

# Mitigating the risk of transfusion-transmitted infections with vector-borne agents solely by means of pathogen reduction

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## Abstract

**Background:** This study evaluated whether pathogen reduction technology (PRT) in plasma and platelets using amotosalen/ultraviolet A light (A/UVA) or in red blood cells using amustaline/glutathione (S-303/GSH) may be used as the sole mitigation strategy preventing transfusion-transmitted West Nile (WNV), dengue (DENV), Zika (ZIKV), and chikungunya (CHIKV) viral, and *Babesia microti*, *Trypanosoma cruzi*, and *Plasmodium* parasitic infections.

**Methods:** Antibody (Ab) status and pathogen loads (copies/mL) were obtained for donations from US blood donors testing nucleic acid (NAT)-positive for WNV, DENV, ZIKV, CHIKV, and *B. microti*. Infectivity titers derived from pathogen loads were compared to published PRT log<sub>10</sub> reduction factors (LRF); LRFs were also reviewed for *Plasmodium* and *T. cruzi*. The potential positive impact on donor retention following removal of deferrals from required questioning and testing for WNV, *Babesia*, *Plasmodium*, and *T. cruzi* was estimated for American Red Cross (ARC) donors.

**Results:** A/UVA and S-303/GSH reduced infectivity to levels in accordance with those recognized by FDA as suitable to replace testing for all agents evaluated. If PRT replaced deferrals resulting from health history questions and/or NAT for WNV, *Babesia*, *Plasmodium*, and *T. cruzi*, 27,758 ARC donors could be retained allowing approximately 50,000 additional donations/year based on 1.79 donations/donor for calendar year 2019 (extrapolated to an estimated 125,000 additional donations nationally).

**Conclusion:** Pathogen loads in donations from US blood donors demonstrated that robust PRT may provide an opportunity to replace deferrals associated with donor questioning and NAT for vector-borne agents allowing for significant donor retention and likely increased blood availability.

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## 1 | INTRODUCTION

The amotosalen (A) and ultraviolet A light (UVA) pathogen reduction technology (INTERCEPT Blood System) inactivates viable leucocytes and reduces infectious pathogen levels in plasma<sup>1</sup> and platelets<sup>2</sup> and is commercially available. The A/UVA INTERCEPT Blood System pathogen reduction technology (PRT) received CE Mark approval in 2002 for platelets and in 2006 for plasma and has been the only PRT approved for both platelets and plasma by the Food and Drug Administration (FDA) since 2014. The amustaline and glutathione (S-303/GSH)-based PRT for red blood cells (RBCs) is not approved in the United States but is under review for CE marking. A/UVA PRT is increasingly recognized by regulatory authorities as a technology that can reduce the risk of transfusion-transmitted infections (TTI) and transfusion-associated graft versus host disease (TA-GVHD). FDA and AABB guidelines allow A/UVA PRT to be used for the ex vivo treatment of plasma and platelet components as an alternative to: gamma irradiation to mitigate the risk of TA-GVHD<sup>1,2</sup>; platelet testing for bacteria<sup>3</sup>; donation testing for Zika virus (ZIKV)<sup>4</sup>; *Babesia*<sup>5</sup>; and donor deferrals associated with screening questions for *Babesia*<sup>5</sup> and malaria.<sup>6</sup> Similar considerations could be given to PRT as an alternative to deferrals associated with donor screening and testing for other vector-borne agents such as *Trypanosoma cruzi*, West Nile (WNV), dengue (DENV), chikungunya (CHIKV) viruses, or parasitic agents for which, depending on the geographic area, mitigation strategies may not be in place, or in place only on a limited basis.<sup>7-9</sup>

This study evaluated PRT using A/UVA and S-303/GSH as an alternative to testing and/or donor screening questions for the mitigation of representative vector-borne disease agents that have emerged over the past two decades. Pre-existing serology and nucleic acid testing (NAT) data from studies that have characterized the natural history of vector-borne infectious diseases in blood donors were accessed. These studies were conducted using standardized operation protocols, systematic sample processing and validated assays, and measured pathogen loads observed in donations from asymptomatic U.S. blood donors infected with WNV, DENV, ZIKV, CHIKV, or *Babesia microti*. Different phases of infection were used to extrapolate infectious titers. Those were then compared to the published inactivation capacity of the A/UVA and S-303/GSH PRT for WNV, DENV, ZIKV, CHIKV, or *B. microti*. Donor retention was estimated for the American Red Cross (ARC) assuming PRT as the sole intervention for vector-borne agents. This was done for those pathogens for which testing currently occurs (i.e., WNV, *Babesia* and *T. cruzi*), as well as a discussion for those for which deferrals of donors are based on questioning only (i.e., *Plasmodium*). Although the agents

and data selected for study were focused on the United States, the findings should be applicable and informative worldwide as it relates to TTI mitigation, donor retention, and blood supply sustainability.

