HHS Public Access

Author manuscript

Transfusion. Author manuscript; available in PMC 2017 August 15.

Published in final edited form as:

Transfusion. 2017 June ; 57(Suppl 2): 1625–1633. doi:10.1111/trf.14164.

Cost projections for implementation of safety interventions to prevent transfusion-transmitted Zika virus infection in the United States

Katherine D. Ellingson[1,2], **Mathew R.P. Sapiano**[1,3], **Kathryn A. Haass**[1], **Alexandra A. Savinkina**[1,4], **Misha L. Baker**[1,5], **Richard A. Henry**[6], **James J. Berger**[6], **Matthew J. Kuehnert**[1], and **Sridhar V. Basavaraju**[1]

[1]Office of Blood, Organ, and Other Tissue Safety, Division of Healthcare Quality Promotion, Atlanta, Georgia

[2]Department of Epidemiology and Biostatistics, The University of Arizona College of Public Health, Tucson, Arizona

[3]Surveillance Branch, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

[4]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee

[5]Northrop Grumman Corporation, Atlanta, Georgia

[6]Office of HIV/AIDS & Infectious Disease Policy, Office of the Assistant Secretary for Health, US Department of Health & Human Services, Washington, DC

Abstract

BACKGROUND—In August 2016, the Food and Drug Administration advised US blood centers to screen all whole blood and apheresis donations for Zika virus (ZIKV) with an individual-donor nucleic acid test (ID-NAT) or to use approved pathogen reduction technology (PRT). The cost of implementing this guidance nationally has not been assessed.

STUDY DESIGN AND METHODS—Scenarios were constructed to characterize approaches to ZIKV screening, including universal ID-NAT, risk-based seasonal allowance of minipool (MP) NAT by state, and universal MP-NAT. Data from the 2015 National Blood Collection and Utilization Survey (NBCUS) were used to characterize the number of donations nationally and by state. For each scenario, the estimated cost per donor ($3–$9 for MP-NAT, $7–$13 for ID-NAT) was multiplied by the estimated number of relevant donations from the NBCUS. Cost of PRT was

Address reprint requests to: Katherine D. Ellingson, The University of Arizona College of Public Health, 1285 N. Martin Avenue, Room A224, Tucson, AZ 85724; kellingson@email.arizona.edu.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention or the US Department of Health and & Human Services. The use of trade names is for identification purposes only and does not constitute endorsement by the US Centers for Disease Control and Prevention or the Department of Health and Human Services.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

calculated by multiplying the cost per unit ($50–$125) by the number of units approved for PRT. Prediction intervals for costs were generated using Monte Carlo simulation methods.

RESULTS—Screening all donations in the 50 states and DC for ZIKV by ID-NAT would cost $137 million (95% confidence interval [CI], $109–$167) annually. Allowing seasonal MP-NAT in states with lower ZIKV risk could reduce NAT screening costs by 18% to 25%. Application of PRT to all platelet (PLT) and plasma units would cost $213 million (95% CI, $156–$304).

CONCLUSION—Universal ID-NAT screening for ZIKV will cost US blood centers more than $100 million annually. The high cost of PRT for apheresis PLTs and plasma could be mitigated if, once validated, testing for transfusion transmissible pathogens could be eliminated.

Optimizing strategies to protect the United States blood supply from Zika virus (ZIKV) is challenging for policy makers and the blood collection community.[1] The rapid spread of ZIKV through the western hemisphere in 2015 and 2016 was coupled with knowledge gaps in disease transmission dynamics, inconsistent surveillance of mosquitoes that transmit ZIKV to humans, and resource constraints in case detection.[2] Despite typically mild presentation in most adults, ZIKV can cause serious adverse outcomes in infants born to women infected during pregnancy, including microcephaly, as well as and fetal loss in pregnant women.[3,4] Although rare, ZIKV has been associated with Guillain-Barré syndrome in previous outbreaks and in 0.3% of US cases reported in the 50 states and the District of Columbia.[5–7]

Approximately 80% of individuals infected with ZIKV are asymptomatic,[8] and sexual transmission from returned infected travelers can result in transmission in nonendemic areas.[9] This unique constellation of characteristics renders ineffective blood donor deferral strategies based on travel history or clinical symptoms alone. As a result, the US Food and Drug Administration (FDA) has recommended that all blood donations in the United States be screened for ZIKV using investigational individual-donor nucleic acid tests (ID-NATs) or alternatively, for apheresis platelets (PLTs) and plasma, that donations be subjected to FDA-approved pathogen reduction technology (PRT).[10,11]

Transfusion-transmitted ZIKV was documented in Brazil during the 2015 and 2016 outbreak via PLT transfusions.[12,13] A retrospective study of archived samples collected from asymptomatic blood donors during the 2013 and 2014 French Polynesia ZIKV outbreak found that 2.8% of donations contained detectable ZIKV,[14,15] and after implementation of NAT screening in Puerto Rico in April 2016, an increasing percentage of donations were reactive, with a peak weekly incidence of 1.1% reactive reported during the second week of June 2016.[16] These findings suggest the potential for transfusion-transmitted infection during outbreaks in the absence of testing or PRT.

