microti*-infected red cell units, NAT-positive units, and recipient infections were applied to the total number of donations in Canada in 2019 to estimate the number of each of these in 2019 (see Figure 1).

TABLE 1 Parameters, modeling input, and logic

Parameters/model input	Methods	Data sources
Estimate number and percentage of donors with *Babesia microti* infection (includes antibody and NAT positive)		
Risk region define	Thirteen risk regions were defined, based on where Lyme disease was reported. All nonrisk regions were assigned 0 Lyme disease cases	
Cumulative number of Lyme disease by region	For cases in Quebec, data were obtained directly from Quebec Public Health registry of diseases, for elsewhere a published report which provided data from 2012 to 2015. A regression model was used to estimate the number of cases from 2016 to 2019 outside of Quebec. The number of Lyme disease cases was multiplied by 10 to adjust for non-reporting	Gasmi et al.[8] Quebec Public Health Non-reporting adjustment—Kugeler et al.[15]
Population by risk region in 2018	The total number of residents in the general population were sorted by Forward Sortation Area. Forward Sortation Area in each risk region were combined to get total population by risk region. The 2016 population data were used as an approximate midpoint of the data time period outside of Quebec and was the first year of Quebec data	Online data, Population by Forward Sortation Area in 2016 Statistics Canada [14]
Prevalence by region and 95% confidence interval	Number of Lyme disease cases divided by population in the corresponding region. The Poisson exact method was used to calculate 95% confidence intervals	
Number of donors by risk region	The number of donors in each Forward Sortation Area was extracted, and Forward Sortation Area combined as per Lyme disease risk regions above (and in non-risk regions)	Donation data in 2019, CBS and HQ databases
Number of Lyme disease cases in Canadian donors by risk region	The number of donors by region was multiplied by the corresponding regional prevalence to estimate the number of donors with Lyme disease	
Tick adjustment factor	The tick adjustment factor refined estimation of Lyme disease to babesiosis based on the percentage of *B. microti* infected ticks from active surveillance and expert opinion Province: % ticks with *B. microti* with correction factor relative to Manitoba Manitoba 1.5% 1 New Brunswick 0.18% 0.12 Quebec 0.12% 0.08 Ontario 0.05% 0.04 All other areas assumed 0	Personal communication, L.R. Lindsay, PHAC
Lyme disease vs. babesiosis ratio	The ratio of reported babesiosis vs. Lyme disease in the US were calculated. Overall ratio of 5.5% and	CDC—reported cases of Lyme disease and Babesiosis in the US[17,18]

(Continues)

TABLE 1 (Continued)

Parameters/model input	Methods	Data sources
	varied between 0.026% and 17%. Range is the minimum and maximum ratio by state with outliers excluded	
Number of donors with *B. microti* infection by risk region	The above ratio was applied to the estimated number of donors with Lyme disease to estimate the number of donors with *B. microti* infection by risk region	
Prevalence of *B. microti* infection by risk region, and 95% confidence intervals	Prevalence of *B. microti* infection was estimated by dividing the number of donors with *B. microti* infection in each region by number of donations in that region. Simulation was used to estimate the 95% confidence interval of Babesia infection prevalence, with both variation in Lyme disease prevalence and Lyme disease vs. babesiosis ratio considered	
Number of *B. microti*-positive donations	Simulation was used A beta distribution was used to generate a random prevalence of *B. microti* infection for each region. A binomial distribution was used to identify each *B. microti*-positive donor. Assumed each positive donor would contribute one donation, and each donation contribute to one red cell unit of product to estimate total number of *B. microti*-positive units (antibody and/or NAT)	
Estimate the number of donations that will be NAT positive or antibody only		
Proportion of *B. microti*-positive donations that are NAT positive	Among *B. microti*-positive units it was assumed only NAT positive have potential to be infectious. From the literature, the NAT-positive proportion among *B. microti*-positive donations ranged from 4% to 20% with mode of 15% In simulation, a random proportion was generated from this range using a beta distribution, and then to determine if a random unit was NAT-positive or not	US blood donor study data[21]
Number of donations that were NAT-positive	Random numbers from binomial distributions according to the random proportion of NAT positives were generated to determine if a *B. microti*-positive unit was NAT-positive or not	
Estimate the number of infectious donations		
Proportion of donations NAT-positive	Calculated as the number of NAT-positive donations divided by total number of donations for each region	

