Inactivation of a broad spectrum of viruses and parasites by photochemical treatment of plasma and platelets using amotosalen and ultraviolet A light

Marion C. Lanteri, Felicia Santa-Maria, Andrew Laughhunn, Yvette A. Girard, Marcus Picard-Maureau, Jean-Marc Payrat, Johannes Isch, Adonis Stassinopoulos, and Peter Bringmann

BACKGROUND: The INTERCEPT Blood System pathogen reduction technology (PRT), which uses amotosalen and ultraviolet A light treatment (amotosalen/UV-PRT), inactivates pathogens in plasma and platelet components (PCs). This review summarizes data describing the inactivation efficacy of amotosalen/UVA-PRT for a broad spectrum of viruses and parasites.

METHODS: Twenty-five enveloped viruses, six nonenveloped viruses (NEVs), and four parasites species were evaluated for sensitivity to amotosalen/UVA-PRT. Pathogens were spiked into plasma and PC at high titers. Samples were collected before and after PRT and assessed for infectivity with cell cultures or animal models. Log reduction factors (LRFs) were defined as the difference in infectious titers before and after amotosalen/UV-PRT.

RESULTS: LRFs of ≥4.0 log were reported for 19 pathogens in plasma (range, ≥4.0 to ≥7.6), 28 pathogens in PC in platelet additive solution (PC-PAS; ≥4.1-≥7.8), and 14 pathogens in PC in 100% plasma (PC-100%; ≥4.3-≥8.4). Twenty-five enveloped viruses and two NEVs were sensitive to amotosalen/UV-PRT; LRF ranged from >2.9 to ≥7.6 in plasma, 2.4 or greater to greater than 6.9 in PC-PAS and >3.5 to >6.5 in PC-100%. Infectious titers for four parasites were reduced by >4.0 log in all PC and plasma (≥4.9 to >8.4).

CONCLUSION: Amotosalen/UVA-PRT demonstrated effective infectious titer reduction for a broad spectrum of viruses and parasites. This confirms the capacity of this system to reduce the risk of viral and parasitic transfusion-transmitted infections by plasma and PCs in various geographies.

Despite the diligent implementation of strategies to minimize the risk of transfusion-transmitted infections (TTIs), blood recipients, who are often vulnerable due to massive bleeding or immunosuppressive treatments, are still at risk for transfusion infectious adverse events. The INTERCEPT Blood System is a pathogen reduction technology (PRT) that uses

ABBREVIATIONS: CHIKV = chikungunya virus; CMV = cytomegalovirus; CoV = coronavirus; EID = emerging infectious diseases; FDAUS = Food and Drug Administration; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; LOD = limit of detection; LRF = log reduction factors; MERS = Middle East respiratory syndrome; NAT = nucleic acid amplification testing; NEV = nonenveloped viruses; PC-100% = platelet component in 100% plasma; PC-PAS = platelet component in platelet additive solution; PCs = platelet components; PFU = plaque-forming units; PRT = pathogen reduction technology; SARS = severe acute respiratory syndrome; TCID_{50} = tissue culture infectious dose-50; TTIs = transfusion-transmitted infections; UVA = ultraviolet A; WNV = West Nile virus; YFV = yellow fever virus; ZIKV = Zika virus.

From the 1Department of Scientific Affairs and 2Department of Microbiology, Cerus Corporation, Concord, California; and the 3Department of Scientific Affairs, Cerus Europe BV, Amersfoort, The Netherlands.

Address reprint requests to: Marion C. Lanteri, PhD, Cerus Corporation, 1220 Concord Avenue, Concord, CA 94520; e-mail: mlanteri@cerus.com

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Received for publication January 9, 2020; revision received March 12, 2020, and accepted March 13, 2020.

doi:10.1111/trf.15807

© 2020 The Authors. Transfusion published by Wiley Periodicals, Inc. on behalf of AABB.

TRANSFUSION 2020;60:1319–1331
amotosalen and ultraviolet A (UVA) light to inactivate pathogens in plasma and platelet components (PCs). The INTERCEPT Blood System is being increasingly used to improve blood transfusion safety and to maintain blood availability globally.3–6 Donor deferral is based on the presence of selected clinical symptoms, history of infections, medical treatments, country of origin, travel to endemic areas, and sexual risk behaviors. However, identification of potentially infected asymptomatic or presymptomatic donors is challenging and donor eligibility heavily relies on donor compliance during the interview process. Additionally, new risk behavior may not be addressed by current questionnaires.7 Travel-based deferrals for risk of infection due to travel history have doubled over the past decade, representing up to 10% of all deferrals, and have adversely impacted blood availability in nonendemic areas.8 Blood screening assays have been developed for a limited number of pathogens,2,9 but are not universally implemented for all geographies.10–15 Geographic differences in the risk of TTI remain influenced by socioeconomic factors, as screening is either not available or not practical.6,14,16,17 Areas of high pathogen prevalence may experience a high rate of donor deferral and subsequent lack of blood availability.7,14,18–25 In this situation, PRT may be beneficial in mitigating the risk of TTI and in improving blood availability. PRT can also help to address the limitations of testing strategies and donor screening. Testing assays have a limit of detection (LOD). Window periods when pathogen loads are below the LOD of the screening assay range from days with nucleic acid amplification testing (NAT) to weeks with serology-based assay.26–33 Recent hepatitis B virus (HBV) TTI cases have been associated with vaccine breakthrough and occult HBV infections can go undetected despite HBV DNA individual NAT screening.26 Blood donations from individuals who are unfamiliar with the window period,34 do not disclose risk behaviors or drug intake,35,36 are noncompliant donors, are test seekers,36,37 and have pathogen loads below the LOD of the screening assay put recipients at risk.38 While blood donor selection and blood screening may fail to prevent TTI, PRTs provide a complementary strategy to further improve blood safety.

The ex vivo photochemical treatment of plasma and PC in plasma (PC-100%) or PC in additive solution (PC-PAS) with amotosalen/UVA-PRT inactivates a wide range of pathogens. Amotosalen penetrates membranes and intercalates into helical regions of nucleic acids. Upon UVA illumination, irreversible covalent adducts are formed,39 which prevents replication, transcription, and translation of contaminating pathogens and leukocytes.40,41 The INTERCEPT Blood System, a Class III medical device, obtained the CE mark for platelets in 2002 and for plasma in 2006. It has been in routine use for more than 15 years, with blood centers in more than 30 countries producing more than 6,900,000 treated products worldwide. It is currently the only PRT for platelets approved by the US Food and Drug Administration (FDA) and several European regulatory agencies.42–46 Evaluated through numerous in vitro studies and extensive clinical trials, as well as through postmarketing surveillance,47–52 the system was shown to preserve the hemostatic properties of plasma and PC while inactivating high levels of a variety of pathogens.48–57 This review is a compendium of previously published or unpublished data that have been obtained to date and together demonstrate the performance of the system to inactivate viruses and parasites (Tables 1–3).