The *Aedes aegypti* mosquito, which is endemic to many regions of the United States, has been implicated as the primary transmitter of ZIKV throughout the western hemisphere, although most reported cases in the mainland United States have been travel-associated.[7,17] The risk of asymptomatic infection among donors – through travel, sexual acquisition, or an unrecognized local outbreak propagated by *A. aegypti* mosquitoes – has motivated the FDA and blood collection centers to consider aggressive screening policies. After the first cluster

of mosquito-transmitted ZIKV cases was identified in the mainland United States, the FDA published recommendations for universal ID-NAT screening or PRT.[18] The FDA advised a phased implementation approach, recommending immediate adoption of ID-NAT in states with documented mosquito-borne transmission, adoption within 4 weeks in high-risk states and adoption within 12 weeks for all other states.[11]

Screening for ZIKV among US blood donations is currently under way using two ID-NAT assays available under investigational new drug (IND) protocols. Guidance for post-IND NAT screening for ZIKV has not yet been released. Specifically, there are no recommendations for appropriate use of minipool (MP) NAT for ZIKV, although MP-NAT has been incorporated into blood center guidance for screening of other transfusion-transmissible pathogens.[19,20] MP-NAT screening for other pathogens, in which donor samples are typically tested in pools of 6 or 16 samples, can enhance efficiency and reduce costs. However, the sensitivity of MP- versus ID-NAT screening for ZIKV must be considered before adoption. Because ZIKV NAT screening technology is currently under development, the relative sensitivity of ID- and MP-NAT screening is still under study.

The aim of this study was to provide context for future planning by projecting the annual cost of blood donor screening for ZIKV, or use of PRT on donated units, in the United States using data from the 2015 National Blood Collection and Utilization Survey (NBCUS). To date, the aggregate national costs of implementing ZIKV assay screening or PRT for routine, noninvestigational purposes have not been characterized. The objectives of this study were: 1) to construct plausible scenarios for ZIKV donation screening including universal ID-NAT, a combination of MP-NAT and ID-NAT dependent on state-specific risk, and universal MP-NAT; 2) to project annual costs of screening under each scenario; and 3) to project costs associated with implementation of FDA-approved PRT for apheresis PLTs and plasma.

MATERIALS AND METHODS

Three scenarios were constructed as a basis for NAT screening cost projections. Scenario 1, “universal ID-NAT,” reflects the current FDA recommendation for ID-NAT of all donations in 50 states and the District of Columbia (Table 1). The NBCUS does not include US territories, so the cost of ZIKV screening in US territories was not considered in this analysis. Scenarios 2a and 2b, “MP-NAT acceptable, low *Aedes* threshold” and “MP-NAT acceptable, high *Aedes* threshold,” respectively, specify conditions under which blood collection centers would perform ID-NAT or MP-NAT based on state-based risk considerations described below. Scenario 3, “universal MP-NAT,” represents an approach that could be considered if MP-NAT were deemed adequate by FDA for ZIKV donor screening.

Scenarios 2a and 2b specify ID-NAT and MP-NAT screening based on state-specific risk characterized by history of locally transmitted mosquito-borne infections, travel patterns from ZIKV-endemic areas, and published estimates of mosquito abundance (Fig. 1).[21] State-specific history of mosquito-borne infections was based on a review of outbreaks including locally-acquired Zika, Chikungunya, or Dengue virus cases reported to the Centers for Disease Control and Prevention (CDC).[18,22] Travel and mosquito abundance characteristics

were based on a 2016 publication quantifying monthly volume of entry to the United States from ZIKV-endemic countries as well as estimated *A. aegypti* abundance in 50 US cities covering the known range of *A. aegypti,* with city-level data extrapolated to each state.[21] Scenarios 2a and 2b specify year-round ID-NAT screening in states with previously documented outbreaks with local transmission of Zika, Chikungunya, or Dengue virus (Florida, Hawaii, Texas) and in states with more than 100,000 monthly returned travelers from ZIKV-endemic countries (California, Arizona, New Mexico, Texas, Florida, Georgia, New York); in all other states, MP-NAT would be allowed unless a threshold of estimated *A. aegypti* was reached in a given month. Scenario 2a would require the following: year-round ID-NAT in states with a history of mosquito-borne outbreaks of Zika, Chikungunya, or Dengue viruses or high-volume travel from ZIKV-endemic countries; for all other states, MP-NAT would be acceptable only during months when projected *A. aegypti* abundance was none to low.[21] Scenario 2b reflects a more flexible approach, which would also require year-round ID-NAT in states with a history of mosquito-borne outbreaks or high-volume travel; for all other states, MP-NAT would be acceptable except during months when projected *A. aegypti* abundance was high.

Estimating the costs of screening nationwide under Scenarios 2a and 2b required calculation of the total number of donations that would be subject to ID-NAT or MP-NAT screening, which is a function of the number of months of the year requiring each type of screening under each scenario. National estimates for whole blood–derived and apheresis donations in 2015 were generated from the 2015 NBCUS, which included a survey of blood collection centers in the 50 US states and the District of Columbia. Detailed methods for survey design and statistical generation of national estimates are published elsewhere.[23] A sampling frame of 222 blood collection centers for the 2015 NBCUS was based primarily on the FDA Blood Establishment Registration (BER) database, which includes an entry for each fixed collection site run by each blood center. Of the 174 blood centers that responded to the NBCUS in 2015, a total of 154 operated in a single state, 11 operated in two states, seven operated in three states and two operated in more than three states. For blood centers with collection sites in a single state, all donations were assigned to the state listed in the FDA BER database. For centers with collection sites in multiple states, the number of donations collected in each state was proportionally assigned based on the number of collection sites in each state divided by the total number of collection sites affiliated with the blood center (Fig. 2A).