TABLE 1 (Continued)

Parameters/model input	Methods	Data sources
	Overall risk was summarized as the number of infectious units divided by all donations in 2019. Note that all donations include repeat donations which are assumed to be NAT negative	
Transmission probability	Transfusion of a NAT-positive unit may or may not cause infection in a recipient. In the simulation this probability was generated from a uniform distribution of 10–25% of NAT-positive units Weighted average from US donor studies N TTB × 3/N NAT-positive units released (×3 times to adjust for nonreporting)	US blood donor studies [21,22] Non-reporting adjustment [20]
Number of clinically relevant transfusion-transmitted cases	A random number was generated from a binomial distribution according to random transmission probability which was applied to a recipient who received a NAT-positive unit	
Total numbers of infectious blood units, and potential transfusion-transmitted cases	Summarized from all regions	

Note: Forward sortation area—first 3 digits of postal code which identifies a geographic region.
Abbreviations: NAT, nucleic acid test; TTB, transfusion transmitted babesiosis.

2.4 | Assumptions

A number of assumptions were made as follows:

1. The proportion of the general population by region with exposure to the tick vector of *B microti* is represented by that with exposure to Lyme disease.
2. The ratio of *B. microti* infection to Lyme disease observed in US states where both infections occur approximates the expected ratio in Canada. In the US, regions where *B. microti* is endemic are also regions where Lyme disease is endemic, but in regions bordering locations where both pathogens are endemic, often only Lyme disease risk is present. It was assumed that that infection prevalence obtained from host-seeking ticks through active surveillance can be used as estimates of infection in ticks (and hence the probability of risk) for *B. microti*.
3. Donors are a subset of the general population with the same probability of *B. microti* infection as the general population.
4. The percentage of donations with a *B. microti* infection over a 12-month period who will be NAT positive (with or without antibody) is approximated by the observed NAT-positive percentage of antibody and/or NAT-positive donations in endemic US states.
5. The percentage of NAT-positive donations that will infect a recipient can be approximated from the percentage observed in endemic US states. Discarded donations were not considered.
6. Each donation will produce one standard red cell unit for transfusion.
7. Red cell units that are antibody positive, and NAT-negative will not result in transfusion transmission.
8. NAT-positive red cell units will result in a transfusion-transmitted infection at the same rate as observed in US studies.
9. Only red cell units will transmit *B. microti*.
10. Each transfused patient receives one red cell unit.

2.5 | Scenarios

Three separate simulations were carried out according to three scenarios as follows:

1. Base Scenario: As described above.

TABLE 2 Estimated *Babesia microti*-positive donations and transfusion transmitted infections