**MATERIALS AND METHODS**

**Blood components**

Blood components include whole blood-derived or apheresis plasma and apheresis PC suspended in either 65% additive solution (PAS-3) and 35% plasma (PC-PAS), or 100% plasma (PC-plasma), with or without leukoreduction. Blood components that met treatment criteria for amotosalen/UVA-PRT were obtained from blood centers located in nonendemic areas. Some blood components were tested for the absence of antibodies against pathogens of interest. Amotosalen/UVA-PRT for plasma and platelets was used for pathogen reduction according to manufacturer’s instructions.58,59

**Experimental design**

All inactivation studies followed the schematic in Fig. 1. Blood components were inoculated with 1/100th of their volume of high infectious titer virus or parasite stocks to maintain the blood component composition. Contaminated units were transferred into either plasma or platelet INTERCEPT Processing Sets containing amotosalen solution and exposed to UVA light according to manufacturer’s instructions. Samples were collected following the addition of 150 μM of amotosalen but before UVA illumination to serve as the preinactivation control. Amotosalen in the absence of UVA light does not impact infectious titers in blood products. Posttreatment samples were collected from each unit immediately following illumination. All collected samples were stored at −80°C until determination of infectious titers.

Scaled-down (1:10) experiments were conducted to enable higher input titers of the pathogen. Pathogen stock was diluted 1:100 in 28.5 or 15 mL of platelets and dosed with 150 μM of amotosalen. Platelets transferred to six-well plates (2 mL/well) were subjected to UVA illumination using a research illuminator (Model FX1019, Nova Biomedical). This process has been validated and results in the delivery of a UVA dose that is equivalent to the one delivered in commercial conditions. Pretreatment samples were collected and stored as described above.
### TABLE 1. Inactivation for 25 enveloped viruses measured by infectivity assays after treatment of platelets and plasma with amotosalen/UVA PRT

| Genus        | Virus                          | Genome | Routinely screened* | Mean log reduction factor (PFU/TCID_{50}/ID_{50}) | Platelets | Plasma                      |
|--------------|--------------------------------|--------|----------------------|-----------------------------------------------|-----------|-----------------------------|
| **Retroviruses** | HIV-1 cell-associated          | ssRNA  | Yes                  | ≥5.4                                          | ≥4.7      | ≥6.2                        |
|              | HIV-1 cell-free                |        |                      | >6.6^{41}                                     | ...       | ≥6.1                        |
|              | HIV-1 clinical Z84             |        |                      | ≥3.3                                          | ≥3.9^{41} | ...                         |
|              | HIV-2 clinical CBL20           |        |                      | ≥2.4                                          | >3.0^{41} | ≥5.2^{3}                   |
|              | HTLV-I                        |        |                      | 4.7                                           | 5.2^{60}  | ≥4.1                        |
|              | HTLV-II                       |        |                      | ≥5.1                                          | 4.6^{60}  | ≥4.7                        |
| **Hepadnaviruses** | HBV                            | dsDNA  | Yes                  | ≥5.6                                          | >6.6^{41} | 4.5^{50}                   |
|              | Duck hepatitis B virus (a model for HBV) | NA    |                      | ≥4.8                                          | >6.7^{41} | 5.7^{50}                   |
| **Flaviviruses** | HCV                            | ssRNA  | Yes                  | ≥4.1                                          | >5.6^{41} | 4.4-4.5                    |
|              | Bovine viral diarrhea virus (a model for HCV) | NA    |                      | ≥4.1                                          | >3.5      | ≥4.3^{1}                   |
|              | West Nile virus                |        |                      | ≥6.3                                          | >6.3      | ≥5.5^{1}                   |
|              | Zika virus                     |        |                      | >5.2^{1}                                      | >5.2^{61} | ≥6.8^{53}                  |
|              | DENV-1                         |        |                      | >5.0^{63}                                     | >6.8^{52} | ...                         |
|              | DENV-2                         |        |                      | >4.1^{1}                                      | >5.2^{63} | ...                         |
|              | DENV-3                         |        |                      | >4.6^{3}                                      | >4.2^{1}  | ≥5.6^{64}                  |
|              | DENV-4                         |        |                      | >5.2^{63}                                     | ...       | ...                         |
|              | Yellow fever virus             |        |                      | ≥5.5^{1}                                      | >5.5^{65} | ...                         |
| **Herpesviruses** | Cytomegalovirus                | dsDNA  | Yes                  | ≥4.9                                          | >6.4^{41} | ≥5.3^{65}                  |
|              | Chikungunya virus              | ssRNA  | No                   | ≥5.7                                          | >6.4^{66} | 6.5                         |
|              | Mayaro virus                   |        |                      | ≥6.9^{67}                                     | ≥7.6^{66} | ...                         |
|              | Ross River virus               |        |                      | ≥5.1^{68}                                     | ...       | ...                         |
| **Coronaviruses** | Severe acute respiratory syndrome (SARS)-CoV | ssRNA  | No                   | ≥6.2^{69}                                     | ≥4.0      | ≥5.5^{53}                  |
|              | Middle East respiratory syndrome-CoV | No    |                      | ≥6.2^{69}                                     | ≥4.5^{70} | >4.7^{71}                  |
|              | Crimean Congo hemorrhagic fever virus | ssRNA | No                   | ≥6.2^{69}                                     | ≥4.5^{70} | >2.9^{72}                  |
| **Poxviruses** | Vaccinia virus                 | dsDNA  | No                   | ≥5.2^{41}                                     | ...       | ...                         |
|              | Arenavirus                     | ssRNA  | No                   | ≥5.2^{41}                                     | ...       | ...                         |
| **Influenza virus** | Influenza A H5N1              | ssRNA  | No                   | ≥5.9                                          | >5.9^{73} | ≥5.7                        |

---

* Indicates inactivation studies not performed.

† Units per milliliter. See log reduction factor (LRF) Calculations in Materials and Methods. “>” indicates that no residual viable organism was detected in any replicate; “≥” indicates that residual viable organisms were detected in some, but not all, test replicates.

‡ Inherent low-level background in noninfected indicator cells precludes “>” for HTLV in platelets.