## 2 | METHODS

### 2.1 | Blood donor cohorts and sample characterization

#### 2.1.1 | WNV-infected blood donors and sample characterization

Donations from WNV-RNA confirmed-positive blood donors ( $n = 1683$ ) were identified from June 2003 through November 2017 by the ARC at locations throughout the continental US as WNV RNA-reactive using routine FDA licensed WNV NAT (Procleix Transcription Mediated Amplification [TMA]; Gen-Probe/Grifols). Viral loads were determined by National Genetics Institute (NGI) using EDTA-plasma or CPD-plasma samples with adequate volume and meeting sample suitability requirements using a commercial assay performed at NGI. Antibody testing as well as mini-pool (MP)-NAT versus individual donation (ID)-NAT were used to stage infections with respect to time of infection. All detection and quantitative methods were previously described.<sup>10</sup>

#### 2.1.2 | DENV-infected blood donors and sample characterization

Donations from DENV-RNA confirmed-positive blood donors were initially identified from June 2010 through June 2013 by the Puerto Rico region of the ARC as NS1-antigen reactive using an NS1Ag assay (Bio-Rad) under an Investigational New Drug application and confirmed DENV RNA-positive ( $n = 44$ ) by a research DENV TMA assay (Gen-Probe/Grifols); viral loads for TMA-reactive, EDTA-plasma, or CPD-plasma samples were performed by the Centers for Disease Control-Dengue Branch. Antibody testing (IgM) was used to stage infections with respect to time of infection. DENV isolates included all four DENV serotypes. All detection and quantitative methods were previously described.<sup>11,12</sup>

#### 2.1.3 | ZIKV-infected blood donors and sample characterization

Donations from ZIKV-RNA-confirmed-positive blood donors ( $n = 246$ ) were identified from April 2016 to May 2017 as ZIKV-RNA-reactive by ZIKV NAT either using

investigational or FDA-licensed reagents (cobas Zika NAT, Roche; or Procleix Zika Virus NAT, Grifols) after collection at Banco de Sangre de Servicios Mutuos in Puerto Rico or the ARC from donations in the continental United States, respectively. Antibody testing (IgM) as well as MP-NAT versus ID-NAT on EDTA or CPD-plasma samples were used to stage infections with respect to time of infection. All detection methods and quantitative PCR assays used were previously described.<sup>13,14</sup>

#### 2.1.4 | CHIKV-infected blood donors and sample characterization

CHIKV viral loads and antibody testing were performed on EDTA-plasma samples collected in Puerto Rico from Banco de Sangre de Servicios Mutuos in 2014–2015 and were supplied as residual samples from those used for routine blood donation screening. All testing including further characterization of CHIKV-RNA-reactive samples for viral loads and antibodies (IgM) were performed as previously described.<sup>15</sup>

#### 2.1.5 | *B. microti*-infected blood donors and sample characterization

Donations from *B. microti*-nucleic acid-confirmed-positive blood donors ( $n = 89$ ) were collected from June 2012 to December 2017 from ARC donors who resided and were collected in four Babesia-endemic US states (Connecticut, Massachusetts, Michigan, Wisconsin). All methods including NAT, antibody confirmation, and quantitative PCR were performed as previously described.<sup>16,17</sup>

#### 2.1.6 | Comparison of infectious titers derived from pathogen genomic loads in infected donors with PRT capacity

Pathogen loads in copies/mL were analyzed for donations during pre- versus post-seroconversion phases of infection (Figure 1A–E). Maximum and 90% pathogen genomic loads (the latter where 10% of the values were above the 90% upper limit of the distribution) were used to calculate infectious titers using published infectious titer: genome equivalent (GEq) ratios (Table 1). Existing data were used to define the efficacy of the A/UVA INTERCEPT Blood Systems for plasma<sup>1</sup> and platelets<sup>2</sup> to inactivate WNV, DENV, ZIKV, CHIKV, and *B. microti* (as well as *Plasmodium falciparum* and *T. cruzi*); and,  $\log_{10}$  reduction factors (LRFs) were used for the difference in infectious titers pre-

and post-PRT treatment during spiking experiments (expressed in  $\log_{10}$  PFU/mL, TCID<sub>50</sub>/mL, or ID<sub>50</sub>/mL). These are presented in Table 2 (as reviewed by Lanteri et al.<sup>21</sup>). Also included in Table 2 were the LRFs for the same agents when using the S-303/GSH PRT for RBC<sup>30–32</sup> (as reviewed by El Dusouqui et al.<sup>33</sup>).

The highest and 90% infectious titers extrapolated from pathogen genomic loads measured in blood donors in different phases of infection were compared to PRT LRFs (Figure 2A,B), as well as the reduction of infectious titers reduced by PRT (Table 3).