Region	Donations	*B. microti*-positive donations (*N*)	NAT-positive donations (*N*)	NAT-positive rate per 100,000 (95% CI)[a]	Transfusion-transmitted cases *N* (95% CI)
(a) Base scenario					
Nova Scotia	35,957	0.42	0.06	0.18 (0, 0.67)	0.01 (0, 0.06)
Prince Edward Island	8232	0	0	0 (0, 0)	0 (0, 0)
New Brunswick	26,951	0.04	0.005	0.02 (0, 0.11)	0.0009 (0, 0.01)
Newfoundland	14,402	0	0	0 (0, 0)	0 (0, 0)
Western Quebec	70,944	0.79	0.12	0.17 (0, 0.54)	0.02 (0, 0.08)
Quebec, all else	143,111	0.06	0.009	0.007 (0, 0.03)	0.002 (0, 001)
Eastern Ontario	52,001	0.17	0.03	0.05 (0, 0.17)	0.004 (0, 0.03)
Central Ontario	164,629	0.06	0.009	0.006 (0, 0.02)	0.002 (0, 0.01)
Southwest Ontario	111,749	0.21	0.03	0.03 (0, 0.13)	0.005 (0, 0.03)
Northern Ontario	29,143	0.06	0.008	0.03 (0, 0.14)	0.001 (0, 0.01)
Manitoba	41,572	1.40	0.21	0.5 (0.02, 1.7)	0.04 (0, 0.14)
Saskatchewan	41,500	0	0	0 (0, 0)	0 (0, 0)
Alberta	166,091	0	0	0 (0, 0)	0 (0, 0)
British Columbia	123,518	0	0	0 (0, 0)	0 (0, 0)
Total	1,029,800	3.20	0.50	0.05 (0.001, 0.17)	0.08 (0, 0.38)
(b) Localized incidence scenario					
Manitoba	41,572	1.4	0.21	0.5 (0.02, 1.7)	0.04 (0, 0.14)
All other areas	988,228	0	0	0 (0, 0)	0 (0, 0)
Total	1,029,800	1.4	0.21	0.02 (0,0.07)	0.04 (0, 0.14)
(c) Donor study informed scenario					
Nova Scotia	35,957	0.42	0.06	0.18 (0, 0.67)	0.01 (0, 0.06)
Prince Edward Island	8232	0	0	0 (0, 0)	0 (0, 0)
New Brunswick	26,951	0.03	0.005	0.02 (0, 0.11)	0.0009 (0, 0.01)
Newfoundland	14,402	0	0	0 (0, 0)	0 (0, 0)
Western Quebec	70,944	0.79	0.12	0.17 (0, 0.54)	0.02 (0, 0.08)
Quebec, all else	143,111	0.06	0.009	0.007 (0, 0.03)	0.002 (0, 0.01)
Eastern Ontario	52,001	0.17	0.03	0.05 (0, 0.17)	0.004 (0, 0.03)
Central Ontario	164,629	0.06	0.009	0.006 (0, 0.02)	0.002 (0, 0.01)
Southwest Ontario	111,749	12.4	1.9	1.7 (0.10, 6.2)	0.33 (0.02, 1.37)
Northern Ontario	29,143	0.0545	0.008	0.03 (0, 0.14)	0.001 (0, 0.01)
Manitoba	41,572	16.8	2.5	6.1 (0.51, 19.0)	0.44 (0.03, 1.56)
Saskatchewan	41,500	0	0	0	0 (0, 0)
Alberta	166,091	0	0	0	0 (0, 0)

TABLE 2 (Continued)

Region	Donations	*B. microti*-positive donations (*N*)	NAT-positive donations (*N*)	NAT-positive rate per 100,000 (95% CI)[a]	Transfusion-transmitted cases *N* (95% CI)
British Columbia	123,518	0	0	0	0 (0, 0)
Total	1,029,800	30.7	4.6	0.45 (0.03, 1.53)	0.81 (0.05, 3.14)

2. Localized Incidence Scenario: Because to date all NAT-positive cases have been identified in Manitoba, and none elsewhere this scenario considers the possibility that *B. microti* risk is limited to Manitoba. Manitoba risk was estimated as in the base scenario and all other regions were presumed to have no *B. microti* AB/NAT-positive donations.
3. Donor Study Informed Scenario:
   Because there is alternative data generated from the donor study to that used in the base scenario for two regions of Canada, this scenario uses these data. The scenario is the same as the base scenario except
   a. For Manitoba, the *B. microti* prevalence in donors was assumed to be the same as identified in the 2018 study (1/1117) and;
   b. For South Western Ontario, the *B. microti* prevalence was assumed to be half the donor seroprevalence in the 2018 study ($4/2105 \times ½$). Only half were assumed to be infected in the current year because these were antibody positive but NAT negative; therefore, some may be older than the 4-year time frame estimated or could be travel-related. There is also a chance that some were not true positive.

3 | RESULTS

In the base scenario, a total of 3.2 *B. microti*-positive donations (antibody or NAT) per year would be expected, mainly from Manitoba and Western Quebec. There would be 0.50 (0.01, 1.75) NAT-positive donations and 0.08 (0, 0.38) recipients would be expected to acquire clinically significant TTB, or about 1 every 12.5 years (see Table 2, part a).

In the localized incidence scenario in which Manitoba was assumed to be the only region with any chance of *B. microti* infection, 1.4 *B. microti* antibody-positive donations would be expected, 0.21 (0, 0.7) NAT-positive donations, and 0.04 (0, 0.14) recipients would be expected to have clinically relevant TTB (about 1 every 25 years), thus about half that of the base scenario (see Table 2, part b).