§ Unpublished studies that have not yet been reviewed by regulatory authorities at the time of submission.

k As outlined in the Methods section, LRFs are per milliliter representing either the input titer or using an LRF calculation based on a theoretical titer of 1. Further information is provided in the cited publications.

DENV = dengue virus; dsDNA = double-stranded DNA; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; ID_{50} = infectious dose-50; NA = not applicable; PAS = platelet additive solution; PFU = plaque-forming units; PRT = pathogen reduction technology; ssRNA = single-stranded RNA; TCID_{50} = tissue culture infectious dose-50; UVA = ultraviolet A.
TABLE 2. Inactivation for six nonenveloped viruses measured by infectivity assays after treatment of platelets and plasma with amotosalen/UVA PRT

| Genus | Virus | Genome | Routinely screened | Mean log reduction factor (PFU/TCID50)§ |
|-------|-------|--------|--------------------|----------------------------------------|
|       |       |        |                    | Platelets                               |
|       |       |        |                    | 65% PAS/35% plasma | 100% plasma | Plasma |
| Reoviruses | Bluetongue virus type 11 model | dsRNA | NA | 5.2 | 6.1 to 6.4 | 4.4 | 4.2 | 5.1 |
| Adenoviruses | Human adenovirus 5 | dsDNA | No | ≥4.9 | >5.7 | ≥5.3 | ≥5.6 | ≥6.8 |
| Caliciviruses | Feline calicivirus model | ssRNA | NA | ... | 0.7 to 2.3 | ... | ... | ... |
| Picornaviruses | Hepatitis A virus | ssRNA | No | ... | 0.74 | ... | ... | 0.76 |
| Picornaviruses | Human parvovirus B-19 | ssRNA | No | ... | 2.1 | 76 | ... | 1.8 | 1.8 to 2.8 |

* Indicates inactivation studies not performed.
† Depending on geographies.
‡ Units per milliliter. Log reduction is calculated as log (pretreatment titer ÷ posttreatment titer). See log reduction factor (LRF) calculations in Materials and Methods. *: indicates that no residual viable organism was detected in any replicate; "*: indicates that residual viable organisms were detected in some, but not all, test replicates.
§ Unpublished studies that have not yet been reviewed by regulatory authorities at the time of submission.
¶ As outlined in the Methods section, LRFs are per milliliter, representing either the input titer or using an LRF calculation based on a theoretical titer of 1. Further information is provided in the cited publications.

For pathogens that do not readily form distinguishable plaques under a solid or semisolid overlay, validated plaque assays were used to determine pre- and posttreatment titers after replicate inoculation of diluted samples onto monolayers of the appropriate cell line. Following incubation, the inoculum was removed, and the cells were overlaid with a mixture of cell culture medium and agarose or microcrystalline cellulose. Following plaque formation, the cell monolayers were stained to visualize and enumerate the plaques. Viral titers were expressed as plaque-forming units (PFU) per milliliter.

For pathogens that do not readily form plaques, titers were determined using a TCID50 assay. This assay scores individual inoculated wells for the presence of cytopathic effect caused by viral infection or for the presence of viable parasites. Following sample inoculation of cell lines and incubation, inoculum was removed and replaced with fresh media. Cells were monitored microscopically for presence of cytopathic effect or viable parasites. Infectious titers were calculated using Reed and Muench82 and expressed as TCID50 per milliliter.

For pathogens for which no cell culture system is available, animal infection models were used to determine titers expressed as infectious dose-50/mL (ID50/mL). Sample dilutions were applied intravenously or intraperitoneally, and infection was monitored until productive infection was established. Babesia infection was monitored in the hamster.

**Viruses and parasites**

Virus and parasite isolates were obtained from ATCC or from collaborating investigators. Isolates were amplified after inoculation of either cell culture or animal models using standard virology and parasitology protocols. In some cases, concentrated viral stocks (100×) were prepared to retain high titers after dilution into blood components. For clinical isolates, viral stocks with the highest available titers were used.

For viruses that are difficult to propagate in cell culture or in animal models, the World Health Organization recommends the use of model viruses,81 which, while biologically similar, do not reflect all properties of the original viruses. However, sublevel input titers are limiting in inactivation studies, and therefore, a selected number of model viruses were used, including duck hepatitis B virus (a model for HBV), bovine viral diarrhea virus (a model for hepatitis C virus [HCV]), pseudorabies virus (a model for cytomegalovirus [CMV]), and bluetongue virus type 11 and feline calicivirus (models for nonenveloped viruses [NEVs]).

**Determination of infectious titers**

Virologic assays were used to define pre- and posttreatment infectious titers including plaque assay, tissue culture infectious dose-50 (TCID50) assay, or propagation through cell culture passaging and genome detection.
model by evaluating a blood smear collected from the tail for viable parasites and determining the percentage of parasitemia. For HCV and HBV, viral infection was confirmed by the appearance of the viral antigen (hepatitis B surface antigen) or antibody (antibody to hepatitis B core antigen, anti-antibody to hepatitis B surface antigen, or anti-HCV) and for the de novo appearance of nucleic acids (HBV DNA or HCV RNA). Serum and liver biopsies were also collected and analyzed for infection.

Log reduction factor calculation

Log reduction factors (LRFs), typically expressed in log PFU per milliliter, were calculated as the difference in infectious titers pre- and post-pathogen reduction treatment with the following equation:

\[
\text{LRF} = \log (\text{pretreatment titer in PFU/mL} / \text{post-treatment titer in PFU/mL}).
\]

In some cases, LRF is expressed as TCID_{50} per milliliter or ID_{50} per milliliter. When no viable pathogen was detected in the posttreatment sample, the titer was determined in one of two ways. In some of the published studies, a theoretical posttreatment titer was determined by calculating the titer as if a single plaque was observed in the highest dilution tested. The LRF was then calculated with the above equation and the theoretical posttreatment titer. In unpublished license enabling in vitro studies, \(^58,59\) if the posttreatment sample was determined to be zero (PFU or TCID_{50}), the log reduction was based on the pretreatment titer.

LRF values are depicted with either a “>” or “≥” symbol. A “>” symbol indicates that there was no residual pathogen detected following treatment for all replicates tested. The “≥” symbol indicates that at least one of the replicates tested had residual pathogen detected following treatment. The absence of a symbol indicates that residual pathogen was detected in all replicates tested.

