



Attaining a Sustainable Blood Safety Paradigm in Transfusion

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Vice President Asia, CERUS

IPFA APAC, March 3rd 2017

Contents

- **Blood Sustainability and Emerging Pathogens**
- Addressing the Need:
The INTERCEPT Blood System
- Moving Toward a Complete Solution
- Conclusion

Blood Sustainability is a Global Challenge

- **Blood shortages – a chronic issue in Asia**
 - Suboptimal use of blood
 - Difficulties to recruit donors
- **Exacerbated by Emerging Pathogens**
as populations grow; urbanization,
global travel increase.

Blood shortage affecting hospitals in Philippines

Could hamper plans to make country centre of medical tourism

Published: 13:40 January 22, 2016
Barbara Mae Dacanay, Correspondent

GULF NEWS



AA+

Manila: Low supply of well-screened blood is now affecting public and private hospitals in the Philippines, making it difficult to make the country a medical tourism hub.

Malaysia blood supply shortage: Encourage blood donation by educating youngsters

28 Jul 2016, Brenda Lau



Manila's government is asking for another day for blood donation before the shortage is resolved after the holiday.

Manila's government is asking friends to fast-track blood donation.

Manila's government is asking friends to fast-track blood donation.

Thai Red Cross in urgent need of blood donations

in General | February 27, 2015 | (742 views) | By Thai PBS Reporters

Like 0

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Tweet



The Thai Red Cross Society is in critical shortage of blood that is needed for transfusions.

China's blood shortage, by the numbers

By Michael Evans | 5th August 2012



5
SOCIAL BUZZ

NATIONAL

Blood supply improves, but India still faces a shortfall of 10 per cent



Samarth Bansal

NEW DELHI: JULY 31, 2016 01:02 IST
UPDATED: JULY 31, 2016 02:34 IST

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VIETNAM

FEATURE: Blood donors multiply, but shortage continues in Vietnam

By Gia Loc
03 February 2016
Viet Nam News (Vietnam)
#People

Infog

Impact of emerging pathogens on blood availability

Blood shortage is exacerbated by emerging pathogens and resulting donor deferrals

▪ Dengue virus

- The donor population is now more impacted: Children used to be the most impacted population in Asia. Recently shifted to more adult population (potential blood donors)
- Deferral for Acute febrile illness.
- Shock syndrome and leakage necessitate blood transfusions

▪ Zika virus

- Deferral for acute febrile illness (20% symptomatic)
- NAT screening or approved PI/PRT (US)
- Deferral of NAT-positive donors once screening is implemented

