The incubation period is usually five to eight days.

The World Health Organization estimates that nearly 100 million people worldwide are infected with dengue each year, with a death rate of about 5 percent.

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Dengue toll in Malaysia up to 70 as pregnant housewife dies

First posted 11:58am (Mla time) Sept 26, 2005
By

KUALA LUMPUR, Malaysia

A Malaysian housewife pregnant with twins has died after contracting dengue fever, pushing the nationwide death toll from the mosquito-borne disease this year to 70, news reports said Monday.

Fairus Aziz, 26, died at a government hospital in the northern Penang state on Saturday after experiencing a high fever for three days, the New Straits Times reported. Her seven-month fetuses also did not survive.

She was the third victim to die from an infection of the virus this year in Penang state and the 70th nationwide.

Penang state health officials were not immediately available for comment.

In southern Negeri Sembilan state, authorities reported that five people have so far died due to a dengue fever outbreak and more than 42 cases were detected last week, a twofold increase compared to the preceding week, the national news agency Bernama reported.

Health officials have earlier said that they were battling to control an outbreak of dengue, which has infected more than 7,000 people across the country so far this year.

Negeri Sembilan's chief minister Mohamad Hassan blamed villagers and farmers for the problem, saying they failed to keep abandoned buildings and mosques clean and that the structures later became breeding grounds for mosquitos, Bernama reported.

The illness causes severe fever and can lead to vomiting, nausea and a body rash. Dengue fever can also cause severe pain in the joints, and some strains of the virus cause internal bleeding.

The U.S. Centers for Diseases Control and Prevention has called dengue this year's "most important mosquito-borne viral disease affecting humans" _ ahead of malaria and encephalitis _ with an estimated 2.5 billion people at risk worldwide.

World Health Organization officials have said Vietnam, Malaysia, Thailand, the Philippines and Singapore all had a large number of dengue cases this year and have scrambled to curtail the spread of the disease.

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医薬品
医薬部外品　研究報告　調査報告書
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識別番号・報告回数			報告日	第一報入手日 2005 年 11 月 4 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人ハプトグロビン		研究報告の公表状況	Transfusion,45(11) 1804-1810,2005	公表国 アメリカ	
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研究報告の概要	使用上の注意記載状況・その他参考事項等
米国においてヒトのバベシア症の症例数の増加に伴って、Babesia microti の輸血感染の報告がここ数年上昇している。献血者の B.microti 抗体測定の幾つかの研究が報告されているが、寄生虫血症と輸血による寄生体の感染リスクについてはよくわかっていない。 コネチカット州の Babesia 流行地及び非流行地における献血者の 7～9 月の供血の B.microti 抗体を検査した。その後、抗体陽性者から追加で集められた検体の B.microti 遺伝子の PCR 検査を行った。 コネチカット州の Babesia 流行地及び Babesia 非流行地の血液ドナーそれぞれ 1,745 人、合計 3,490 人のうち、30 人(0.9%)が抗体陽性であり、7 月がピークであった。Babesia 流行地の血清学的陽性血液ドナーは 24 人（1.4%）で、Babesia 非流行地の血清学的陽性血液ドナーの 6 人（0.3%）より多かった。また、血清学的陽性の血液ドナー19 人のうち 10 人（53%）が PCR により陽性であった。コネチカット州の Babesia 流行地では B. microti 抗体陽性者が多く、B. microti 抗体陽性者の半数以上から原虫血症が証明されたことにより輸血による B. microti 感染リスクが高いと思われる。	2. 重要な基本的注意 (1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理(ナノフィルトレーション)を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
米国においてヒトのバベシア症の症例数の増加に平行して、B. microtiの輸血感染の報告がここ数年上昇しており、コネチカット州のBabesia流行地ではB. microti抗体陽性者が多く、B. microti抗体陽性者の半数以上から原虫血症が証明されたことにより輸血によるB. microti感染リスクが高いという報告である。 血漿分画製剤からのバベシア原虫伝播の事例は報告されていない。また、万一原料血漿にB. microtiが混入したとしても、除菌ろ過等の製造工程において十分に除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