### Results

**Broad spectrum inactivation of pathogens by INTERCEPT blood system**

Previous publications have reported the efficacy of amotosalen/UVA-PRT for the inactivation of viruses in PC.\(^41\) Updates for PC and plasma have also been published.\(^40\) The current review will provide an update of inactivation studies performed since 2011 for viruses (Tables 1 and 2) and parasites (Table 3) and from recent emerging or reemerging vector-borne infectious agents.\(^83\)

**Inactivation of flaviviruses**

Flaviviruses have ranked high on the priority list of agents posing a threat to the blood supply.\(^77\) Their sensitivity to inactivation by amotosalen/UVA was first demonstrated for West Nile virus (WNV)\(^41,53\) and dengue virus,\(^63,64,84\) and was further confirmed with Zika virus (ZIKV)\(^61,62\) and yellow
fever virus (YFV). The LRF for all emerging flaviviruses tested is >4.0 log in plasma and PC-PAS or PC-100% (Table 1).

Inactivation of alphaviruses
Since its emergence in the Indian Ocean in 2006, chikungunya virus (CHIKV) has become endemic in Latin America and Asia and has been responsible for recurrent outbreaks in Europe. The efficacy of amotosalen/UVA-PRT to inactivate high levels of CHIKV has been demonstrated with an LRF of >5.0 log in both plasma and PC (Table 1).

Additionally, other alphaviruses predicted to be important emerging agents have been successfully inactivated by amotosalen/UVA-PRT in PC. The high sensitivity of alphaviruses to treatment was confirmed with Ross River virus, which had an LRF of >5.1 log, and Mayaro virus, which had an LRF of >6.9 log (Table 1).

Inactivation of coronaviruses
Severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2003 and caused more than 8000 symptomatic cases across 26 countries within weeks. Previous studies have documented the efficacy of amotosalen/UVA-PRT to inactivate ≥4.0 to >6.2 log of SARS-CoV. The emergence of the Middle East respiratory syndrome (MERS) CoV in Saudi Arabia in 2012 in the blood donor population has led to concerns on the risk for potentially explosive outbreaks.
Recent studies have demonstrated the efficacy of amotosalen/UVA-PRT to inactivate >4.7 log of a MERS-CoV clinical isolate in plasma73 and ≥4.5 log of the virus in platelets.70 These studies confirmed the sensitivity of coronaviruses to amotosalen/UVA treatment (Table 1). This is of interest as the newly identified SARS-CoV-2, which is responsible for more than 100,000 cases of COVID-19 as of March 7, 2020, is raising concerns over blood safety globally.94 With more than 70% genetic similarity to SARS-CoV,95 sensitivity of SARS-CoV-2 to amotosalen/UVA-PRT would be highly probable.94

**Inactivation of CMV**

CMV, a herpesvirus, can be transfusion transmitted and is responsible for severe complications in immunocompromised patients, including high disease mortality rates in patients who have undergone bone marrow transplant and in CMV pneumonia.96 Leukoreduction of blood components is used to decrease the risk of CMV transmission but has failed to completely prevent TTI.97 The provision of CMV antibody-negative components for specific recipient populations is another mitigation strategy. Amotosalen/UVA-PRT of platelets reduces CMV infectious levels by ≥4.9 log for PC-PAS (Table 1) and demonstration of mitigation of CMV TTI in T-cell deficient animal models has also been reported.98,99

**Inactivation of NEVs**

Studies with reoviruses and human adenoviruses, which are of clinical importance for pediatric patients, have demonstrated LRFs of >4.0 log after amotosalen/UVA-PRT of plasma and PC. However, LRFs <3 log have been reported for the NEV feline calicivirus, hepatitis A virus, and human parvovirus B-19 (Table 2), suggesting that NEVs are generally less sensitive to amotosalen/UVA-PRT. Several studies have investigated the potential to improve human parvovirus B19 inactivation by preincubating the contaminated PC with amotosalen before UVA illumination is performed. Sawyer et al.76 reported increased LRF from 2.1 log to up to 5.8 log for parvovirus B19 using this approach.

**Inactivation of parasites**

The causative agents of malaria, Chagas disease and babesiosis, rank as the highest threats among blood and tissue protozoa that have the largest global impact on transfusion recipients, and most notably on immunocompromised transfusion recipients.

Results from inactivation studies performed on members of the *Leishmania* genus (*mexicana* and *major* Jish at different development stages), *Babesia microti*, *Plasmodium falciparum*, and *Trypanosoma cruzi* were summarized previously by Irsch et al.40 Recent studies were performed to increase the dynamic range of the system by spiking higher parasite titers. The results presented in Table 3 show an increased inactivation capacity with LRF ≥6.0 log and up to ≥6.9 log for *P. falciparum*, >5.0 log and up to ≥7.8 log for *T. cruzi* and >4.5 log and up to >5.3 log for *B. microti* when input parasite titers were increased.

**DISCUSSION**

Current mitigation strategies have limitations, and the constant threat of emerging infectious diseases (EIDs) result in a persistent threat to blood transfusion safety and blood availability. The need to optimize current donor screening strategies could be alleviated by the use of robust PRT.6 As presented here, the amotosalen/UVA PRT may offer substantial benefits by inactivating high levels of a range of clinically relevant viruses (Tables 1 and 2) and parasites (Table 3) in plasma and PC. LRF of ≥4.0 log were reported for 19 pathogens in plasma, 28 pathogens in PC-PAS, and 14 pathogens in PC-100%. Twenty-five enveloped viruses and two NEVs were sensitive to PRT with LRFs ranging from >2.9 to ≥7.6 log in plasma, ≥2.4 to >6.9 log in PC-PAS, and >3.5 to >6.5 log in PC-100%. Infectious titers for four parasites were reduced by >4.0 log in all PC and plasma.