▪ Chikungunya virus

- Deferral for acute febrile illness

▪ Co-circulation of arboviruses

The Problem with Emerging Pathogens – Unpredictability

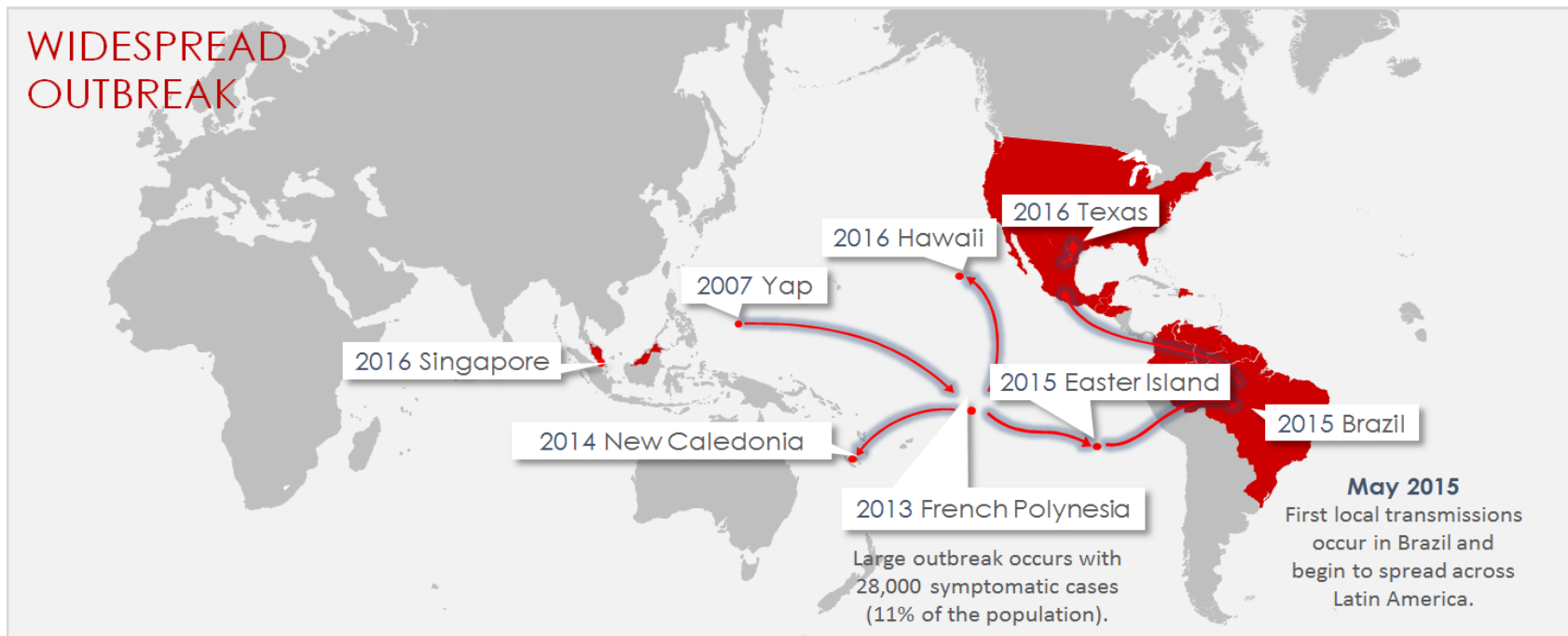
Eg. ZIKV Outbreaks in Americas ... is SE Asia a sitting target?



- **ZIKV circulated throughout Africa, SE Asia for decades**, yet only recently caused outbreaks (2007, 2013, 2015) due to widespread presence of *Aedes* vectors, urbanization, increased travel.
- **Reports of Zika in Asia have been sparse until ~2016 in Singapore, Thailand**
 - Under-reported or misdiagnosed since symptoms and serology similar to Dengue, Chikv
 - Population may already be protected by cross-reactivity from Dengue
- **Enhanced Zika infection by pre-existing anti-DENV antibodies.^{1,2}**

1. Wikan N et al. Asian Pacific Journal of Tropical Medicine 2017;10(1):1-5.

2. Stettler K. et al. Science 2016;353(6301):823-826.



Sustainability: Reactive Approaches Alone Have Limits

Published July 2016

EDITORIAL

Assuring blood safety and availability: Zika virus, the latest emerging infectious disease battlefield

Threats to blood safety from infectious agents, and subsequent public health action, are hardly novel. Transfusion transmission of *Treponema pallidum*, the etiologic agent of syphilis, was recognized in the early 20th century soon after the first successful transfusions, and in response, donor tests for syphilis-related antibodies were introduced.¹ Later in the 1960s, hepatitis B virus was found to cause posttransfusion jaundice, and sensitive donor screening tests for hepatitis B surface antigen (HBsAg) were added to donor testing in the early 1970s. The AIDS epidemic in the 1980s presented an entirely new kind of challenge to blood safety, with the need to respond urgently to a newly emerging blood-borne and sexually transmitted infection with catastrophic implications. A massive scientific and public health response to AIDS resulted in discovery of human immunodeficiency virus (HIV) as the etiologic agent and then licensure of blood donor screening tests a year later. Since the emergence of HIV, numerous recognized and emerging blood safety concerns (e.g., human T-lymphotropic virus, hepatitis C virus [HCV], cytomegalovirus, malaria, variant Creutzfeldt-Jakob disease, Chagas disease, and bacterial contamination) have been addressed by a multitiered approach comprising donor deferrals through education and risk factor-based screening with questionnaires; a limited physical examination; use of deferral registries to prevent future unsuitable collections; laboratory testing for markers of infection including nucleic acid tests (NATs) for some agents; and use of pathogen reduction technologies (PRTs) for certain blood components, all within a system highly regulated by the US Food and Drug Administration (FDA). Nevertheless, more recently emerging threats, including arboviruses and parasites, have presented novel challenges related to unpredictable local vector-borne spread and have exposed continued vulnerabilities to blood safety that call for urgent action.