In the donor study informed scenario which assumed there would be higher risk in areas where AB/NAT-positive donations were identified in the 2018 donor study (all other areas as per the base scenario) there would be 30.7 *B. microti* antibody-positive donations and 4.60 (0.3, 15.8) NAT-positive donations expected. This would result in 0.81 (0.05, 3.14) clinically relevant TTB cases per year (see Table 2, part c).

4 | DISCUSSION

In Canada, tick populations where both *B. microti* and *B. burgdorferi* are endemic occur in areas close to the US border.[17,18] Reports of Lyme disease are increasing in areas of Canada adjacent to endemic areas in the US, and although rare, endemic *B. microti* infection occurs. With global warming, it is likely that the tick populations will continue to expand northward into new regions and tick-borne illnesses such as Lyme disease and babesiosis may become more frequent.[6,7] This is the first quantitative estimate of the risk of transfusion transmitted clinically relevant *B. microti* infection in Canada. The estimated risk is low in all scenarios consistent with the current rarity of endemic babesiosis cases.

We chose to estimate the risk of TTB according to a base scenario, which assumed most areas with Lyme disease had some risk of *B. microti* and used Canadian and US public health data to obtain estimates. We then modified the base scenario in two alternate scenarios. The localized incidence scenario assumed that only donations from Manitoba had any chance of *B. microti* infection. To date, the three known endemically acquired *B. microti* infections have all occurred in Manitoba, and active tick surveillance has identified *B. microti* in Manitoba but only sporadically elsewhere.[9] Localized incidence would be consistent with reported data, but *B. microti* infections are frequently unrecognized in healthy people and the antibody-positive results from our 2018 study should not be ignored.[23] We therefore included a third scenario which was based on study data in Manitoba and Southwestern Ontario, and the base scenario elsewhere.

In the US, TTB risk has been assessed in three studies.[20,24,25] All three estimated the cost effectiveness of donor testing strategies, necessitating somewhat different approaches than ours. Unlike in Canada, *B. microti* is well established in certain areas in the US.[5] Each of the risk estimates from the US focused on endemic states, although Goodell et al also estimated risk for all of the US.[20]

Fundamental to any estimate of TTB risk is the prevalence of *B. microti* AB/NAT-positive blood donations. However, as the prevalence of *B. microti* in blood donors is not known for much of the US, only one of the three US risk estimates was based on donation data whereby estimates were limited to endemic areas.[25] Of the other two, the estimate by Simon et al was based on public health surveillance in endemic counties and Goodell et al used babesiosis health insurance claims and notifiable disease monitoring.[20,24] Given the rarity of *B. microti* in Canada, neither blood donor data nor general population data would provide a robust prevalence estimate. We therefore based our estimate on the assumption that exposure to ticks capable of carrying *B. microti* could be extrapolated from Lyme disease cases.

The proportion of people with Lyme disease was then adjusted using the ratio of babesiosis to Lyme disease in the US to quantify the rate of babesiosis. While we cannot rule out differential reporting bias by infection in the US or ecological differences between the US and Canada, the 5.5% that we used is plausible as it is clear that Lyme disease is much more prevalent than babesiosis. To take into account uncertainty around the true proportion of babesiosis to Lyme disease, a range of uncertainty using the highest and lowest proportions by state was included in our estimate. Importantly, the geographic range of the two agents is different. The reason for this is unknown but hypotheses include reliance on mice for the lifecycle of *B. microti* but not *B. burgdorferi*, more efficient movement by birds which act as a reservoir for *B. burgdorferi* but not *B. microti*, and more efficient host-tick transmission of *B. burgdorferi*.[5] Active tick surveillance in Canada has identified areas of Canada where *B. burgdorferi* is prevalent in ticks but *B. microti* is only rarely detected if at all.[19] We applied an adjustment factor which lowered proportions in Quebec, New Brunswick and Ontario, assumed zero elsewhere. Although data for adjustment is imperfect, failure to take this into account would have greatly over-estimated *B. microti* prevalence. It is important to note limitations to some key assumptions were made. The under-reporting adjustment factor of 10 for Lyme disease is very conservative. The ratio of *B. microti* to Lyme disease does not consider the age distribution in cases relative to donors, differential reporting in children, or that Lyme disease may be clinically recognized more frequently than babesiosis.