### 3 | RESULTS

#### 3.1 | Asymptomatic blood donors infected with vector-borne agents present with wide ranges of pathogen loads

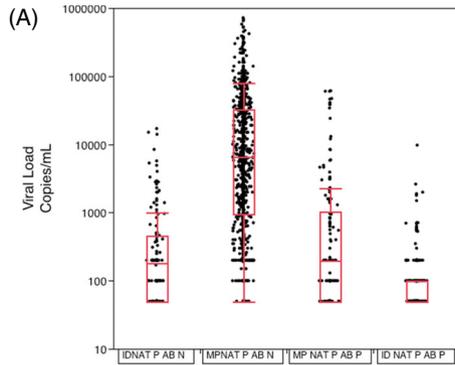
A fraction of U.S. donors donating blood after passing the donor interview and the health history questionnaire test reactive for vector-borne agents during routine, investigational, or retrospective donation screening. These donations have a wide range of pathogen loads despite donors being asymptomatic and afebrile at presentation. Antibody status and pathogen loads were collected from donations identified as NAT-positive for WNV ( $n = 1683$ ), DENV ( $n = 44$ ), ZIKV ( $n = 246$ ), CHIKV ( $n = 56$ ), and *B. microti* ( $n = 89$ ) (Figure 1A–E). Pathogen loads were plotted for donations grouped according to antibody status to discriminate pathogen levels and infectivity in the pre-seroconversion (IgM-negative/IgG-negative) or post-seroconversion (IgM-positive/IgG-negative or positive) phases of infection, and according to NAT status (MP or ID-NAT reactive), as available.

In general, viral loads peaked during the early pre-seroconversion phase of infections, corresponding to MP-NAT reactivity, with the 90th percentile to maximum peaks ranging from 75,000 to 720,000 (or 4.74 to 5.85  $\log_{10}$ ) copies/mL for WNV (Figure 1A), from 31,766,899 to 77,971,520 (or 7.46 to 7.89  $\log_{10}$ ) copies/mL for DENV (Figure 1B), from 1,548,000 to 83,565,000 (or 6.08 to 7.92  $\log_{10}$ ) copies/mL for ZIKV (Figure 1C), and from 116,600,000 to 130,000,000 (or 8.08 to 8.11  $\log_{10}$ ) copies/mL for CHIKV (Figure 1D). *B. microti* parasite loads peaked after seroconversion with the 90th percentile to maximum peak ranging from 71,762 to 2,990,624 (or 4.86 to 6.47  $\log_{10}$ ) copies/mL (Figure 1E); pre-seroconversion *B. microti* parasite loads were much lower with the 90th percentile and maximum values of 2665 to 11,022 (or 3.43 to 4.04  $\log_{10}$ ) copies/mL, respectively (Figure 1E).

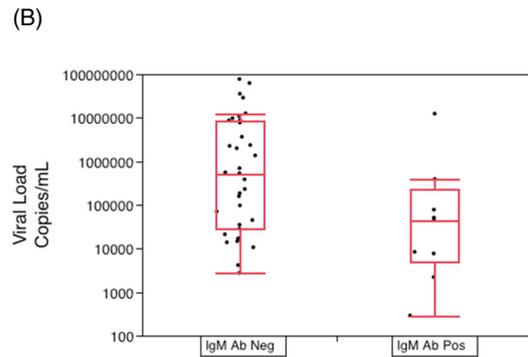
### 3.2 | Infectious titers are orders of magnitude lower than pathogen loads measured by NAT

Pathogen loads are quantified using molecular assays based on the amplification of target pathogen nucleic acid sequences expressed as genome equivalents (copies). PRT efficacy is based on the ability to reduce infectivity titers as assessed in cell culture systems and

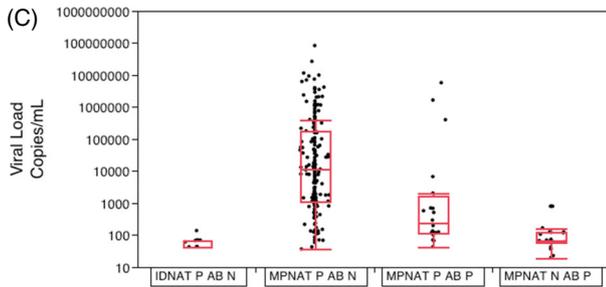
reported as LRFs. For the vector-borne agents of interest in this study, ranges of infectious titers to genome equivalent ratios published in the literature were reviewed. Those were 1:400–1:850 for WNV,<sup>34–36</sup> 1:10<sup>4</sup>–1:10<sup>5</sup> for DENV,<sup>20</sup> 1:10<sup>3</sup>–1:10<sup>5</sup> for ZIKV,<sup>23</sup> 1:100–1:200 for CHIKV,<sup>37,38</sup> and 1:100 for *B. microti*.<sup>16</sup> For the current analysis, conservative ratios of 1:400 for WNV, 1:10,000 for DENV, 1:1000 for ZIKV, 1:100 for CHIKV, and 1:100 for *B. microti* were used to derive infectious titers



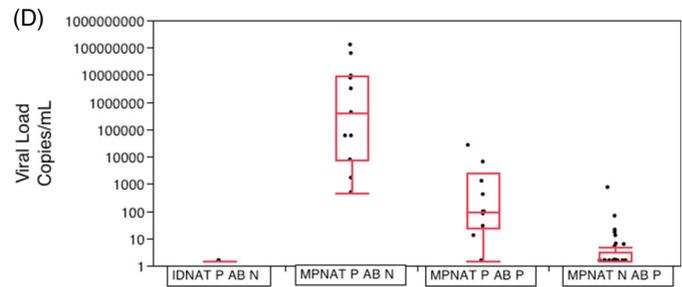
Level	Minimum	10%	25%	Median	75%	90%	Maximum
IDNAT P AB N (n=152)	50	50	50	185	455	2070	17000
MPNAT P AB N (n=1047)	50	200	950	6500	33000	75000	720000
MPNAT P AB P (n=150)	50	50	50	200	1052.5	5890	61000
IDNAT P AB P (n=334)	50	50	50	100	100	200	9700
All (n=1683)	50	50	50	1100	13000	55000	720000