Arboviruses, transmitted by arthropods (primarily mosquitoes), are relatively new emerging threats to

blood safety and present a particular challenge due to rapid and large-scale epidemics affecting the United States and its territories. While more than 100 pathogenic arboviruses are known to exist and some, particularly yellow fever and dengue, have been associated with outbreaks historically in the continental United States, none has caused recent outbreaks before the emergence of West Nile virus (WNV) in 2002. Unlike typical blood-borne viruses such as hepatitis viruses and HIV, which establish chronic infections, arboviruses cause predominantly acute infections, thus presenting a threat to blood safety only while a donor is transiently viremic, either during the disease incubation period or with an asymptomatic or a mild, undetected symptomatic infection. The challenge arises from rapid epidemic spread of an arbovirus in new geographic areas, resulting in immediate safety risks to the blood supply and an urgent need for intervention. Additionally, direct viral detection in donated blood, a generally costly measure, is needed since testing for antibodies, which take time to develop after infection and persist, would fail to interdict most infectious donations and result in deferral of large numbers of acceptable donors with previously resolved infections.

The US WNV epidemic was the first example of a large-scale arboviral threat to the US blood supply, requiring an urgent response across government and nongovernment agencies. Beginning with reports in August 2002 of a WNV infection acquired by organ transplantation, ultimately being traced to a WNV-infected blood transfusion received by the organ donor, awareness of a rapidly spreading vector-borne, transfusion-transmitted agent associated with morbidity (e.g., neurologic disease) and mortality led to calls for blood donor screening tests for WNV.² Collaborations among federal agencies, state public health laboratories, blood collection organizations, and test kit manufacturers led to the availability of investigational donor screening tests within 7 months of a November 2002 workshop in which consensus had been reached on the urgency and path forward. Fortunately, WNV isolates had been sequenced and were available for sharing, and technology platforms for NAT of blood donations for HIV and HCV could be readily adapted to WNV by the manufacturers. WNV has since become endemic in the United States, necessitating an indefinite program of donation testing. A decade later, there have been regional outbreaks of other arboviral diseases, namely chikungunya,

The conclusions, findings, and opinions expressed by authors contributing to this work do not necessarily reflect the official position of the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control and Prevention, or the Food and Drug Administration.

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Volume 56, July 2016 TRANSFUSION 1669

“Interventions are needed that are both precautionary and independent of the specific threat such as PRT for all blood components”

Kuehnert MJ and Epstein JS. Transfusion. July 2016.

■ Reactive approaches like testing are problematic:

- Delayed implementation due to development time, regulatory reviews, etc.
- Potential cost/logistics impact due to additive testing

ing Zika virus epidemic. More broadly, as increasing numbers of emerging infections threaten blood safety, progressive addition of donor screening tests targeting individual pathogens has become problematic for many reasons, including uncertainty and delay in their implementation as well as increased costs for and impacts on blood center logistics. A new paradigm is needed!