Clinically relevant levels of infectivity are difficult to define, and the wide variation in immune responses in healthy people and patients may be highly variable depending on disease, therapy, and underlying conditions. Thus, it is best to assume that there is no safe level of contamination. Inactivation studies are designed to investigate the upper limit of the PRT system for inactivation of the highest infectivity levels toward ensuring maximum safety margins.100-102 Of note, most studies of infected blood donors report pathogen loads based on standard NAT quantitation by genome equivalence rather than infectivity levels; however, in vitro, the equivalence between these methods is difficult to define.103 In vivo, risk of TTI and clinical outcomes will differ based on infectious titers and minimum infectious doses, on donor and recipient immunity, and on passive transfer of antibodies through cotransfused components. While there are no guidelines defining the needed inactivation efficacy of PRT, LRFs of ≥4.0 log are generally considered the minimum requirement for viruses and parasites based on regulatory standards per the Committee for Human Medicinal Products.104 However, requirements for labile blood components may differ,101 and, ultimately, the demonstrated LRF attained by PRT will be relevant only to define the extent to which other procedures (tests and deferrals) will need to be used in tandem with PRT. Evaluating requirements for PRT performance with respect to the limitations/absence of other current mitigation strategies is challenging and depends on the context of regulations within different geographies. Therefore, a PRT with the broadest and most robust level of inactivation may not only offer maximum protection independently of any other screening strategy but will allow for greater applicability and contribution to blood safety worldwide.100
PRTs with high LRFs enable blood product continuity and sustainability during EID outbreaks, when no licensed screening tests are available. In 2018, a large CHIKV outbreak in Italy raised concerns over blood safety. Collections were stopped and PRT implemented for platelet continuity, as used in the past when CHIKV emerged in La Reunion. During the global ZIKV outbreak, proactive implementation of PRT allowed for platelet continuity in French Polynesia and in Puerto Rico several weeks before ZIKV investigational NAT assays became available. Learning from these experience, blood centers in Europe are implementing PRT proactively as part of their EID preparedness programs. There is an inherent gap between the time the pathogen responsible for an outbreak is characterized and the time a screening assay becomes available. Alternatively, PRT is a broad-spectrum intervention, implemented proactively, and can maintain blood availability while reducing TTI risk during outbreaks, especially when uncharacterized pathogenic agents are emerging. The emergence of SARS-CoV-2 and its rapid spread globally is yet another example of an unpredictable EID that has raised concerns over global blood safety. Incubation lasting up to 14 days, viral RNA detected in plasma from COVID-19 patients, and asymptomatic carriers suggest a risk for TTI.Containment strategies and deferrals have impacted blood availability, creating fear in donors and blood shortages in many countries. Considering the efficacy of the amotosalen/UVA-PRT to inactivate CoVs, this system could be evaluated as an acceptable mitigation strategy to maintain platelet and plasma safety and availability.

Additionally, deferrals for travel in areas where arboviruses are circulating have increased over the years as endemic areas are expanding and travel is increasing, which means blood availability is often reduced. The reemergence of YFV in Angola in 2015 and in large areas of Brazil in 2017-2018, resulted in the deferral of thousands of platelet donors for several weeks following vaccination with live virus. The amotosalen/UVA-PRT may be considered in the future as an alternative approach to deferrals during massive YFV vaccination campaigns. In Europe, the expansion of Aedes species and Culex species mosquitoes and associated dengue virus, CHIKV, and WNV outbreaks have led to more deferrals and blood screening requirements. The experience in the United States has also shown that WNV TTIs continue to occur despite WNV ID-NAT screening. Proactive implementation of PRT may address a vast number of nonspecific pathogens, reduce the need for novel testing, and maintain blood continuity and availability to best satisfy the need for sustained preparedness.

In the United States, Babesia NAT screening has been implemented in selected Northeastern states. However, B. microti is becoming a concern in other parts of the United States, where deferrals are not effectively preventing TTIs. More data are being collected to define optimal testing algorithms in endemic versus nonendemic areas and to determine the appropriate time frame for the reinstallment of positively screened donors. In the meantime, and even though the risk of B. microti TTI is more highly associated with red blood cell (RBC) transfusion, the use of amotosalen/UVA treatment to mitigate the risk of Babesia TTI through platelets is part of the strategies recommended by the FDA.

As reviewed by Leiby et al., mitigation strategies to address the risk of parasite TTI are heterogeneous. In nonendemic countries, donor loss due to travel deferrals and difficulties to reinstall deferred donors are adversely impacting blood availability. In the United States, 1.1% of donors are deferred for malaria risk after travels to endemic areas, while semi-immune donors (asymptomatic, chronic carriers) fail to be detected. Canada applies a permanent deferral after a history of malaria infection and France implemented testing for all donors born in endemic areas. While the majority of transmissions are from RBCs, PCs have also been implicated, likely due of the presence of RBCs in the platelet concentrates. With high inactivation levels of P. falciparum, the amotosalen/UVA PRT has been used to replace malaria deferral policies in some blood centers.

With increased emigration and the high prevalence of T. cruzi in donors from endemic areas of Latin America, Chagas disease TTI became a global concern, and T. cruzi blood screening was implemented in the United States and in some European countries. However, chronically infected asymptomatic individuals can maintain intermittent low-level parasitemia, which can be missed by blood screening. The amotosalen/UVA PRT with high efficacy against T. cruzi could offer an interesting alternative to the challenges associated with testing and donor selection, especially when most T. cruzi TTIs occurred through transfusion of contaminated PCs.

Furthermore, PRT may provide a technological solution to solve ethical concerns and allow for inclusion of donors that may be excluded temporarily or permanently from blood donation based on country of origin, race/ethnicity, and sexual behavior. While surveillance studies are monitoring the potential risk associated with the relaxation of deferrals for men who have sex with men, the risk associated with window-period donations could be covered by PRT.

Additionally, some noncompliant donors may not fully disclose their risk behaviors or their infection status. Concerns have been raised over donors using HIV pre-exposure prophylaxis or antiretroviral treatments not reporting drug intake, risk exposure, or infectious status. Recent studies have reported the presence of antiretroviral drugs in donated blood. Viral loads suppressed below the screening assay LOD as a result of these treatments may still be high enough in contaminated donations to lead to TTI. Therefore, pathogen reduction could represent a technological solution to address social issues while mitigating the risk of TTI associated with noncompliant donors.
However, all PRTs have limitations. Real-life experience demonstrated that hepatitis E virus (HEV) may not be efficiently inactivated by amotosalen/UVA-PRT. There are also inherent limitations to the performance of HEV inactivation studies, as there is no robust in vitro system to propagate the virus and generate high-titer virus stock. HEV assay systems to determine infectious titers in a given sample often produce variable results, and HEV characteristics are different in vitro versus in the clinical setting. Amotosalen/UVA-PRT has shown some limited inactivation capacity toward caliciviruses, once considered model viruses for HEV but has since been recognized as an inadequate model virus. The emergence of HEV in Europe has become a concern for blood safety, and several countries have recently implemented HEV NAT screening. The virus is transmitted mostly through the fecal-oral route through water contamination in Asia and pork meat in Europe; however, the risk of severe outcome in immunosuppressed recipients undergoing liver transplantation highlights the need for screening of donations directed to such high-risk patients.

