recent evidence—albeit in hamsters—that PCR-positive and/or antibody-positive (titer ≥ 256) units caused symptomatic infections in 34% of subjects. However, they are not supported by human data. Of 29 known PCR-positive units that were transfused, only one recipient (3.4%) became symptomatically ill, and there were no reported symptomatic cases from those receiving the 29 PCR-negative units. Using the transmissibility and progression estimates from Bish and coworkers, we would suppose that in 29 known PCR-positive units transfused, five to six recipients would develop uncomplicated yet symptomatic infections, while three to four would have complicated babesiosis with a mortality of 12%. Thus, Bish and colleagues have likely overstated the burden of TTB morbidity and mortality.

In summary, while decision analysis and cost-effectiveness modeling are well suited to inform policy on this topic, the most recent analysis likely overestimates the burden of transfusion-transmitted babesiosis and the cost-effectiveness of blood screening in endemic areas. Policy-makers would be well served to closely inspect all available models and each of their strengths and limitations before promulgating guidance.

CONFLICT OF INTEREST

BC is and EB was employed by Blood Systems Inc. (BSI) when this letter was written. BSI has supported development of a B. microti ELISA with Immunetics. EB participates in ongoing studies of donor screening and follow-up using the Immunetics ELISA. The other authors have disclosed no conflicts of interest.

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REFERENCES


Cost-effectiveness of a Babesia microti blood donation intervention based on real-time prospective screening in endemic areas of the United States

We appreciate the feedback provided by Goodell et al.1 in their letter responding to our publication, “Cost-effectiveness of Babesia microti antibody and nucleic acid blood donation screening using results from prospective investigational studies.” The letter highlights differences in methods and data sources among three studies assessing putative screening scenarios. Our study found that universal polymerase chain reaction (PCR) is the most cost-effective (CE) strategy at $26,000 to $83,000 per quality-adjusted life-year (QALY); corresponding CE ratios in other studies cited by Goodell and colleagues were $760,000/QALY for an antibody screening strategy and $5,006,000/QALY for a PCR screening strategy, respectively, using differing model inputs.

The base case scenario discussed by Bish and coworkers2 is based on real-time donation screening experience as part of a pivotal investigational new drug (IND) trial in collaboration with IMUGEN, Inc. (Norwood, MA), as well as rates of transfusion-transmitted babesiosis (TTB) at the American Red Cross (ARC). The discussion in Bish et al. highlights the sources of variability between the ARC study and other CE studies, including test performance characteristics, costs, and transmission probabilities. These variables can, indeed, have a substantial impact on the results of the model.

In Bish et al., the probability of a “symptomatic” TTB transmission was considered and sensitivity analyses of that variable performed. Disease progression was similar
to that used with asymptomatic TTB cases carrying no treatment or other costs. Therefore, from a CE analysis perspective, an asymptomatic TTB case was similar to a “no TTB” case. The major difference in the CE analysis of Bish and colleagues lies in the transmission probabilities of a symptomatic infection. Of note, since the decision trees work by multiplying conditional probabilities on each branch, from a numerical perspective, varying the transmission probabilities actually corresponds to various scenarios where disease progression or fatality rates could have been modified instead. The extensive sensitivity analysis on transmission probabilities actually covered a wide range of scenarios where other disease progression variables could have been varied.

Bish and coworkers carefully separated infectivity based on PCR positivity versus PCR negativity. A strategy that includes PCR would intuitively be most effective at preventing TTB as the presence of DNA is most closely correlated to infectivity as indicated from prior human studies and hamster infectivity data. In a separate research study published by Johnson and coworkers, cellular components from donors testing PCR positive were implicated in 33.3% of TTB cases, while those from donors testing PCR negative were only implicated in 2.9%; these were the data used for transmissibility by Bish and colleagues. Data from hamsters, a sensitive animal model for B. microti infection dating back to the 1970s, also suggest that PCR positivity correlates to infectivity. During the IND trial, samples from index donations with an antibody titer of 512 or higher with or without PCR positivity were injected into hamsters. For PCR-positive and PCR-negative samples, using standard methods of the ARC IND, 54 and 4% were infectious, respectively; the 4% represented only two samples, one of which could be detected by an enhanced PCR method. Due to the limitations of extrapolating hamster data to humans, these data were not included in the model, but add further evidence that PCR positivity is a better correlate to infectivity than antibody.

Recipient tracing data from donors identified in the IND trial are not designed to draw inference about infectivity. These data are passively collected and only 34 recipients have been tested. These recipients received prior donations dating back 12 months from a positive donor, not the index donation, and none of these prior donations were available for hamster challenge. Johnson and coworkers found that positive donations at index (i.e., those testing positive at presentation and transfused) were infectious in 50% of tested recipients (4/8), whereas only 7.3% (4/55) of prior cellular components were infectious; in the ARC IND study, index units were not transfused.

During the IND trial, ARC investigated 22 confirmed TTB cases occurring in seven endemic states. The resulting rates from these cases were the source data for Table 6 in Bish et al. Table 6 includes 131 to 169 TTB cases averted per year in the seven-state model, assuming an overall prevalence rate that is fivefold lower than that used for highly endemic areas (including those in Tables 4 and 5). If one refers to the 22 TTB cases that occurred in the seven endemic states and assumes 10% to 15% clinical case underreporting, this translates to 110 to 165 TTB cases averted per year, very close to that reported in Table 6.