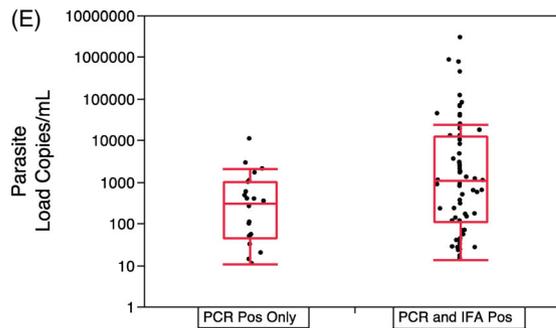
Level	Minimum	10%	25%	Median	75%	90%	Maximum
IgM Ab Neg (n=35)	2769.81	12717.2	28727.38	531251.3	8679066	31766899	77971520
IgM Ab Pos (n=9)	290	290	4991.481	44600	234230	12488521	12488521
All (n=44)	290	5976.75	18397	208000	6752663	29078165	77971520



Level	Minimum	10%	25%	Median	75%	90%	Maximum
IDNAT P AB N (n=9)	43.065	43.065	43.785	67.5	70.65	138.6	138.6
MPNAT P AB N (n=190)	36.81	220.8465	1141.088	11722.5	180450	1548000	83565000
MPNAT P AB P (n=20)	43.155	67.86	119.7	247.725	1712.138	1534905	5782500
MPNAT N AB N (n=27)	20.0	34.182	59.4	67.5	122.4	800	800
All (n=246)	20	67.5	218.464	2706.75	83126.3	1225800	83565000



Level	Minimum	10%	25%	Median	75%	90%	Maximum
IDNAT P AB N (n=2)	1.58	1.58	1.58	1.58	1.58	1.58	1.58
MPNAT P AB N (n=11)	500	740	7900	430000	9500000	1.166e+8	1.3e+8
MPNAT P AB P (n=10)	1.58	2.722	25	98	2625	24960	27000
MPNAT N AB N (n=33)	1.58	1.58	1.58	1.58	3.39	19.4	760
All (n=56)	1.58	1.58	1.58	3.39	695	1261000	1.3e+8



Level	Minimum	10%	25%	Median	75%	90%	Maximum
PCR Pos Only (n=22)	11	14	45.5	306	1025	2665.6	11022
PCR and IFA Pos (n=67)	14	27	117	1100	13000	71762	2990624
All (n=89)	11	24	69	638	3305.5	44441	2990624

**FIGURE 1** (A) West Nile viral loads in blood donations reactive by nucleic acid testing. Viral load distributions are shown for 1683 WNV-RNA confirmed-positive blood donations identified by blood donation screening from June 2003 to November 2017 in the continental United States. Viral loads are expressed in copies/mL and displayed by stage of infection beginning with donation samples testing individual donation nucleic acid test (IDNAT) positive (P) and antibody (AB) negative (N) ( $n = 152$ ), mini-pool NAT (MPNAT) P AB N ( $n = 1047$ ), MPNAT P AB P ( $n = 150$ ), and IDNAT P AB P ( $n = 334$ ). Box and whisker plots include the median and 25th and 75th percentiles. Maximum viral load was  $7.2 \times 10^5$  copies/mL. (B) Dengue viral loads from blood donations reactive by nucleic acid testing. Viral load distributions are shown for 44 DENV confirmed-positive blood donors identified by blood donation screening from June 2010 to June 2013 in Puerto Rico. Viral loads are expressed in copies/mL and displayed by stage of infection beginning with samples testing negative for anti-DENV IgM antibodies (IgM Ab Neg) ( $n = 35$ ) and those testing positive for anti-DENV IgM antibodies (IgM Ab Pos) ( $n = 9$ ). Box and whisker plots include the median and 25th and 75th percentiles. Maximum viral load was  $7.79 \times 10^7$  copies/mL. (C) Zika viral loads from blood donations reactive by nucleic acid testing.<sup>13,14</sup> Viral load distributions are shown for 246 ZIKV confirmed-positive blood donors enrolled from April 2016 to May 2017 primarily in Puerto Rico but also including confirmed-positive donations identified in the continental US. Viral loads are expressed in copies/mL and displayed by stage of infection beginning with samples testing IDNAT positive (P), IgM negative (AB N) ( $n = 14$ ), MPNAT P, AB N ( $n = 192$ ), MPNAT P, AB P ( $n = 26$ ), and IDNAT P, AB P ( $n = 93$ ). Box and whisker plots include the median and 25th and 75th percentiles. Maximum viral load was  $8.3 \times 10^7$  copies/mL. (D) Chikungunya viral loads from blood donations reactive by nucleic acid testing.<sup>15</sup> Viral load distributions are shown for 56 CHIKV confirmed-positive blood donors enrolled from the second half of 2014 to March 2015 in Puerto Rico. Viral loads are expressed in copies/mL and displayed by stage of infection beginning with samples testing IDNAT positive (P), IgM negative (AB N) ( $n = 2$ ), MPNAT P, AB N ( $n = 11$ ), MPNAT P, AB P ( $n = 10$ ), and IDNAT P, AB P ( $n = 33$ ). Positive samples with unquantifiable viral loads are plotted as being at the limit of quantification (3.16 copies/mL) and were included in calculation of medians (horizontal bars). Maximum viral load was  $1.3 \times 10^8$  copies/mL. (E) *Babesia microti* loads in blood donations. Parasite load distributions (parasites/mL) were measured in 89 *B. microti* confirmed-positive blood donations collected from June 2012 to December 2017 in the US states of CT, MA, MN, and WI. Parasite load distributions are shown for donations testing *B. microti* positive by PCR only (PCR Pos) ( $n = 22$ ) and by PCR and IFA (PCR and IFA Pos) ( $n = 67$ ). Box and whisker plots include the median and 25th and 75th percentiles. Maximum parasite load was  $2.99 \times 10^6$  copies/mL. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Projected maximum infectious pathogen loads measured in blood donors