Demonstrable parasitemia among Connecticut blood donors with antibodies to *Babesia microti*

David A. Leiby, Amy P.S. Chung, Jennifer E. Gill, Raymond L. Houghton, David H. Persing, Stanley Badon, and Ritchard G. Cable

BACKGROUND: Reports of transfusion-transmitted *Babesia microti* have risen steadily during the past several years, reflecting a concurrent increase in US cases of human babesiosis. Although several studies have measured *B. microti* antibodies in blood donors, little is known about associated parasitemia and the inherent risk of transmitting the parasite by transfusion.

STUDY DESIGN AND METHODS: Donations from blood donors located in *Babesia*-endemic and nonendemic areas of Connecticut were tested for *B. microti* antibodies from July through September. Subsequently, an additional blood sample was collected from selected seropositive donors and tested by nested polymerase chain reaction (PCR) for *B. microti* nucleic acids.

RESULTS: A total of 3490 donations, 1745 each from endemic and nonendemic areas, were tested for *B. microti* antibodies; 30 (0.9%) were confirmed as positive and seroprevalence rates peaked in July. Significantly more seropositive donations were from endemic areas (24, 1.4%) than nonendemic areas (6, 0.3%). Ten (53%) of 19 seropositive donors subsequently tested by PCR were positive.

CONCLUSION: *B. microti* seroprevalence was highest in those areas of Connecticut where the parasite is endemic. More than half of seropositive donors tested had demonstrable parasitemia, indicating that many are at risk for transmitting *B. microti* by blood transfusion. Three donors were identified as parasitemic in October, suggesting that donors may be at risk for transmitting the parasite outside of the peak period of community-acquired infection.

For the past several years, blood safety concerns in the United States have focused primarily on a series of newly emerging agents and diseases.[1] In the late 1990s, a variant form of Creutzfeldt-Jakob disease was described in humans that appears now to be transmissible by transfusion. Thereafter, the first US case of West Nile virus appeared in humans during 1999 followed closely in 2002 by reports of 23 transfusion cases involving this agent. As demonstrated by the emergence of severe acute respiratory syndrome (SARS) in 2003, each new emerging agent is assessed for potential transmission by blood transfusion. Unfortunately, the ongoing preoccupation with newly emerging agents has allowed previously described agents, some of which pose significant blood safety threats, to be overshadowed. Among these agents is the intraerythrocytic protozoan parasite *Babesia microti*, the primary agent of human babesiosis in the United States.

B. microti is endemic to the northeastern and upper midwestern United States where it is transmitted naturally by exposure to black-legged ticks (*Ixodes scapularis*) infected with this parasite. Since the first US case of babesiosis was described in 1966,[2] hundreds of human cases

ABBREVIATIONS: IFA = indirect immunofluorescent antibody; PBST = phosphate-buffered saline containing 0.1 percent Tween 20; RT = room temperature.

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have been reported, but many more go unrecognized and unreported.[3-6] Indeed, human infections with *B. microti* are generally subclinical or mild, characterized by fever, headache, malaise, and myalgias that usually resolve within a few weeks. More severe disease, however, can occur in newborn, elderly, immunocompromised, and asplenic patients that may be characterized by hemolytic anemia, thrombocytopenia, renal failure, or even death. Unfortunately, this group of patients is at particular risk for acquiring the parasite via blood transfusion because these patients are frequently transfusion recipients. During the past 10 years, reports of transfusion-transmitted *Babesia* have increased noticeably, with multiple cases reported in each of the past several years. More than 50 cases of transfusion-transmitted *B. microti* have been reported since 1980,[7] but this figure is likely an underestimate because many cases probably go unrecognized or unreported.