Derived independently of the donor study prevalence data, the base scenario identified 3.2 *B. microti* antibody positive donations in 1 year, with 0.5 NAT positive donations. In the 2018 study sample 1 *B. microti* NAT-positive donation was identified of 50,000 tested.[11] Then the following year a donor was identified post-donation as described earlier who had a *B. microti* infection.[12] It is impossible to know if these were isolated events, although the lack of any antibody-positive donations identified in Manitoba may reflect an element of serendipity. Nevertheless, it would be prudent to assume that infections could be more frequent than the 0.5 per year estimated by the base scenario. The study informed scenario uses the study data from the two regions where positive donations were identified (NAT or antibody) and retains the public health data derived estimates elsewhere. It yielded an estimate of 30.7 antibody-positive donations (4.6 NAT positive) per year. As the study data are constrained by very rare AB/NAT-positive donations this could be an over-estimate. The true number of AB/NAT positives is likely somewhere between the base scenario and the study informed scenario.

The second part of the analysis estimates the risk of transmitting a clinically relevant infection. We assumed that antibody-only positive red cell units would not transmit an infection. While a low proportion of antibody-positive NAT-negative units have been associated with TTB, this is likely ascribed to low level or intermittent parasitemia being missed by NAT.[26] While our estimate of the number of antibody-only positive donations had no implications for the estimated risk of TTB we believe it is important to include because in a low incidence setting it may be advantageous to monitor. The transmissibility of *B. microti* has been estimated to be about 33% for patients receiving NAT-positive blood in lookback studies.[26] We estimated this to be somewhat lower based on two more recent studies in which the proportion could be estimated using the number of *B. microti* NAT-positive red cell units transfused from studies and transfusion-transmitted infections from lookback/traceback.[21,22] Because some TTB cases were likely not recognized, an adjustment factor of 3 was applied.[20] This approach had the advantage of basing expected transmission on observed TTB rates in patients, which is therefore focused on clinically relevant infection.

Because *B. microti* is more prevalent in the US, and TTB has been identified as a substantive risk in the US prior to the implementation of testing, a much lower estimated risk is expected in Canada. Compared with the US national estimate of Goodell et al in which about 10,000 red cell units would be seropositive, and 100 would cause TTB roughly translating into about 7 clinically relevant infections per year for a population the size of Canada,

our base estimate of 0.08 (0.008 per 100,000 transfusions) is roughly 90 times lower.[20] Our donor study informed scenario of 0.8 (0.08 per 100,000 transfusions) is about 9 times less. These are also much lower than the estimate of Simon et al. of 3.6 TTB cases per 100,000 transfusions, and 32.7 TTB per 100,000 as estimated by Bish et al.[24,25] However, these two studies are not directly comparable because they focus on high prevalence states. Whether the true risk in Canada is closer to the base scenario or the study informed scenario, it is clear that it is much less than in the US.

While low risk may be expected given the rarity of documented infections, it is clearly not zero. It is difficult for policy makers to make decisions without a quantitative risk assessment. This is because the number of infections identified in studies is from a sample; the number in the donor population will be higher, yet the risk of a clinically relevant infection depends on both the probability of transmitting the infection from a NAT-positive donation and the probability of a symptomatic disease if transmitted.

This risk assessment was spurred by a growing recognition that *B. microti* has gained a foothold in Canada. In 2018, the FDA issued a draft Guidance for Industry stipulating that donations in 14 US states and Washington DC must test all donations.[13] Historically, over 95% of all cases of TTB in the US have implicated donations originating in these locations.[13] Estimated risk in endemic states is much higher than our estimate for Canada. It is quite possible that if testing was to be implemented, we would detect *B. microti* antibody or NAT-positive donations; however, the likelihood of a clinically relevant transfusion transmitted infection is low. Our results suggest that testing would have little utility in Canada at this time. Ongoing pathogen surveillance in vector ticks is important as *B. microti* prevalence appears to be slowly increasing in Canada.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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