To calculate the number of donations per blood center, the following NBCUS variables were summed: number of manual whole blood collections, number of apheresis red blood cell (RBC) collections (excluding collections concurrent with apheresis collection of PLTs or plasma), number of apheresis PLT collections, and number of apheresis plasma collections. Information on the number of collections involving PLTs and plasma concurrently was not collected through the NBCUS. To account for nonresponse and missing data, weighting and imputation were used per methods described previously.[23]

For Scenarios 2a and 2b, each state was assigned ID-NAT or MP-NAT for each month of the year depending on history of local transmission, travel volume from ZIKV-endemic countries, and mosquito abundance; based on monthly characterization of risk, each state

was assigned a proportion of the year for which ID-NAT would be specified and a proportion for which MP-NAT would be specified. These proportions were multiplied by the total number of donations collected annually in each state, which resulted in an estimated number of donations screened by ID-NAT and MP-NAT, respectively. The number of donations for each test type was then aggregated to the national level by testing type for cost calculation.

Cost estimates per donation for ID- and MP-NAT screening were based on personal communications with blood center administrators and published estimates for NAT donor screening for other transfusion-transmitted infections. All cost inputs were based on anticipated post-IND costs. During IND, costs paid by blood centers cannot include recoupment of research and development expenses.[24] Post-IND cost estimates from literature involving other transfusion-transmitted infections ranged from $7 to $18 for MP-NAT and from $5 to $33 for ID-NAT, although these studies were published in the early to mid 2000s.[20–28] The cost inputs used for these analyses were based primarily on personal communications with blood center administrators, who based anticipated costs of post-IND ZIKV screening on current costs for West Nile Virus testing (Personal communication with Louis M. Katz MD, Chief Medical Officer, America's Blood Centers, 2016). For MP-NAT, the estimated cost input used for in this study was $6 (range, $3–$9) per donation, and for ID-NAT, the estimated cost per donation was $10 (range, $7–$13). These per donation cost estimates included expenses related to reagents, consumables, and labor, but did not consider testing platform and infrastructure costs.

For each of the screening scenarios, the number of donations subject to ID-NAT or MP-NAT nationally was multiplied by the cost of each screening test: (number of donations screened by ID-NAT) × (cost per donation for ID-NAT) + (number of donations screened by MP-NAT) × (cost per donation for MP-NAT). Donations included all manual whole blood collections and apheresis collections. Monte Carlo simulations were used to create prediction intervals that incorporate error from both donation and cost estimates. For the simulations, donations were assigned a normal distribution based on the standard error of the NBCUS estimate, and screening costs were assigned triangular distributions. Prediction intervals were generated based on 10,000 simulations.

Because cost calculations for screening scenarios required state-specific blood donation estimates from the 2015 NBCUS, state-specific rates of donation could be estimated to provide context for interpretation of cost estimates. To calculate rates of donation per 1000 population by state, the total number of manual whole blood, apheresis RBC, and apheresis PLT collections in each state was divided by the population eligible for donation and multiplied by 1000 (Fig. 2B). The eligible donor population was estimated from age-specific census data, with the upper bound for donor eligibility was set at age 74, and the lower bound was set at 17, except in states that allow 16-year-olds to donate.[31]

Interstate distribution patterns were also examined by state to estimate how blood products are shared between states and how sharing might affect the impact of state-specific screening requirements. Calculating imports and exports required an analysis of units rather than donations. Imports and exports were only calculated for RBC units collected by either

manually (i.e., whole blood) or by apheresis, since the distribution data were sufficiently robust for RBCs but not for other blood products. Imports were determined by subtracting the number of units distributed from the number of units transfused in each state; exports were determined by subtracting the number of units transfused in each state from the number of units distributed. To estimate the number of transfused RBC units by state, transfused units were assigned to states based on location of the transfusing hospital listed in the 2013 American Hospital Association database. To estimate the number of units distributed per state, units were assigned to the location of the blood collection center listed in the FDA BER; if the blood center had collection sites in multiple states, units were assigned to states based on the apportioning methods described above (Fig. 2C).

To estimate costs of PRT, a cost estimate of $75 (range, $50–$125) per unit was used. This estimate was based on personal communication with blood center administrators and was consistent with cost reported in published literature.[30–32] The cost per unit was then multiplied by the total number of apheresis PLT and plasma units distributed in the United States based on the 2015 NBCUS survey. For this analysis, the units considered for PRT were apheresis PLT and apheresis plasma units only. Currently PRT is not FDA approved for use with whole blood–derived PLTs and therefore whole blood–derived PLTs were not included. While PRT is approved for whole blood–derived plasma, these units were assumed to be collected concurrently with RBC units, for which PRT is not currently approved; in this instance PRT on whole blood–derived plasma units would be redundant for ZIKV prevention since the entire donation (RBC and plasma) would be NAT screened. For net PRT costs, the cost of ID-NAT screening ($10 per donation) was subtracted from the cost of PRT for eligible units. No calculations were made for PRT for whole blood–derived or apheresis RBC units, since PRT for RBC units is not FDA approved.[11] Monte Carlo methods using 10,000 simulations were employed to create prediction intervals, with apheresis PLTs and plasma units assigned a normal distribution and PRT costs assigned a beta distribution. All analyses were conducted using statistical software (SAS, Version 9.3, SAS Institute).