The current rate of TTB from unscreened blood in the 10 counties where prospective investigational screening has occurred is now 1:18,000 (1:19,500 was noted in the footnote of Table 6). This residual risk is comparable to that of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus after first-generation screening in the late 1980s to early 1990s when the cost of such testing was considered acceptable. However, residual risks after initial test implementation drove the need for improved methods and additional testing, measures with an extremely high marginal cost–benefit ratio. In contrast, the estimated CE for blood donation screening for another parasitic infection, Trypanosoma cruzi, the agent of Chagas disease, used an endemic non-US geographic model as one option (vs. a US geographic selection model as discussed for B. microti), yielding a CE of $173,000/QALY for all recipients and $29,000/QALY for a younger age group. However, this CE analysis used a transmission rate of 1:200,000, a significant overestimate versus the finding of only nine cases of transfusion-transmitted Chagas disease documented since 1989 in the United States and Canada for a rate of approximately one transmission every 3 years.

Data availability and uncertainty represent important challenges in any CE analysis. Thus, such analyses require extensive sensitivity analyses and discussions of key data and assumptions that impact the CE results, as well as calibration with respect to actual outcome data as they become available. As noted by Goodell and colleagues, it is important to closely review all available models and model inputs for their strengths and limitations before promulgating policy.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest. EM and SS are investigators in a study of the efficacy of investigational B. microti antibody and DNA screening in blood donors in endemic areas of the United States.

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Significant methemoglobinemia with bovine hemoglobin infusion in a case with severe autoimmune hemolytic anemia

Bovine hemoglobin glutamer-250 (Hemopure [HP], HbO2 Therapeutics LLC, Souderton, PA) is a chemically stabilized, polymerized bovine hemoglobin (Hb) approved for the treatment of acute anemia in surgical patients in South Africa. It is under evaluation by the Food and Drug Administration (FDA) as an acellular oxygen carrier in humans in the United States, and its use is still controver-

sial due to multiple side effects including abdominal pain, jaundice, hematuria, rash, and an increase in methemoglobin (MetHb). The increase of MetHb is proportional to the total volume of HP transfused. HP has been used to treat severe anemia in multiple conditions with mixed results, including a few cases of successful treatment of severe autoimmune hemolytic anemia (AIHA). We report a case of severe AIHA treated with HP, resulting in a marked increase of MetHb and a poor clinical outcome.

A 24-year-old African American male with a history of refractory Evan’s syndrome presented at an outside institution with active hemolysis (Hb 8.9 g/dL), hematemesis, hematuria, fatigue, weakness, and thoracoabdominal pain after receiving 2 weeks of oral amoxicillin for a urinary tract infection. He received a splenectomy 3 years earlier for refractory immune thrombocytopenia. He had no personal or family history of a hemoglobinopathy or glucose-6-phosphate dehydrogenase deficiency. He was started on methylprednisone (1000 mg daily) and given one dose of rituximab (750 mg) and cyclophosphamide (1500 mg). Over the next 48 hours, he rapidly declined, with laboratory evidence of multiorgan damage. He was intubated and ultimately transferred to our institution.

On arrival, his Hb was 2.3 g/dL with a positive direct antiglobulin test (IgG 1+, C3-negative) and a positive antibody screen due to warm autoantibodies. Additional labs included a platelet count of 112 × 10^9/L, absolute neutrophil count of 3 × 10^9/L, reticulocytes of 23.7%, hemoglobin of less than 10 mg/dL, and total and indirect bilirubin of 6.5 and 4.2 mg/dL, respectively. Peripheral smear showed spherocytes, compatible with immune-mediated extravascular hemolysis. He was continued on methylprednisone. Initial MetHb levels by arterial blood gas (ABG) were not reportable due to interference by increased bilirubin, but MetHb was eventually measured at 18.5%, believed to be elevated secondary to ongoing severe hemolysis. He received methylene blue (MB), resulting in a modest MetHb decrease (8.7%). Given the ongoing hemolysis with warm autoantibodies, red blood cell (RBC) transfusion was initially delayed. However, 6 units of Rh, K- matched RBCs were eventually transfused and Hb appropriately increased (complete blood count, 7.1 g/dL; total Hb, 6.3 g/dL by ABG). Hb by ABG remained relatively stable after the third RBC transfusion; however, he remained progressively hypoxic as evidenced by O2Hb (fraction of oxygenated Hb) of 65% to 79% even though pO2 was consistently greater than 150 mmHg due to FiO2 (fraction of inspired oxygen) of 100%. He also developed significant lactic acidosis (19-26 mmol/L). By this time, he had been treated with maximal medical therapy, including rituximab, cyclophosphamide, and steroids, as well as one dose of eculizumab (900 mg) and epoetin alfa. Given his continued dire clinical status despite medical intervention, he received an initial trial of 2 units of HP; followed by 2 additional HP units, all under an FDA compassionate usage protocol.