While this review focused on the inactivation of viruses and parasites, the amotosalen/UVA PRT has proven efficacy to prevent transfusion-associated graft-versus-host disease and bacterial TTIs, the most significant infectious risk in transfusion today. PRT is now considered an alternative to bacterial screening, irradiation, and CMV testing. Various regulatory guidelines and variances have also allowed for use of PRT as an alternative to Zika and Babesia screening and to deferrals for travel to malaria-endemic areas. Indeed, the testing paradigm may have reached its limit, as the cumulative addition of screening assays is neither cost efficient nor fully covers the infectious risk associated with transfusion. Overall, PRT represents an alternative to some screening strategies and blood component processing procedures.

While the ultimate intention of eliminating the risk associated with blood transfusion is challenged by regional ecologic and economic considerations and globalization, blood bank regulatory authorities and medical communities have the responsibility to maintain the availability of a safe blood supply for patients in need. As evidenced in this review, PRT, in addition to and when robust enough as an alternative to other mitigation strategies, can further improve platelet and plasma safety and availability worldwide.

ACKNOWLEDGMENT
The authors acknowledge Colleen Elliott, PhD, of CME Science Writers, LLC for providing editorial support.

CONFLICT OF INTEREST
All authors are or were employees of Cerus Corporation.

REFERENCES
1. Dodd R, Kurt Roth W, Ashford P, et al. Transfusion medicine and safety. Biologicals 2009;37:62-70.
2. Busch MP, Bloch EM, Kleinman SH. Prevention of transfusion transmitted infections. Blood 2019;133:1854-64.
3. US Department of Health and Human Services. September: bacterial risk control strategies for blood collection establishments and transfusion services to enhance the safety and availability of platelets for transfusion - guidance for industry, FDA-2014-D-1814. Food and Drug Administration, Center for Biologics Evaluation and Research. 2019. [cited 2020 Dec 03]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bacterial-risk-control-strategies-blood-collection-establishments-and-transfusion-services-enhance.
4. US Department of Health and Human Services. February: recommendations for donor screening, deferral, and product management to reduce the risk of transfusion transmission of Zika virus - guidance for industry. Food and Drug Administration, Center for Biologics Evaluation and Research. 2016. [cited 2020 Dec 03]. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf.
5. US Department of Health and Human Services. Recommendations for reducing the risk of transfusion-transmitted babesiosis - guidance for industry. Food and Drug Administration, Center for Biologics Evaluation and Research. 2019. [cited 2020 Dec 03]. Available from: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
6. Marks PW, Epstein JS, Borio LL. Maintaining a safe blood supply in an era of emerging pathogens. J Infect Dis 2016;213:1676-7.
7. Czerwinski M, Grabarczyk P, Stepien M, et al. What weighs more-low compliance with self-deferral or minor medical procedures? Explaining the high rate of hepatitis C virus window-period donations in Poland. Transfusion 2017;57:1998-2006.
8. Muller-Steinhardt M, Weidmann C, Kluter H. Changes in the whole blood donor population in South-West Germany: 2010 versus 2016. Transfus Med Hemother 2017;44:217-23.
9. Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. Transfusion 2010;50:2080-99.
10. Dalton HR, Seghatchian J. Hepatitis E virus: emerging from the shadows in developed countries. Transfus Apher Sci 2016;55:274-4.
11. Levin AE, Krause PJ. Transfusion-transmitted babesiosis: is it time to screen the blood supply? Curr Opin Hematol 2016;23:573-80.
12. Petersen LR, Stramer SL, Powers AM. Chikungunya virus: possible impact on transfusion medicine. Transfus Med Rev 2010;24:15-21.
13. Tilak R, Ray S, Tilak VW, et al. Dengue, chikungunya ... and the missing entity - Zika fever: a new emerging threat. Med J Armed Forces India 2016;72:157-63.
14. Wendel S. Rational testing for transmissible diseases. ISBT Sci Ser 2007;2:19-24.
15. Willyard C. Screening: in the nature. Nature 2017;549:S19-21.
16. Dodd R. Managing the microbiological safety of blood for transfusion: a US perspective. Future Microbiol 2009;4:807-18.
17. Murphy WG. Disease transmission by blood products: past, present and future. Pathophysiol Haemost Thromb 2002;32 (Suppl 1):1-4.
18. Bloch EM, Shah A, Kaidarova Z, et al. A pilot external quality assurance study of transfusion screening for HIV, HCV and HBsAg in 12 African countries. Vox Sang 2014;107:333-42.
19. Butler EK, McCullough J. Pathogen reduction combined with rapid diagnostic tests to reduce the risk of transfusion-transmitted infections in Uganda. Transfusion 2018;58:854-61.
20. Custer B, Zou S, Glynn SA, et al. Addressing gaps in international blood availability and transfusion safety in low- and middle-income countries: a NHLBI workshop. Transfusion 2018;58:1307-17.
21. El Ekiaby M, Lelie N, Allain JP. Nucleic acid testing (NAT) in high prevalence-low resource settings. Biologicals 2010;38:59-64.
22. Kleinman SH, Lelie N, Busch MP. Infectivity of human immunodeficiency virus-1, hepatitis C virus, and hepatitis B virus and risk of transmission by transfusion. Transfusion 2009;49:2454-89.
23. Leiby DA, O'Brien SF, Wendel S, et al. International survey on the impact of parasitic infections: frequency of transmission and current mitigation strategies. Vox Sang 2019;114:17-27.
24. Ware AD, Jacquot C, Tobian AAR, et al. Pathogen reduction and blood transfusion safety in Africa: strengths, limitations and challenges of implementation in low-resource settings. Vox Sang 2018;113:3-12.
25. Weimer A, Tagny CT, Tapko JB, et al. Blood transfusion safety in sub-Saharan Africa: a literature review of changes and challenges in the 21st century. Transfusion 2019;59:412-27.
26. Candotti D, Assennato SM, Laperche S, et al. Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose. Gut 2019;68:313-21.
27. Candotti D, Sauvage C, Cappy P, et al. High rate of hepatitis C virus and human immunodeficiency virus false-positive results in serologic screening in sub-Saharan Africa: adverse impact on the blood supply. Transfusion 2020;60:106-16.
28. Groves JA, Shafi H, Nomura JH, et al. A probable case of West Nile virus transfusion transmission. Transfusion 2017;57:850-6.
29. Hayes C, Stephens L, Fridey JL, et al. Probable transfusion transmission of West Nile virus from an apheresis platelet that screened non-reactive by individual donor-nucleic acid testing. Transfusion 2020;60:424-9.
30. Ling AE, Robbins KE, Brown TM, et al. Failure of routine HIV-1 tests in a case involving transmission with preseroconversion blood components during the infectious window period. JAMA 2000;284:210-4.
31. Vermeulen M, Coleman C, Mitchell J, et al. Comparison of human immunodeficiency virus assays in window phase and elite controller samples: viral load distribution and implications for transmission risk. Transfusion 2013;53:2384-98.