RESULTS

In 2015, a total of 13,769,000 (95% confidence interval [CI], 13,127,000–14,411,000) donations were collected at blood centers in the 50 states and the District of Columbia (Table 1). These donations were collected across states with variability in the risk of ZIKV infection among donors based on history of mosquito-borne outbreaks, travel patterns, and *A. aegypti* abundance. For scenarios dependent on state-specific risk factors, states would be required to implement ID-NAT, versus MP-NAT, screening from zero to 12 months of the year (Fig. 1), which led to differences in national cost estimates.

States also varied in the number of donations, population rates of donation, and RBC import and export (within the 50 states and the District of Columbia) activity. Five states (California, Florida, New York, Pennsylvania, and Texas) had more than 500,000 donations in 2015, and 15 states (Alaska, Alabama, Colorado, Connecticut, Delaware, Hawaii, Maine, North Dakota, New Hampshire, New Mexico, Rhode Island, South Dakota, Vermont, West Virginia, Wyoming) had fewer than 100,000 donations (Fig. 2A). Rates of donation per 100,000 donor-eligible population were highest (>80 per 1000) in Arkansas, Idaho,

Montana, North Dakota, Nebraska, South Dakota, and Wisconsin (Fig. 2B). In 2015, the five states that exported more than 100,000 RBC units to other states included Arkansas, Iowa, Missouri, Montana, and Wisconsin; the five states that imported more than 100,000 RBC units from other states included California, Florida, Maryland, New Jersey, and Pennsylvania (Fig. 2C).

Under NAT screening Scenario 1, which represents universal ID-NAT screening for ZIKV, 100% of donations would be subject to screening by ID-NAT (Table 1). The projected cost of screening all units annually for ID-NAT is $137 million (95% prediction interval, $109–$167 million) (Table 2). Under Scenario 2a, which would allow MP-NAT in states with lower risk of ZIKV importation and transmission, but only during months when *A. aegypti* abundance was estimated to be none to low, 53.8% of donations would be tested by ID-NAT and 46.2% by MP-NAT. The total calculated cost of screening under this scenario was $112 million (95% prediction interval, $91–$134 million) annually. Under Scenario 2b, which would allow MP-NAT in states with a lower risk of ZIKV transmission and importation except when *A. aegypti* abundance was high, 36.9% of donations would be screened by ID-NAT and 63.2% by MP-NAT at an estimated cost of $103 million (95% prediction interval, $81–$125 million) annually. Finally, the estimated cost of NAT screening in Scenario 3, which represents universal MP-NAT initial screening, was $82 million (95% prediction interval, $54–$111 million) annually.

If PRT were to be applied to the 2,803,000 (95% CI, 2,521,000–3,085,000) units of apheresis PLTs and apheresis plasma collected in the United States annually, the total annual cost of pathogen inactivation would be $213 million (95% prediction interval, $156–$304 million). The cost savings conferred by not testing apheresis PLT and plasma units with ID-NAT for ZIKV would be $12 million (95% prediction interval, $10–$15 million), with a net cost of $201 million (95% prediction interval, $143–$292 million).

DISCUSSION

Blood centers in the 50 states and the District of Columbia collect an estimated 13.8 million whole blood and apheresis donations annually, and the FDA currently requires screening of all donations for ZIKV by ID-NAT under IND. Once research protocol testing concludes, and if ZIKV screening is implemented routinely following current FDA guidance, ID-NAT screening for ZIKV alone in the United States could cost blood centers $137 million (95% CI, $109–$167) annually. This cost estimate is consistent with an estimate presented by the AABB at a November 2016 FDA Blood Products Advisory Committee meeting, suggesting that the FDA recommendation for universal ID-NAT for ZIKV would “incur direct costs well in excess of one hundred million dollars per year.” [33] Scenarios that allow MP-NAT in states with lower risk of importation and local transmission during months with lower estimated *A. aegypti* abundance could reduce screening costs by 18.2% to 24.8% nationally. These findings can be used to guide future discussions regarding transfusion-transmitted ZIKV prevention strategies as the epidemiology of the virus in the United States and transmission dynamics are better understood.

Scenarios allowing MP-NAT screening in lower risk regions of the United States follow a logic similar to FDA recommendations for West Nile virus (WNV) MP-NAT screening with triggering for ID-NAT.[19] However, unlike WNV recommendations for ID-NAT triggering when a WNV-positive donor threshold is reached, this study examined scenarios that assigned states to ID- and MP-NAT screening protocols based on projected seasonal and geographic risk, irrespective of case detection. Use of a ZIKV risk-projection model, including seasonal mosquito abundance, travel patterns, and history of local transmission,[21] is particularly important with ZIKV given the limitations and variations in real-time mosquito surveillance and case detection across the United States. Mosquito-borne (i.e., locally acquired) ZIKV transmission in the United States was first reported in Puerto Rico in December 2015.[34] During June through August 2016, southern Florida experienced the first outbreak on the US mainland, which resulted in 139 reported infections.[18] Although the number of reported locally acquired cases in the 50 states and the District of Columbia is low and appears to have been contained geographically with aggressive vector control efforts, the possibility of further geographic spread of ZIKV exists in regions where *A. aegypti* mosquitos are found.