Seroprevalence estimates for *B. microti* among blood donors are limited and range from 0.3 percent in Wisconsin donors to 4.3 percent in Shelter Island, New York donors, but rates are dramatically influenced by inherent seasonality and geographic variations.[8-10] This study was designed to compare the seroprevalence rates in blood donors from *B. microti* endemic and nonendemic areas of Connecticut during and shortly after the reported period of peak transmission (July through September). Additionally, to develop estimates of parasitemia and the likelihood of transfusion transmission, selected seropositive donors were tested by polymerase chain reaction (PCR) for DNA of *B. microti*.

MATERIALS AND METHODS

Study population

From July through September 1999, all blood donors presenting at selected blood drives in the American Red Cross Connecticut Region were recruited for the *B. microti* seroprevalence study. At donation, donors received an information sheet describing the study, including potential testing of their blood for antibodies to *B. microti*. Donors not wishing to participate informed the nursing staff and were excluded from the study. For those donors presenting at blood drives located in the *Babesia*-endemic area of Connecticut, serum samples were obtained from available retention tubes (n = 1745) of all consenting donors approximately 1 week after donation. The endemic area was defined as New London County, Middlesex County south of Middletown, and three towns in Windham County. An equal number of samples (n = 1745) were randomly selected from available retention tubes of consenting donors presenting at blood drives in the designated nonendemic area (Hartford County) during the same period. The regions designated as *Babesia*-endemic and nonendemic were defined based on existing case reports, seroprevalence studies, and discussions with recognized leaders in the epidemiology of tick-borne diseases.[11,12]

Serologic testing

Serum samples from endemic and nonendemic areas of Connecticut were tested for antibodies to *B. microti* with a sequential, two-step testing algorithm to determine seropositive blood donors. All samples were initially screened by an experimental, research-based enzyme immunoassay (EIA) for antibodies to *B. microti*, and those found positive by EIA were then tested by a supplemental indirect immunofluorescent antibody (IFA) test. Only those donors found positive by both tests were considered to be seropositive for *B. microti*.

The antigen source for the experimental EIA was the recombinant *B. microti* proteins BMN1-17 and MN-10 (Corixa Corp., Seattle, WA).[13] Briefly, 96-well microtiter plates (Corning, Acton, MA) were coated overnight at 4°C with the recombinant proteins (200 ng/well) and then aspirated and blocked for 2 hours at room temperature (RT) with phosphate-buffered saline (PBS) containing 1 percent bovine serum albumin (BSA). Plates were washed five times with PBS containing 0.1 percent Tween 20 (PBST) with an automatic plate washer (Model ELx50, Bio-Tek Instruments, Winooski, VT). Serum samples and positive and/or negative controls, diluted with PBS containing 0.1 percent BSA to a final dilution of 1 in 50, were added to antigen coated plates, incubated for 30 minutes (RT), and washed five times with PBST. Positive controls were provided by P.J. Krause (University of Connecticut School of Medicine, Hartford, CT). Plates were then incubated with protein A–horseradish peroxidase conjugate (1/10,000 dilution; Sigma-Aldrich Corp., St Louis, MO) for 30 minutes (RT), washed five times with PBST, and then incubated with tetramethylbenzidine substrate (Zymed Laboratories, San Francisco, CA) for 30 minutes (RT). The reaction was stopped with 1 N sulfuric acid and the plates were read at 450 nm with an automated plate reader (Model ELx808, Bio-Tek Instruments). The cutoff for assays was determined from the mean of the negative controls plus 3 standard deviations of the mean.

As indicated above, samples that were positive by EIA were subjected to follow-up testing by IFA as per the manufacturer's instructions (Focus Technologies, Inc., Cypress, CA). Briefly, serum was diluted 1 in 64 in PBS, and 20 µL was added to each slide well containing fixed *B. microti* antigen and incubated at 37°C for 30 minutes in a humid chamber. After incubation, slides were washed for 10 minutes in PBS by agitation, rinsed in distilled water, and air-dried. Diluted fluorescein-labeled goat anti-human immunoglobulin G conjugate (Focus Technologies) was then added to each well and again incubated at 37°C for 30 minutes in a humid chamber. Slides were then washed for 10 minutes in PBS by agitation,

rinsed in distilled water, and air-dried. Samples were examined by fluorescence microscopy at 400× magnification. Positive samples were titered to endpoint. Appropriate negative and positive controls, as described above, were included as part of all IFA testing.