32. Vermeulen M, Lelie N, Coleman C, et al. Assessment of HIV transmission risk in South Africa: a 10-year analysis following implementation of individual donation nucleic acid amplification technology testing and donor demographics eligibility changes. Transfusion 2019;59:267-76.
56. Snyder EL, Stramer SL, Benjamin RJ. The safety of the blood supply-time to raise the bar. N Engl J Med 2015;372:1882-5.
57. Schlenke P, Hagena W, Isra J, et al. Safety and clinical efficacy of platelet components prepared with pathogen inactivation in routine use for thrombocytopenic patients. Ann Hematol 2011;90:1457-65.
58. Osselaer JC, Messe N, Hervig T, et al. A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. Transfusion 2008;48:1061-71.
59. Schlenke P, Hagenah W, Isra J, et al. Safety and clinical efficacy of platelet components prepared with pathogen inactivation treatment. Transfusion 2008;48:1061-71.
60. Corash L. The hemostatic efficacy of platelet components prepared with pathogen inactivation. Transfusion 2011;51:1355-6 author reply 6-7.
61. Snyder EL, Stramer SL, Benjamin RJ. The safety of the blood supply-time to raise the bar. N Engl J Med 2015;372:1882-5.
62. Schlenke P, Hagena W, Isra J, et al. Safety and clinical efficacy of platelet components prepared with pathogen inactivation in routine use for thrombocytopenic patients. Ann Hematol 2011;90:1457-65.
76. Sawyer L, Hanson D, Castro G, et al. Inactivation of parvovirus B19 in human platelet concentrates by treatment with amotosalen and ultraviolet A illumination. Transfusion 2007;47:1062-70.
77. Stramer SL, Hollinger FB, Katz LM, et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion 2009;49(Suppl 2):15-29S.
78. Grellicier P, Benach J, Labaied M, et al. Photochemical inactivation with amotosalen and long-wavelength ultraviolet light of Plasmodium and Babesia in platelet and plasma components. Transfusion 2008;48:1676-84.
79. Van Voorhis WC, Barrett JK, Eastman RT, et al. Trypanosoma cruzi inactivation in human platelet concentrates and plasma by a psoralen (amotosalen HCl) and long-wavelength UV. Antimicrob Agents Chemother 2003;47:475-9.
80. Eastman RT, Barrett JK, Dupuis K, et al. Leishmania inactivation in human platelets by a psoralen (amotosalen HCl) and long-wavelength ultraviolet irradiation. Transfusion 2005;45:1459-63.
81. World Health Organization WHO. Who expert committee on biological standardization: fifty-second report. Geneva, Switzerland: World Health Organization; 2004. Available from: https://apps.who.int/iris/handle/10665/42921
82. Reed LJ, Muench H. A simple method of estimating fifty percent endpoints. J Hyg 1938;27:493-7.
83. Petersen LR, Beard CB, Visser SN. Combating the increasing threat of vector-borne disease in the United States with a national vector-borne disease prevention and control system. Am J Trop Med Hyg 2019;100:242-5.
84. Dupuis K, Stassinopoulos A, Green J. All four serotypes of dengue virus are inactivated by treatment with amotosalen and UVA light. P:216. Vox Sang 2014;107:126-7.
85. Girard YA, Santa Maria F, Lanteri MC. Inactivation of yellow fever virus with amotosalen and ultraviolet A light pathogen-reduction technology. Transfusion 2020;60:622-7.
86. Pierielli L, Vacc A, Zini G, et al. Emergency response of four transfusion centers during the last Chikungunya outbreak in Italy. Transfusion 2018;58:3027-30.
87. Aubry M, Teissier A, Huart M, et al. Ross River virus seroprevalence, French Polynesia, 2014-2015. Emerg Infect Dis 2017; 23:1751-3.
88. Faddy HM, Tran TV, Hoad VC, et al. Ross River virus in Australian blood donors: possible implications for blood transfusion safety. Transfusion 2018;58:485-92.
89. Lau C, Aubry M, Musso D, et al. New evidence for endemic circulation of Ross River virus in the Pacific Islands and the potential for emergence. Int J Infect Dis 2017; 57:73-6.
90. da Costa VG, de Rezende Feres VC, Sai wished MV, et al. Silent emergence of Mayaro and Oropouche viruses in humans in Central Brazil. Int J Infect Dis 2017:62:84-5.
91. Mavian C, Rife BD, Dollar JI, et al. Emergence of recombinant Mayaro virus strains from the Amazon basin. Sci Rep 2017;7: 8718. https://doi.org/10.1038/s41598-017-15988-9
92. Rodriguez-Morales AJ, Paniz-Mondolfi AE, Villamil-Gomez WE, et al. Mayaro, Oropouche and Venezuelan equine encephalitis viruses: following in the footsteps of Zika? Travel Med Infect Dis 2017;15:72-3.
93. Aly M, Elrobih M, Alzayer M, et al. Occurrence of the Middle East respiratory syndrome coronavirus (MERS-CoV) across the gulf corporation council countries: four years update. PLoS One 2017;12:e0183850.
94. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. Transfus Med Rev 2020. https://doi.org/10.1016/j.tmrv.2020.02.003
95. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264-6.
96. Sable CA, Donovitz GR. Infections in bone marrow transplant recipients. Clin Infect Dis 1994;18:273-81.
97. Wu Y, Zou S, Cable R, et al. Direct assessment of cytomegalovirus transfusion-transmitted risks after universal leukoreduction. Transfusion 2010;50:776-86.
98. Jordan CT, Saakadze N, Newman JL, et al. Photochemical treatment of platelet concentrates with amotosalen hydrochloride and ultraviolet A light inactivates free and latent cytomegalovirus in a murine transfusion model. Transfusion 2004;44:1159-65.
99. Roback JD, Conlan M, Drew WL, et al. The role of photochemical treatment with amotosalen and UV-A light in the prevention of transfusion-transmitted cytomegalovirus infections. Transfus Med Rev 2006;20:45-56.
100. Dodd RY. Concerning the efficacy of pathogen inactivation. Transfusion 2019;59:1162.
101. Goodrich RP, Custer B, Keil S, et al. Defining “adequate” pathogen reduction performance for transfused blood components. Transfusion 2010;50:1827-37.
102. McCullough J, Alter HJ, Ness PM. Interpretation of pathogen load in relationship to infectivity and pathogen reduction efficacy. Transfusion 2019;59:1132-46.
103. Klasse PJ. Molecular determinants of the ratio of inert to infecting virus particles. Prog Mol Biol Transl Sci 2015;129: 285-326.
104. Nahler G. Committee for Proprietary Medicinal Products (CPMP). In: Dictionary of pharmaceutical medicine. Vienna: Springer; 2009.
105. Rasongles P, Angelini-Tibert MF, Simon P, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Reunion. Transfusion 2009;49:1083-91.
106. Brouard C, Bernillon P, Quatresous I, et al. Estimated risk of Chikungunya viremic blood donation during an epidemic on Reunion Island in the Indian Ocean, 2005 to 2007. Transfusion 2008;48:1333-41.
107. Weiner E, Velez E, Alsina VE, et al. Implementation of the INTERCEPT™ Blood System for platelets in Puerto Rico to help safeguard against Zika. Transfusion 2016;56: 201A.
108. Stone M, Lanteri MC, Bakkour S, et al. Relative analytical sensitivity of donor nucleic acid amplification technology.
screening and diagnostic real-time polymerase chain reaction assays for detection of Zika virus RNA. Transfusion 2017;57:734-47.