Because ZIKV is sexually transmitted, additional considerations beyond likelihood of mosquito-borne transmission, such as travel volume from endemic countries, were considered in Scenarios 2a and 2b. A scenario for universal initial screening of all donations for ZIKV by MP-NAT (Scenario 3) was also considered assuming adequate sensitivity of MP-NAT screening to prevent transmissions, and the potential that prevalence of ZIKV in blood donors remains rare in the mainland United States. Although not the most sensitive approach, this is the standard for NAT screening donations for most viral blood-borne pathogens in the United States. Currently the FDA recommends MP-NAT for viral blood-borne pathogens including human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus, with ID-NAT follow-up on positive MPs.[20]

The examination of state variation in collections, imports, exports, and population donation rates provides potentially useful context for discussion of national screening policies for ZIKV and other emerging pathogens. States with the highest risk of Zika importation and transmission (e.g., Florida, California, and New York) also have large numbers of imported blood products from other parts of the country (Fig. 2). The states exporting the most blood (e.g., Iowa, Montana, and Wisconsin) are low-ZIKV-risk states. Further, the rates of donation tend to be higher in low ZIKV-risk states (e.g., Idaho, Montana, Nebraska, North Dakota, and South Dakota). As a nation, the United States relies more heavily, in a relative sense, on states in the North and Midwest to maintain the blood supply. Allowing MP-NAT screening for ZIKV in low-risk regions, assuming that MP-NAT screening achieves adequate sensitivity, may reduce the national cost burden of implementing ZIKV screening.

Adoption of PRT for apheresis PLT and plasma products confers an added benefit in mitigating the risk associated with other emerging transfusion-transmitted infections.[35] However, the high cost associated with the technology may prohibit adoption. Additionally, PRT is not approved for RBC products, which constitute the majority of transfused blood products, although clinical trials evaluating safety and efficacy are under way.[36] The cost of PRT adoption was not modeled such that current routine donor screening for transfusion-

transmitted infections (e.g., HIV, WNV, and Hepatitis) could be discontinued. Additionally, cost savings associated with elimination of bacterial testing and irradiation for licensed PRT components at blood centers were not considered. Although PRT might obviate the need for leukoreduction, no cost savings related to leukoreduction were included in the net PRT calculations as only apheresis units were considered, and apheresis methods include leukoreduction. Future studies should assess whether PRT may provide sufficient safety enhancement and risk reduction to obviate some current routine donor laboratory screening for transfusion-transmitted infections as well as other per-unit processing costs.

These findings are subject to a number of limitations. First, several assumptions are required to estimate the cost per donation for routine ZIKV screening and PRT. Screening is currently implemented via an IND protocol, so the cost of licensed ZIKV NAT screening was not available. Therefore, cost of licensed ZIKV NAT screening may be higher or lower than what was used in this analysis. Estimates from the literature for routine donor testing by ID- and MP-NAT for other pathogens were highly variable. Costs of PRT were highly variable based on personal communications with blood center administrators and were primarily based on costs reported in the recent literature.[31] Second, while the 2015 NBCUS had a response rate of 90% for non–hospital-based blood collection centers and 72% for hospital-based blood collection centers, responses were weighted for nonresponse and missing data were imputed to develop national estimates. Estimation at the state level may introduce a greater level of error. The NBCUS survey was not designed to estimate state-level collections and the pattern of nonresponse in 2015 was such that a simple weighted population estimate would have deficiencies due to the small number of blood centers in each state. Therefore, the number of units collected in a given state were approximated based on the proportion of local collection centers in that state; this method assumes that collections are equivalent at each site, and the impact of this assumption is unknown.

Third, the relative sensitivity of ID- versus MP-NAT, as well as the sensitivity required to prevent transmission, is still under study. Therefore, the cost projections presented here do not consider the costs associated with the possibility of transfusion-associated infection and related complications, resulting from a ZIKV donor infection missed with a lower sensitivity screening approach such as MP-NAT. This study was based on the assumption that FDA's recommendation to test all donors for ZIKV, or to perform PRT on all donated units, will continue indefinitely, although it is possible that the recommendation could change if risk of infection in the donor population diminishes drastically as the outbreak in the Americas subsides. Finally, the cost associated with implementation of screening or PRT was estimated but the safety benefit was not quantified. The number of adverse pregnancy outcomes or Guillain-Barré syndrome cases that would be averted through ZIKV NAT screening of the blood supply is unknown. Once sufficient data on US ZIKV epidemiology, transmission dynamics, and transmissibility are available, further study on number of recipient infections averted, and donor infections missed, under each scenario used in this analysis is required.