Pathogen	Highest genomic load ( $\log_{10}$ copies/mL)	90th percentile genomic load ( $\log_{10}$ copies/mL)	Projected ratio infectivity: GEq <sup>a</sup>	Projected highest infectious titers ( $\log_{10}$ copies/mL)	Projected 90th percentile infectious titers ( $\log_{10}$ copies/mL)
WNV	$7.2 \times 10^5$ (5.85)	55,000 (4.74)	1:400	1800 (3.25)	137.5 (2.14)
DENV	$7.79 \times 10^7$ (7.89)	$2.9 \times 10^7$ (7.46)	1:10 <sup>4</sup>	7790 (3.89)	2900 (3.46)
ZIKV	$8.3 \times 10^7$ (7.92)	$1.2 \times 10^6$ (6.08)	1:10 <sup>3</sup>	83,565 (4.92)	1200 (3.08)
CHIKV	$1.3 \times 10^8$ (8.11)	$1.2 \times 10^8$ (8.11)	1:100	$1.3 \times 10^6$ (6.11)	13,000 (4.11)
<i>Babesia microti</i> NAT+/Ab-	11,022 (4.04)	2666 (3.43)	1:100	110.2 (2.04)	27 (1.43)
<i>B. microti</i> NAT+/Ab+	$2.99 \times 10^6$ (6.47)	71,762 (4.86)	1:100	29,906 (4.48)	718 (2.86)

<sup>a</sup>Projected number of genome copies to cause infection obtained from published studies.

Pathogen	Log reduction factors ( $\log_{10}$ copies/mL)			
	Plasma	Platelets		RBC <sup>18</sup>
		100% plasma	65%PAS/35%plasma	
WNV	$\geq 6.8^{19}$	$> 6.3^2$	$\geq 6.3^2$	N/A
DENV	$> 5.6^{20}$	$> 4.6^{21}$	$> 4.1^{21}$	$> 6.6^{22}$
ZIKV	$> 6.6^{23}$	$> 5.2^{24}$	$> 5.4^{24}$	$> 6.0^{25}$
CHIKV	$\geq 7.6^{26}$	$> 6.5^2$	$> 6.4^{26}$	$> 5.8^{27}$
<i>Babesia microti</i>	$\geq 4.9^1$	$> 4.5^{2,28}$	$\geq 4.9^2$	$> 5.0^{28}$
<i>Plasmodium falciparum</i>	$> 6.5^1$	$> 6.5^2$	$\geq 6.6^2$	$> 5.2^{29}$
<i>Trypanosoma cruzi</i>	$> 6.7^1$	$> 8.4^2$	$\geq 7.8^2$	N/A

Note: Based on published studies or US package insert.

Abbreviation: CHIKV, chikungunya virus; DENV, dengue virus; N/A, not available; WNV, West Nile virus; ZIKV, Zika virus.