109. Lanteri MC, Kleinman SH, Glynn SA, et al. Zika virus: a new threat to the safety of the blood supply with worldwide impact and implications. Transfusion 2016;56:1907-14.

110. Saa P, Chiu C, Grimm K, et al. Acute Zika virus infection in an asymptomatic blood donor at the onset of the Puerto Rico epidemic. Transfusion 2019;59:3164-70.

111. World Health Organization. Angola grapples with worst yellow fever outbreak in 30 years [monograph on the internet]. 2016. [cited 2020 Dec 03]. Available from: http://www.who.int/features/2016/angola-worst-yellow-fever/en/

112. World Health Organization WHO. Yellow fever – Brazil Disease outbreak news [monograph on the internet]. 2018. [cited 2020 Dec 03]. Available from: http://www.who.int/csr/don/27-february-2018-yellow-fever-brazil/en/

113. Domanovic D, Ushiro-Lumb I, Compernolle V, et al. Pathogen reduction of blood components during outbreaks of infectious diseases in the European Union: an expert opinion from the European Centre for Disease Prevention and Control consultation meeting. Blood Transfus 2019;17:433-48.

114. Ward SJ, Stramer SL, Szczepiorkowski ZM. Assessing the risk of Babesia to the United States blood supply using a risk-based decision-making approach: report of AABB’s Ad Hoc Babesia Policy Working Group (original report). Transfusion 2018;58:1916-23.

115. Food and Drug Administration. Guidance for industry recommendations for donor questioning, deferral, reentry and product management to reduce the risk of transfusion-transmitted malaria [monograph on the internet]. 2014. [cited 2020 Dec 03]. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

116. Leiby DA, Nguyen ML, Notari EP. Impact of donor deferrals for malaria on blood availability in the United States. Transfusion 2008;48:2222-8.

117. Bruneel F, Thellier M, Eloy O, et al. Transfusion-transmitted malaria. Intensive Care Med 2004;30:1851-2.

118. Food and Drug Administration. Exceptions and alternative procedures approved under 21 CFR 640.120, 21 CFR 630.10(a), 630.10(h), 630.30(b)(1). SilverSpring, MD: FDA; 2019.

119. Angeheben A, Boix L, Buonfrate D, et al. Chagas disease and transfusion medicine: a perspective from non-endemic countries. Blood Transfus 2015;13:540-50.

120. Dodd RY, Stramer SL. Technical solutions to social issues? Transfusion 2019;59:9-11.

121. Wentz AE, Merchant RC, Clark MA, et al. Blood donation, sexual practices, and self-perceived risk for HIV in the United States among young adult men who have sex with men. Public Health Rep 2019;134:36-46.

122. Custer B, Quiner C, Haaland R, et al. Detection of antiretroviral therapy use in US blood donors. Transfusion 2019;59 (Suppl S3):9A.

123. Davison KL, Gregoire Y, Germain M, et al. Changing the deferral for men who have sex with men - an improved model to estimate HIV residual risk. Vox Sang 2019;114:666-74.

124. Sykes V, Van den Berg K, Jacobs G, et al. Discovery of false elite controllers: HIV antibody-positive RNA-negative blood donors found to be on antiretroviral therapy. J Infect Dis 2019;220:643-7.

125. Seed CR, Yang H, Lee JF. Blood safety implications of donors using HIV pre-exposure prophylaxis. Vox Sang 2017;112:473-6.

126. Petrik J, Lozano M, Seed CR, et al. Hepatitis E. Vox Sang 2016;110:93-130.

127. de Vos AS, Jansen MP, Zaaijer HL, et al. Cost-effectiveness of the screening of blood donations for hepatitis E virus in the Netherlands. Transfusion 2017;57:258-66.

128. Domanovic D, Tedder R, Blumel J, et al. Hepatitis E and blood donation safety in selected European countries: a shift to screening? Euro Surveill 2017;22. https://doi.org/10.2807/1560-7917.ES.2017.22.16.30514

129. Slot E, Zaaijer HL, Molier M, et al. Meat consumption is a major risk factor for hepatitis E virus infection. PLoS One 2017;12:e0176414.

130. Willems SB, Bezurz DL, Blom P, et al. Hepatitis E virus infection and hepatic GvHD in allogeic hematopoietic stem cell transplantation recipients. Bone Marrow Transplant 2017;52:622-4.

131. Benjamin RJ, Braschler T, Weingand T, et al. Hemovigilance monitoring of platelet septic reactions with effective bacterial protection systems. Transfusion 2017;57:2946-57.

132. Castro G, Merkel PA, Giclas HE, et al. Amotosalen/UVA treatment inactivates T cells more effectively than the recommended gamma dose for prevention of transfusion-associated graft-versus-host disease. Transfusion 2018;58:1506-15.

133. Kleinman S, Stassinopoulos A. Transfusion-associated graft-versus-host disease reexamined: potential for improved prevention using a universally applied intervention. Transfusion 2018;58:2545-63.

134. Sim J, Tsoi WC, Lee CK, et al. Transfusion of pathogen-reduced platelet components without leukoreduction. Transfusion 2019;59:1953-61.