In conclusion, the costs associated with protecting the blood supply through universal ID-NAT for ZIKV for all donors in the United States are substantial. While the safety benefits of PRT are promising, its costs currently far exceed costs of screening, particularly given

that RBC donations will continue to require screening until the technology can receive regulatory approval. The high cost of PRT could be mitigated if, once validated, routine screening for many transfusion-transmissible infections were eliminated. As the transmissibility dynamics, pathogenesis, and epidemiology of ZIKV are better understood, the cost projections presented in this study could inform cost–benefit analyses. Finally, this study demonstrates that the NBCUS national survey data can be utilized to project the costs of various blood safety interventions.

ABBREVIATIONS

BER	Blood Establishment Registration
ID	individual donor
IND	investigational new drug
MP(s)	minipool(s)
NBCUS	National Blood Collection and Utilization Survey
PRT	pathogen reduction technology
WNV	West Nile virus
ZIKV	Zika virus

References

1. Kuehnert MJ, Epstein JS. Assuring blood safety and availability: Zika virus, the latest emerging infectious disease battlefront. Transfusion. 2016; 56:1669–72. [PubMed: 27389990]
2. Fauci AS, Morens DM. Zika virus in the Americas--yet another arbovirus threat. N Engl J Med. 2016; 374:601–4. [PubMed: 26761185]
3. Rasmussen SA, Jamieson DJ, Honein MA, et al. Zika virus and birth defects--reviewing the evidence for causality. N Engl J Med. 2016; 374:1981–7. [PubMed: 27074377]
4. Ventura CV, Maia M, Dias N, et al. Zika: neurological and ocular findings in infant without microcephaly. Lancet. 2016; 387:2502. [PubMed: 27287830]
5. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016; 387:1531–9. [PubMed: 26948433]
6. Dirlikov E, Major CG, Mayshack M, et al. Guillain-Barré syndrome during ongoing Zika virus transmission - Puerto Rico, January 1–July 31, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:910–4. [PubMed: 27584942]
7. Case counts in the US [Internet]. Atlanta: Centers for Disease Control and Prevention; 2017. [cited 2017 Feb 6]. Available from: https://www.cdc.gov/zika/geo/united-states.html
8. Hayes EB. Zika virus outside Africa. Emerg Infect Dis. 2009; 15:1347–50. [PubMed: 19788800]
9. Freour, T., Mirallie, S., Hubert, B., et al. Euro Surveill; Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area; France. April 2016; 2016. p. 21
10. Donor screening recommendations to reduce the risk of transmission of Zika virus by human cells, tissues, and cellular and tissue-based products: guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2016.
11. Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components: guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2016.

12. Barjas-Castro ML, Angerami RN, Cunha MS, et al. Probable transfusion-transmitted Zika virus in Brazil. Transfusion. 2016; 56:1684–8. [PubMed: 27329551]
13. Motta IJ, Spencer BR, Cordeiro da Silva SG, et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. 2016; 375:1101–3. [PubMed: 27532622]
14. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. Clin Microbiol Infect. 2014; 20:O595–6. [PubMed: 24909208]
15. Gallian P, Cabié A, Richard P, et al. Zika virus in asymptomatic blood donors in Martinique. Blood. 2017; 129:263–6. [PubMed: 27827826]
16. Kuehnert MJ, Basavaraju SV, Moseley RR, et al. Screening of blood donations for Zika virus infection - Puerto Rico, April 3–June 11, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:627–8. [PubMed: 27337368]
17. Hennessey M, Fischer M, Staples JE. Zika virus spreads to new areas - region of the Americas, May 2015–January 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:55–8. [PubMed: 26820163]
18. Likos A, Griffin I, Bingham AM, et al. Local mosquito-borne transmission of Zika Virus - Miami-Dade and Broward counties, Florida, June–August 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:1032–8. [PubMed: 27684886]
19. Guidance for industry: use of nucleic acid tests to reduce the risk of transmission of West Nile virus from donors of whole blood and blood components intended for transfusion. Silver Spring (MD): U.S. Food and Drug Administration; 2009.
20. Guidance for industry: nucleic acid testing (NAT) for human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV): testing, product disposition, and donor deferral and reentry. Silver Spring (MD): U.S. Food and Drug Administration; 2010.
21. Monaghan AJ, Morin CW, Steinhoff DF, et al. On the seasonal occurrence and abundance of the Zika virus vector mosquito Aedes aegypti in the contiguous United States. PLoS Curr. 2016:8.
22. USGS and CDC disease maps [Internet]. Reston (VA): U.S. Department of the Interior, U.S. Geological Survey; 2016. [cited yyyy mmm dd]. Available from: https://diseasemaps.usgs.gov/index.html
23. Ellingson K, Sapiano M, Haass K, Savinkina A, Baker M, Chang K, Henry R, Berger J, Kuehnert M, Basavaraju S. Continued Decline in Blood Collection and Transfusion in the United States – 2015. Transfusion. 2017 (In Press).
24. Code of Federal Regulations, Charging for investigational new drugs under an IND, title 21, sec. 312.8.
25. Jackson BR, Busch MP, Stramer SL, et al. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. Transfusion. 2003; 43:721–9. [PubMed: 12757522]
26. Marshall DA, Kleinman SH, Wong JB, et al. Cost-effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. Vox Sang. 2004; 86:28–40. [PubMed: 14984557]
27. Shehata N, Kohli M, Detsky A. The cost-effectiveness of screening blood donors for malaria by PCR. Transfusion. 2004; 44:217–28. [PubMed: 14962313]
28. Custer B, Busch MP, Marfin AA, et al. The cost-effectiveness of screening the U.S. blood supply for West Nile virus. Ann Intern Med. 2005; 143:486–92. [PubMed: 16204161]
29. Population estimates by state and age. Washington (DC): U.S. Census Bureau; 2015.
30. Bell CE, Botteman MF, Gao X, et al. Cost-effectiveness of transfusion of platelet components prepared with pathogen inactivation treatment in the United States. Clin Ther. 2003; 25:2464–86. [PubMed: 14604745]
31. Custer B, Agapova M, Martinez RH. The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model. Transfusion. 2010; 50:2461–73. [PubMed: 20497512]
32. Girona-Llobera E, Jimenez-Marco T, Galmes-Trueba A, et al. Reducing the financial impact of pathogen inactivation technology for platelet components: our experience. Transfusion. 2014; 54:158–68. [PubMed: 23656485]
33. 114th meeting of the Blood Products Advisory Committee. Silver Spring (MD): Food and Drug Administration, Center for Biologics Evaluation and Research; 2016.