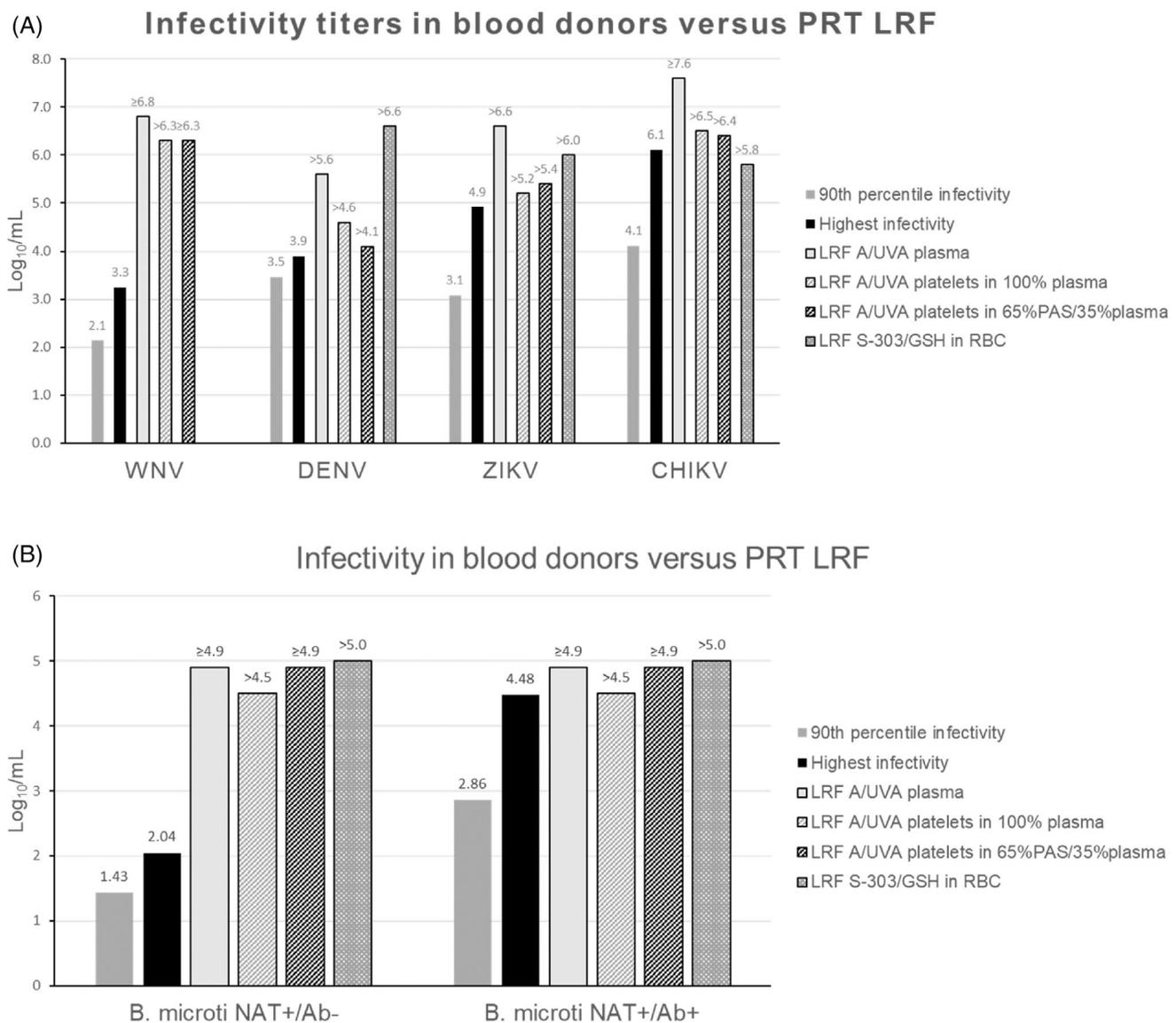
**TABLE 2** Susceptibility of vector-borne pathogens to A/UVA treatment of plasma and platelet units resuspended in 100% plasma or 35% plasma/65%platelet additive solution and S-303/GSH treatment of red blood cell units

associated with the highest pathogen loads measured in blood donors (Table 1).

Applying these ratios to the highest pathogen loads measured in donor samples captured during the pre-seroconversion phase of infections, infectious titers up to 3.25 log<sub>10</sub>/mL were extrapolated for WNV, 3.89 log<sub>10</sub>/mL for DENV, 4.92 log<sub>10</sub>/mL for ZIKV, 6.11 log<sub>10</sub>/mL for CHIKV, and 2.04 log<sub>10</sub>/mL for *B. microti* (Table 1). Unlike viral infections in which peak titers occur before seroconversion, for *B. microti*, parasite loads peaked following seroconversion (4.48 log<sub>10</sub>/mL).

### 3.3 | Comparing infectivity levels identified in blood donors with PRT inactivation capacity

LRFs of the A/UVA PRT<sup>21</sup> for plasma, platelets resuspended in 65% PAS/35% plasma, platelets resuspended in 100% plasma, and LRFs of the S-303/GSH PRT<sup>33</sup> for RBCs (Table 2) were compared for each pathogen to the infectivity titers associated with the highest viral loads observed in infected donors (Figure 2A) and in donors infected by *B. microti* before



**FIGURE 2** (A) Comparing viral infectious titers with PRT log reduction factors. Maximum and 90% percentile infectivity levels and log reduction factors (LRF) for each pathogen obtained with the A/UVA treatment in plasma, platelets resuspended in 100% plasma or platelets resuspended in 65% platelet additive solution/35% plasma, and LRF for each pathogen obtained with the S-303/GSH treatment in red blood cells expressed in log<sub>10</sub> copies/mL were compared. (B) Comparing *Babesia microti* infectious titers with PRT log reduction factors. Maximum and 90% percentile infectivity levels and LRF for *B. microti* obtained with the A/UVA treatment in plasma, platelets resuspended in 100% plasma or platelets resuspended in 65% platelet additive solution/35% plasma, and LRF for *B. microti* obtained with the S-303/GSH treatment in red blood cells expressed in log<sub>10</sub> copies/mL were compared.