Detection of *B. microti* DNA through PCR

A portion of seropositive donors provided a subsequent whole-blood sample for analysis by PCR. All donors with IFA titers ≥ 1:256 and approximately 75 and 50 percent of randomly selected donors with titers of 1:128 and 1:64, respectively, were selected for PCR analysis. Briefly, donors selected were contacted via letter and notified of their initial test results indicating the presence of antibodies to *B. microti*. Donors received information regarding an expanded study investigating the relationship between antibodies to *B. microti* and the potential presence of the parasite and were invited to participate. Informed consent was obtained from all donors agreeing to participate, as well as, four 7 mL ethylenediaminetetraacetate tubes to be used for serologic testing and PCR analysis. Test results were reported to participants via letter. All PCR-positive donors were considered *B. microti*–infected, contacted for counseling, asked to complete a brief questionnaire regarding risk factors for babesiosis, referred to their physician for evaluation and possible treatment, and indefinitely deferred from future American Red Cross blood and tissue donations. Later, based on the results in this article, all donors seropositive by IFA for *B. microti* were deferred.

All blood samples were analyzed with a nested PCR protocol, modified from the original, designed to amplify the 18S ribosomal RNA gene of *B. microti*.[14] Parasite DNA was extracted from whole blood with a DNA blood kit (QIAamp DNA blood mini kit, Qiagen, Inc., Valencia, CA) as per the manufacturer's instructions and resuspended in 200 µL final volume. The initial PCR was performed by adding 10 µL of extracted DNA to 40 µL of PCR master mix containing 12.5 pmol per µL of primers Bab1 (5′-CTTAG TATAAGCTTTTATACAGC-3′) and Bab4 (5′-ATAGGTCA GAAACTTGAATGATACA-3′), 1.25 U of AmpliTaq Gold *Taq* polymerase, GeneAmp 10× Buffer I (10 mmol/L Tris, pH 8.3, 1.5 mmol/L $MgCl_2$, 50 mmol/L KCl, and 0.001 percent gelatin), GeneAmp dNTP blend (250 µmol/L each dNTP; all from Perkin-Elmer), and sterile water. An additional 1 mol per L $MgCl_2$ (Sigma-Aldrich Corp.) was added to a final concentration of 2.5 mmol per L. Amplification was performed in a thermal cycler (GeneAmp 9700, Applied Biosystems, Foster City, CA) with the following settings: 95°C for 15 minutes, 35 cycles of 94°C for 30 seconds, 60°C for 30 seconds, 72°C for 1.5 minutes, and then final extension at 72°C for 10 minutes. The nested PCR was performed with 5 µL of the initial Bab1-Bab4 amplification product (238 bp) diluted 1:10, 45 µL of PCR master mix (described above) containing 5 pmol per µL primers Bab2 (5′-GTTATAGTTTATTTGATGTTCGTTT-3′) and Bab3 (5′-AAGCCATGCGATTCGCTAAT-3′), and sterile water for a total reaction volume of 50 µL. No additional $MgCl_2$ was added. The amplification settings were the same as described above; however, the annealing temperature was 55°C. The 155-bp products were visualized on a 2 percent agarose gel stained with ethidium bromide in 1× TAE buffer (Invitrogen Corp., Carlsbad, CA). Appropriate positive controls (again provided by P.J. Krause), negative controls, and extractions controls were included.

Statistical analyses

Statistical analyses were performed when appropriate with the chi-square test. A p value of less than 0.05 was considered significant in all cases.