34. Thomas DL, Sharp TM, Torres J, et al. Local transmission of Zika Virus--Puerto Rico, November 23, 2015–January 28, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:154–8. [PubMed: 26890470]

35. Jacobs MR, Lazarus HM, Maitta RW. The safety of the blood supply--time to raise the bar. N Engl J Med. 2015; 373:882.

36. Cerus announces agreement with BARDA for potential funding of up to approximately $180 million to advance its INTERCEPT red blood cell program [press release]. Concord (CA): Cerus Corp; 2016.

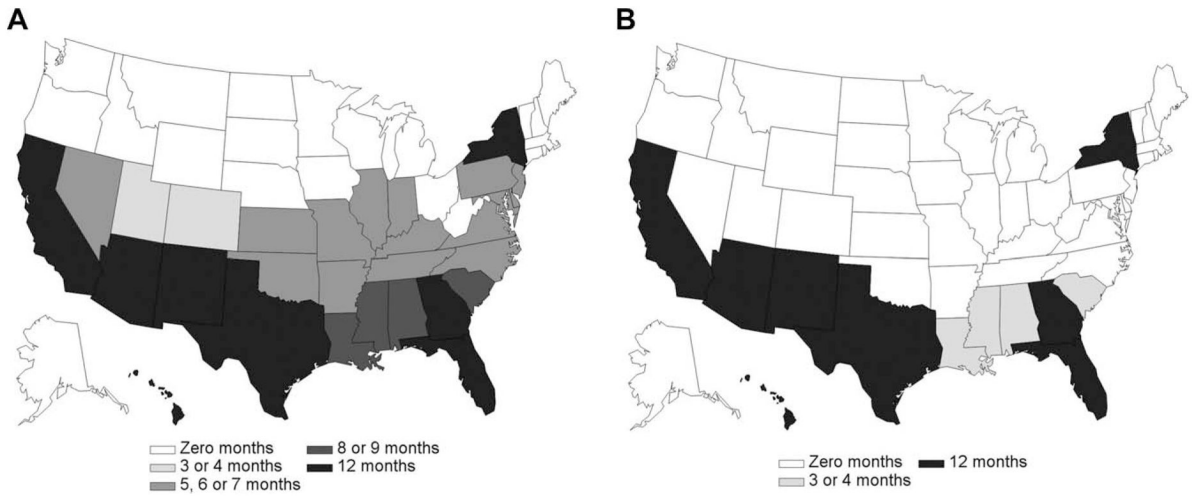

Fig. 1.

(A) Number of months per year that would require ID-NAT screening, versus MP-NAT screening, for Zika virus under Scenario 2a, "MP-NAT acceptable, low *Aedes* threshold," by state. (B) Number of months per year that would require ID-NAT screening, versus MP-NAT screening, for Zika virus under Scenario 2b, "MP-NAT acceptable, high *Aedes* threshold," by state.