TABLE 3 Percentage of donations in which infectious titers would be within PRT inactivation capacity

Pathogen	A/UVA P RTs			S-303/GSH PRT Red blood cells
	Plasma	Platelets in 100% plasma	Platelets in 65%PAS/35% plasma	
WNV	100%	100%	100%	N/A
DENV	100%	100%	100%	100%
ZIKV	100%	100%	100%	100%
CHIKV	100%	100%	100%	>98.2%
<i>Babesia microti</i>	100%	100%	100%	100%

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; WNV, West Nile virus; ZIKV, Zika virus.

TABLE 4 Number of donors deferred for risk of infection with or testing reactive for vector-borne pathogens at the American Red Cross in 2019<sup>a</sup>

Vector-borne agent	Available U.S. mitigation options	Number of deferred donors	Number of additional platelet donations with A/UVA PRT <sup>b</sup>	Number of additional RBC donations with S-303/GSH PRT <sup>b</sup>
WNV	MP-NAT/ID-NAT	45	5	40
<i>Babesia</i>	Deferral, ID-NAT, PRT	89	9	80
<i>Plasmodium</i>	Deferral due to travel, PRT	26,673	2667	24,006
<i>Trypanosoma cruzi</i>	Deferral, first time serology	951	95	856
Total		27,758 <sup>c</sup>	2776	24,982

<sup>a</sup>The number of donations from ARC blood donors deferred in 2019, as required by FDA guidance due to affirmative responses to donor questioning for risk of *Plasmodium* infection due to travel and those deferred due to reactive results following testing by NAT or antibodies to WNV, *Babesia*, or *T. cruzi* are reported.

<sup>b</sup>Based on 10.35% of all collections during 2019 at the ARC representing platelet donors (476,752 collections involving apheresis-derived platelets/4,605,660 total collections including 4,128,908 involving whole blood or apheresis-derived red cells).

<sup>c</sup>1.79 donations/donor based on 4,605,660 donations in 2019 from 2,574,695 donors.

and after seroconversion (Figure 2B). For all viral agents, the A/UVA PRT inactivation capacity surpassed the level of infectivity found in infected blood donors (Figure 2A; Table 3); PRT for CHIKV inactivation in RBCs was comparable to the highest level of infectivity with >98.2% of donations having presumed infectious titers below the PRT LRF (Table 3). For *B. microti*, the inactivation capacity of PRT surpassed the highest level of infectivity measured in samples from seronegative and seropositive infected donors.

## 4 | DISCUSSION

This study confirmed that A/UVA PRT could mitigate the risk associated with ZIKV and *B. microti*, as already recognized by FDA,<sup>4,5</sup> and demonstrated potential mitigations for the risks associated with WNV, DENV, and CHIKV. Although not directly assessed by this study, the robust inactivation for all agents in all components

shown in Table 2 would be expected to have the same impact on *T. cruzi*; that is, to be able to replace donation testing, and for all species of *Plasmodium* (assuming *P. falciparum* is an appropriate model) to, at minimum, replace donor deferrals due to travel.<sup>6</sup> With the use of PRT for all blood components to replace testing and donor deferrals, approximately 28,000 ARC donors could be retained (24,982 RBC donors and an additional 2776 platelet donors). These estimates, using ARC data collected in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic as an example year, projected at least 50,000 additional donations, based on 1.79 ARC donations/donor, or an estimated 125,000 additional donations nationally (considering that the ARC collects approximately 40% of the US blood supply) (Table 4).

Although derived from studies of U.S. blood donors, these findings should also apply globally. Pathogen loads reported in donations from U.S. blood donors were in range with those reported from studies of blood donors in other geographies.<sup>23,39–41</sup> Furthermore, like in the United States,

PRT has been recognized in other countries as a replacement for some deferrals and/or blood donation screening.<sup>8</sup> In the United States, A/UVA treatment of plasma and platelets can be used in lieu of deferrals and screening for ZIKV since 2016,<sup>4</sup> *B. microti* since 2018,<sup>5</sup> and as a replacement of the 3-month malaria deferrals after traveling to endemic areas since 2020.<sup>6</sup> In Europe, regulatory authorities such as the Paul Ehrlich Institute (PEI) in Germany, are now recommending the use of PRT as an alternative to WNV deferrals and screening to maintain the platelet supply.<sup>8</sup> In 2016 and 2017, respectively, WHO and ECDC issued guidance recommending PRT as an option to mitigate risks related to ZIKV outbreaks.<sup>7,9</sup> Such guidance was put in place to sustain both blood safety and availability. Several examples have shown how emerging pathogens have disrupted blood availability, including CHIKV, DENV, and ZIKV outbreaks on French Ile de La Réunion,<sup>42</sup> in Guadeloupe and Martinique,<sup>39,43</sup> in French Polynesia,<sup>44</sup> and in the Caribbean region,<sup>45,46</sup> as well as in Italy.<sup>47</sup> In all cases, deferrals and testing methodologies alone were insufficient to mitigate TTI-risk-related supply disruption due to prolonged development and regulatory approval timelines; meanwhile, the A/UVA PRT of platelets and plasma helped to enable blood sustainability.<sup>20,24,42,47–52</sup>