RESULTS

Seroprevalence screening

From July through September 1999, a total of 3490 blood donations from *Babesia*-endemic (n = 1745) and nonendemic (n = 1745) areas of Connecticut were tested for antibodies to *B. microti*. Two-hundred and three (5.8%) were positive by EIA, and when tested by the supplemental IFA, 30 (0.9%) were confirmed positive (Table 1). When endemic and nonendemic areas were compared, there was no significant difference ($\chi^2 = 3.5$; $p = 0.06$) in the initial reactive rates as determined by EIA, but when those samples positive by EIA were tested by the supplemental IFA, a significantly greater number of donations ($\chi^2 = 9.7$; $p < 0.002$) from the endemic area (1.4%) were confirmed as positive compared to the nonendemic area (0.3%). The geographic distribution of seropositive donors (based on residence) in the endemic and nonendemic areas of Connecticut is detailed in Fig. 1.

The initial reactive rates for the combined *Babesia*-endemic and nonendemic areas were similar each month when measured by EIA (Fig. 2). When the monthly rates for endemic and nonendemic areas were compared, however, different trends were observed. For endemic areas, the EIA-reactive rate dropped from a high of 8.2 percent in July to 5.0 percent in September. In contrast, the non-

TABLE 1. Serologic testing of blood donors from endemic and nonendemic areas of Connecticut for antibodies to *B. microti*

Area	Number	EIA-positive (%)	IFA-positive (%)
Endemic	1745	115 (6.6)	24 (1.4)*
Nonendemic	1745	88 (5.0)	6 (0.3)
Totals	3490	203 (5.8)	30 (0.9)

* Seroprevalence in the endemic region was significantly greater than that of the nonendemic region ($\chi^2 = 9.7$; $p = 0.002$).

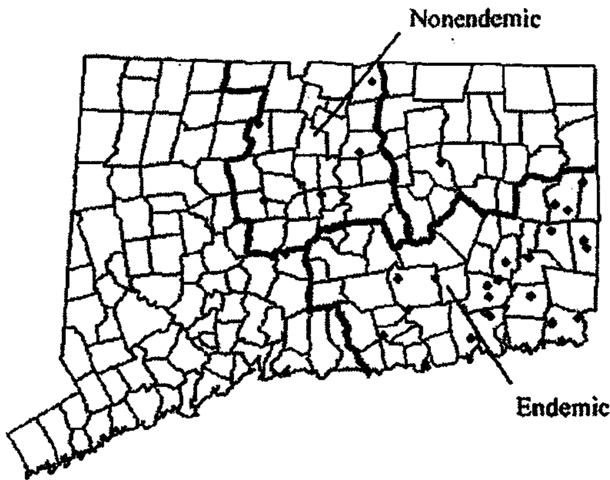

Fig. 1. Map of Connecticut depicting the areas of the state designated as nonendemic and endemic for *B. microti*. (◆) relative locations, based on residence, of blood donors identified as seropositive for *B. microti* in the nonendemic (n = 6) and endemic areas (n = 24). One seropositive donor identified in the nonendemic area resided outside of our designated endemic and/or nonendemic areas.

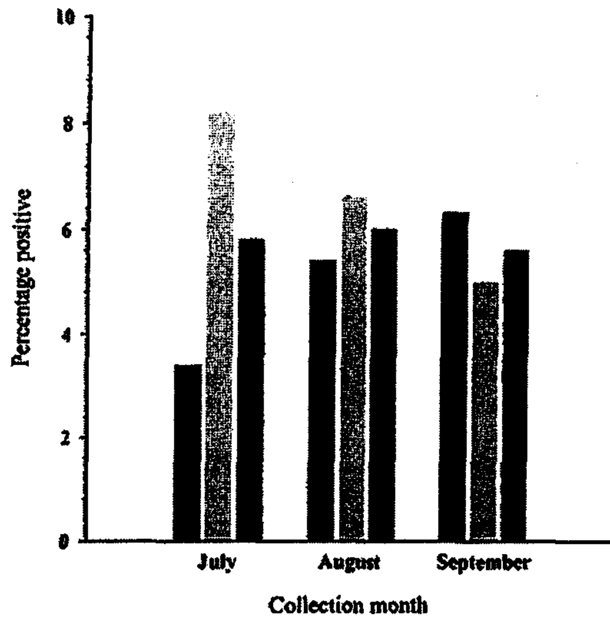

Fig. 2. Comparison of the percentage of blood donors seropositive for *B. microti* by EIA, from the nonendemic (■), endemic (▩), and combined areas of Connecticut (■), during the months of July through September.