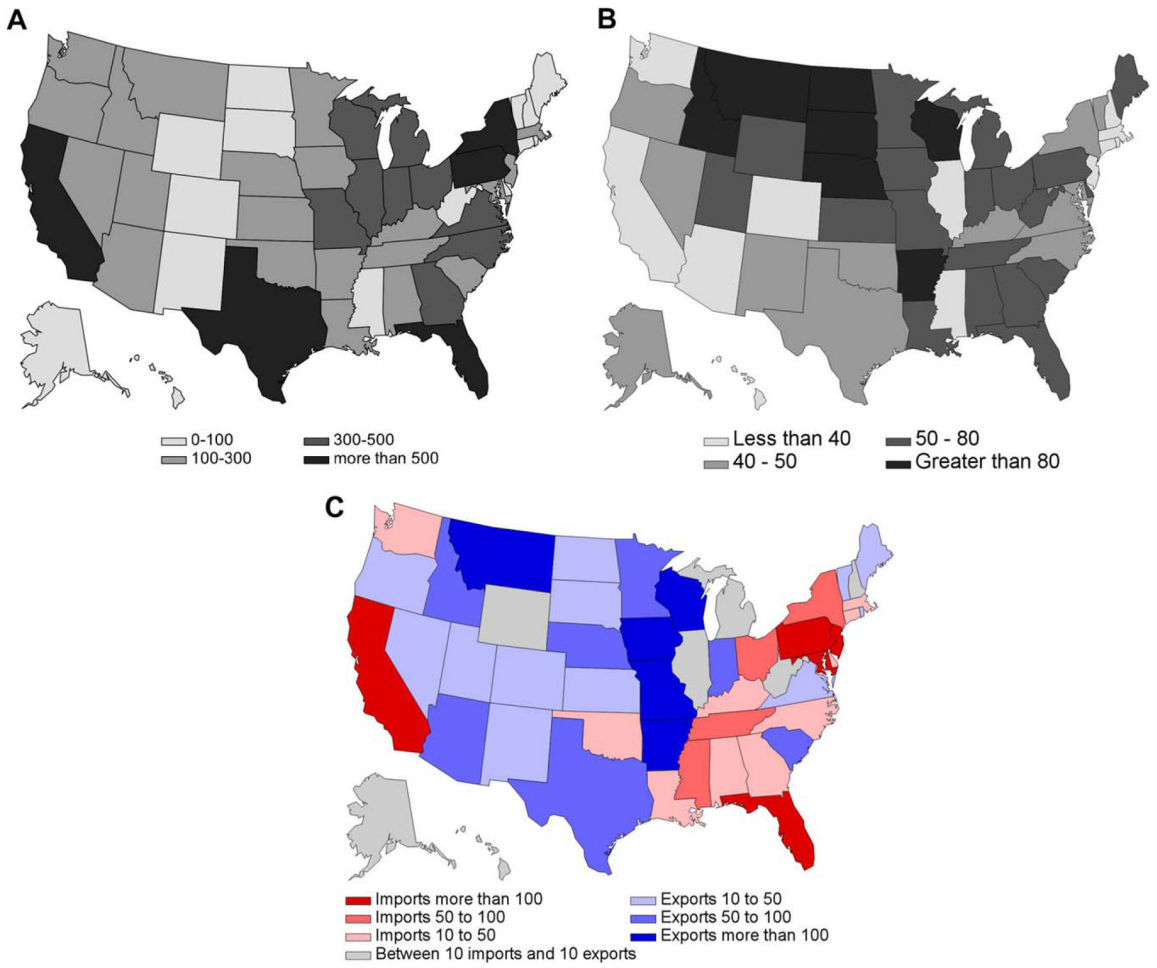

Fig. 2.

(A) Number of donations (in thousands) per state, defined as the sum of manual whole blood an apheresis collections in 2015. (B) Estimates of rate of donation per thousand donor-eligible population, by state, for 2015. (C) Estimated number of RBC units (in thousands) imported and exported, by state, in 2015.

TABLE 1

Scenarios constructed for screening the blood supply by various combinations of ID-NAT and MP-NAT methods

Scenario title	Scenario description	Percentage of donations initially screened by ID-NAT	Percentage of donations initially screened by MP-NAT
1. Universal ID-NAT	Assume current FDA recommendations hold for ID-NAT in all states year round	100.0	0.0
2a. MP-NAT acceptable, low *Aedes* threshold[†]	• Year-round ID-NAT in states with history of local transmission or high travel volume[*] • For all other states, MP-NAT only allowed during months when estimated *A. aegypti* abundance none to low	53.8	46.2
2b. MP-NAT acceptable, high *Aedes* threshold[†]	• Year-round ID-NAT in states with history of local transmission or high travel volume[*] • For all other states, MP-NAT allowed except during months with high *A. aegypti* abundance	36.9	63.1
3. Universal MP-NAT[†]	Possible future scenario if risk of Zika-infected donors is extremely low and MP-NAT deemed adequate for all donors	0.0	100.0

[*]History of outbreaks was defined as locally transmitted (by mosquito) Dengue, Chikungunya, or Zika virus reported to CDC, and high travel volume was defined as more than 100,000 travelers entering the state monthly from a Zika-endemic country.

[†]Scenario assumes that any MP testing positive by MP-NAT would be screened with ID-NAT, although the follow-up ID-NAT testing is not incorporated into the estimated percentage of units screened by each method.

TABLE 2

Estimated number of donations (in thousands) that would be subject to Zika virus NAT by ID or MP screening based on 2015 estimates with national cost estimates for scenarios (in millions)

Scenario	Donations, in thousands* (95% CI)		Cost, in millions (95% prediction interval)
	ID-NAT screening	MP-NAT screening	
1. Universal ID-NAT	13,769 (13,127–14,411)		$137 ($109–$167)
2a. MP-NAT acceptable, low Aedes threshold	7,414 (6,510–8,317)	6,355 (5,550–7,161)	$112 ($91–$134)
2b. MP-NAT acceptable, high Aedes threshold	5,084 (4,248–5,920)	8,685 (7,792–9,578)	$103 ($81–$125)
3. Universal MP-NAT		13,769 (13,127–14,411)	$82 ($54–$111)

*Includes manual whole blood collections, apheresis RBC collections (excluding collections concurrent with apheresis PLT or apheresis plasma collections), apheresis PLT collections, and apheresis plasma collections.