Most recently, the SARS-CoV-2 pandemic and associated COVID-19 has highlighted concerns about health system infrastructure vulnerability and the potential impact on blood product availability.<sup>53</sup> Donations decreased due to canceled donation appointments and donor deferrals, while blood usage increased with a surge in re-scheduled elective surgeries. Transfusion transmission of SARS-CoV-2 was considered theoretical, but to date no TTI cases have been documented.<sup>54</sup> However, the anticipated impact of SARS-CoV-2 or future emerging pathogens on blood availability prompted FDA to release a revised guidance on malarial TTI mitigation, including the shortening of the deferral period from 12 to 3 months for those with a malaria travel risk, allowing for the complete elimination of this deferral with the use of an FDA-approved PRT for platelet and plasma donations.<sup>6</sup>

The findings of this study are subject to some limitations. To investigate the capacity of the A/UVA and S-303/GSH PRT to mitigate the risk of TTI in the absence of any other mitigation strategies, this study used a worst-case scenario approach; analyses focused on the (i) highest pathogen loads observed in the pre-seroconversion phase of infection; when (ii) associated infectivity is not dampened by neutralizing antibodies; (iii) using assumptions of infectious titers:gEq ratios that may not reflect human susceptibility; (iv) using PRT LRFs based on experimental input titers; (v) irrespective of blood components transfused and pathogen compartmentalization; and (vi) regardless of recipient underlying

conditions and immunocompetent status. Documented TTI cases for such agents are scarce and pathogen loads in implicated donations of suspect blood donors and their components, if available, are most often investigated for genomic loads but rarely for infectious titers. When using infectious titers:gEq ratios described in the literature, one caution is that those are primarily based on in vitro cell culture assays or experimentation in immunocompromised animal models, which may not reflect infectious levels in transfused blood components causing TTIs in humans. On the other hand, the vast majority of blood components are transfused to hemato-oncological patients who are immunosuppressed and thus very vulnerable and prone to get infected via a contaminated unit. In addition, PRT LRFs preceded by a “>” or “≥” symbol (all in Table 2) indicate that infectivity can be reduced to the limit of detection while acknowledging that the PRT system may be able to have an even higher inactivation capacity than could be assessed due to limits in the respective pathogen titers used in the assays; for example, similar infectivity and LRFs were achieved for CHIKV in RBCs and *Babesia* following seroconversion but LRFs in each case were greater than could be assessed (Figures 2A,B). For this study, we considered the inactivation capacity of the PRT based solely on input titers used in PRT inactivation studies, disregarding the potential for higher inactivation capacity. Despite this and considering the odds of collecting blood from infected donors presenting with the highest pathogen loads and disregarding other factors that may contribute to lowering infectivity levels, this study suggests reasonable safety margins for the A/UVA and S-303/GSH PRT.

Documented experience confirmed PRT efficacy and the absence of breakthrough TTIs after transfusion of PRT-treated platelets when the A/UVA PRT was used in the French Antilles to secure the blood supply during CHIKV and ZIKV outbreaks; the investigation of post-donation information cases demonstrated the absence of TTIs after transfusion of A/UVA-treated (PR) platelets collected from CHIKV- and ZIKV-infected donors.<sup>49</sup> While up to 10<sup>5</sup> PFU/mL infectious titers of CHIKV were measured in co-components, no TTI was observed in the recipients of PR-platelet components collected from CHIKV RNA-positive donors and no remaining CHIKV infectivity was present in aliquots of the transfused PR-platelet components after PRT treatment.<sup>49</sup> Similarly, no TTI was observed in the recipients of PR-platelet components collected from ZIKV RNA-positive donors and no ZIKV infectivity was present in aliquots of the transfused PR-platelet components after PRT treatment.<sup>49</sup>

The findings in this study are promising and should trigger various levels of interest depending on current

strategies in place to mitigate the risk of TTIs by vector-borne pathogens in the United States. Of note, TTIs continue to be reported, albeit infrequently, for WNV<sup>10,55,56</sup> and *Plasmodium*,<sup>57–59</sup> as examples, even with the current interventions of donor health histories and/or testing in place. In Europe, seasonal deferrals and blood donation screening for WNV,<sup>60–66</sup> DENV, and CHIKV have been implemented in some of the Mediterranean countries, but regulatory authorities such as PEI in Germany,<sup>8</sup> are now recommending the use of PRT as an alternative to WNV deferrals and screening to maintain the platelet supply. In the meantime, the prevalence and incidence of the closely related Usutu virus are increasing in European blood donors.<sup>60,61,67,68</sup> Based on its mode of action, the nucleic acid targeting A/UVA PRT could be used to mitigate the risk associated with pathogens that are structurally similar to those already proven to be sensitive to PR treatment. Indeed, considering the spread of vectors as climate changes and the spread of infectious agents with increased global trade and travel,<sup>63,69–72</sup> INTERCEPT Blood System's broad-spectrum inactivation of many vector-borne viruses and parasites offers a proactive solution to help safeguard the blood supply in terms of safety and availability.<sup>21,73</sup>

## CONFLICTS OF INTEREST

Marion C. Lanteri is an employee of Cerus Corporation. The remaining authors declare no conflicts of interest.

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