endemic rate increased from 3.4 percent in July to 6.3 percent in September. Rates for donations identified as positive by the supplemental IFA (Fig. 3) were consistent, whether overall or by area, decreasing each month during the collection period.

Follow-up serologic and parasitemia testing

Twenty-six of the 30 donors with corresponding seropositive donations were invited to provide an additional blood sample for subsequent serologic and parasitemia testing; 19 donors were enrolled (16 endemic, 3 nonendemic). Samples were collected approximately 3 weeks to 2 months after the donor's initial blood donation (Table 2). Overall, 10 of 19 (53%) samples were positive by PCR; 8 of 16 (50%) from the endemic area and 2 of 3 (66%) from the nonendemic area. In most cases, IFA titers determined on different assay runs were little changed between the initial draw and the subsequent follow-up sample. Previous studies have shown minimal test-to-test variability for this assay system.[15,16] Initial IFA titers for Donors 2 and 7, however, were 1:256, but subsequent titers were observed to be less than 1:64, despite also being PCR-positive.

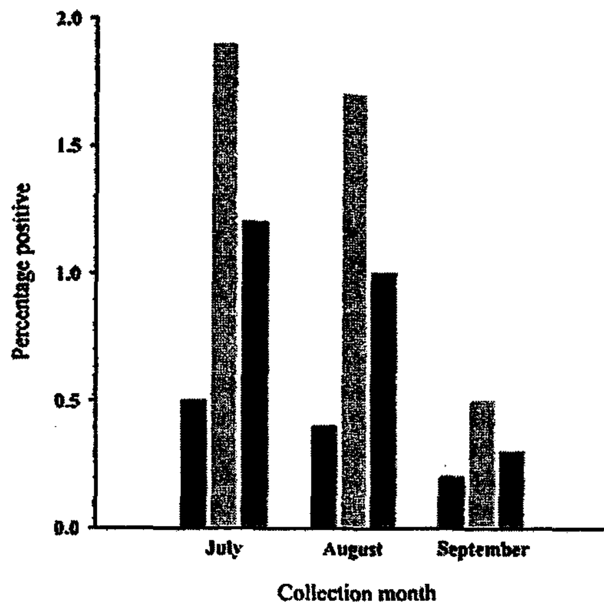

Fig. 3. Comparison of the percentage of blood donors seropositive for *B. microti* by IFA, from the nonendemic (■), endemic (▩), and combined areas of Connecticut (■), during the months of July through September.

DISCUSSION

During the past 20 years, contact between humans and ticks in the northeast United States has escalated rapidly owing to a variety of factors. First, the white-tail deer pop-

TABLE 2. Results of subsequent serologic and parasitemia testing of seropositive blood donors with nested PCR

Sample	Region	Initial IFA titer	Subsequent IFA titer	Days between draws	PCR result
1	Endemic	1:512	1:512	28	Positive
2	Nonendemic	1:256	<1:64	29	Positive
3	Endemic	1:64	<1:64	38	Negative
4	Endemic	1:512	1:256	32	Negative
5	Endemic	1:512	1:512	18	Positive
6	Endemic	1:256	1:128	35	Positive
7	Endemic	1:256	<1:64	30	Positive
8	Endemic	1:1024	1:1024	34	Positive
9	Endemic	1:512	1:256	29	Negative
10	Nonendemic	1:512	1:512	29	Negative
11	Endemic	1:1024	1:1024	33	Negative
12	Endemic	1:64	1:64	29	Negative
13	Endemic	1:256	1:64	34	Negative
14	Endemic	1:2048	1:1024	29	Negative
15	Endemic	1:4096	1:512	32	Negative
16	Endemic	1:512	1:512	17	Positive
17	Endemic	1:256	1:256	32	Positive
18	Nonendemic	1:512	1:512	30	Positive
19	Endemic	1:512	1:512	63	Positive

ulation, which serves as the main host for adult *I. scapularis* ticks, has increased in part owing to a lack of predators, but also owing to the reforestation of agricultural land and suburban neighborhoods that provide suitable habitat. Concurrently, humans have increased outdoor recreational activities and built homes that place them in close proximity to tick populations.[17] These interactions with ticks have led to a dramatic rise in reports of tick-borne diseases throughout the northeast, especially Lyme disease, babesiosis, and ehrlichiosis.[18-20] Although the increase in cases of Lyme disease is well documented, the steady increase in cases of babesiosis due to infections with *B. microti* has gone largely unnoticed. Previous studies have identified blood donors with antibodies to *B. microti* and this study indicates that many are also demonstrably parasitemic. Indeed, the high percentage (53%) of donors with demonstrable parasitemia mirrors the high numbers of transfusion cases reported in recent years. These observations suggest that blood donors seropositive for *B. microti* may pose a greater risk for blood safety than once thought.

Previously, we reported seroprevalence rates for *B. microti* in Connecticut blood donors to range from 0.3 to 0.6 percent.[10] These samples, however, were collected primarily during late fall and winter (i.e., October to March) when tick exposure is at a minimum and new infections are unlikely to be acquired. This study clearly demonstrates the influence of seasonality on overall seroprevalence rates because the rate of confirmed IFA positives peaked in July (1.2%), rapidly declining thereafter to 0.3 percent in September. Perhaps peak seroprevalence actually occurred earlier than July, but further studies bracketing the entire tick season would be needed to more precisely define this period. Seroprevalence rates are also dramatically influenced by geographic location with significantly more confirmed positive donors identified in *Babesia*-endemic versus nonendemic areas. The defined areas of *B. microti* endemicity are continually expanding,[21] however, and thus may now encompass areas previously designated as nonendemic. Alternatively, residents of nonendemic areas can acquire infections during visits to *Babesia*-endemic areas. This scenario led to the only case of transfusion-transmitted *B. microti* reported in Canada.[22] Similarly, infected donors from a *Babesia*-endemic area may donate blood in a nearby nonendemic area as part of a local or work-related blood drive. Although the defined areas of *Babesia* spp. endemicity are expanding in some parts of the United States, the parasite has not been identified in many states or regions. Therefore, selective geographic testing has been suggested as a possible intervention, but this paradigm has not been commonly used in operational blood banking.

As already noted, in addition to measurable antibody titers, a majority of seropositive donors identified in this study were also shown to be parasitemic based on PCR. The presence of parasite DNA is thought to be indicative of an active infection, because free DNA or dead parasites would be cleared rapidly from the peripheral blood.[23] It is unclear, however, how long our donors were demonstrably parasitemic, because only a single sample was tested by PCR. Of the three donors whose samples were drawn for PCR testing during October, all three were identified as PCR-positive, suggesting that parasitemia in some cases is persistent, occurring outside of the reported period during which tick-borne diseases are primarily transmitted. Indeed, past studies have suggested that *Babesia* infections may recrudesce after long periods of silence (i.e., 26 months),[23] but the possibility of reinfection must also be considered, particularly in *Babesia*-endemic areas. Persistent, perhaps year-round, infections suggest that proposed donor management policies that avoid collection of blood in endemic areas during the summer months when transmission is thought to be at its peak would be partially, though not completely effective. As stated above, it is not only difficult to define the peak transmission period, but ongoing persistent infections suggest that many donors may be at risk for transmitting *B. microti* throughout the year.[24] Thus, these observations suggest that seasonally based collection criteria, much like reported geographic areas of agent endemicity, only partially reduce the risk of transmission, while producing detrimental effects on blood availability.