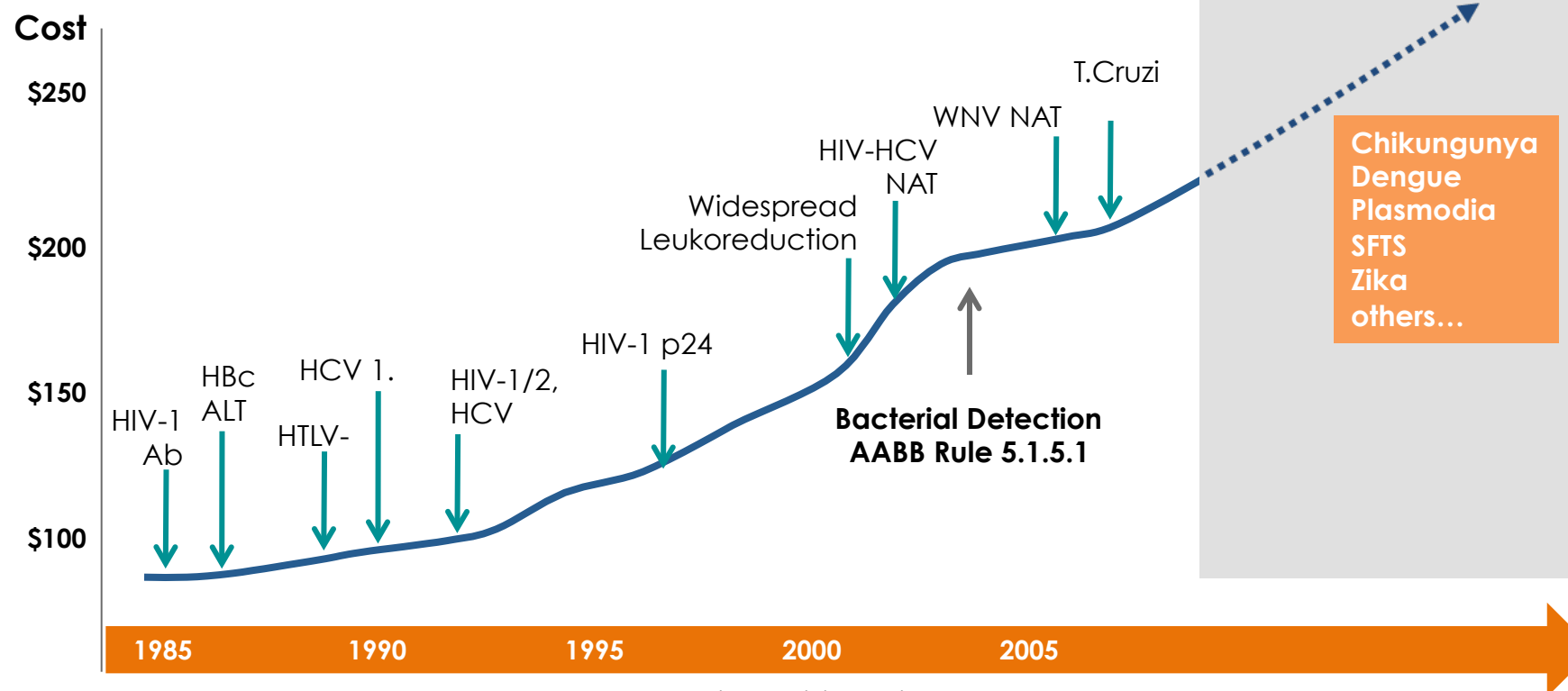


Emerging Pathogens: Can Tests Keep Up?

Development time, cost, continual addition of new pathogens

25 years of testing = partial protection against just 7 agents

HIV, Hepatitis B, Hepatitis C, HTLV, bacteria, West Nile virus, T. Cruzi



RBC price data adapted from B Custer & JS Hoch, *Transfusion Medicine Reviews*, 23, No 1 (January), 2009: pp 1-12

Emerging Pathogens – Current Mitigations Have Limits

- **No FDA-licensed **test** for donor screening exists for certain emerging pathogens**
- **AABB Bulletin February 2016: Zika, chikungunya, dengue travel **deferrals****
- **Post donation information/illness **reporting****
 - Risk still exists with components transfused from asymptomatic donors.
- ****Stop** routine collections, attain components elsewhere**
 - Puerto Rico, Florida due to dengue (One Blood in 2013).
 - Not ideal for platelets, disruptive due to limited shelf-life and shipping time.
- **Pathogen reduction (PR)**
 - FDA approved for arboviruses including chikungunya, dengue, WNV.¹
 - FDA Guidance for Zika released revised guidance in August 2016, recommends PR as option for all US.²
 - WHO Guidance released February 2016 recommends PR for areas with active transmission of ZIKV.³



1. INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016. 2. FDA Zika Guidance for Industry August 2016. 3. WHO Interim guidance WHO/ZIKV/HS/16.1 February 2016.

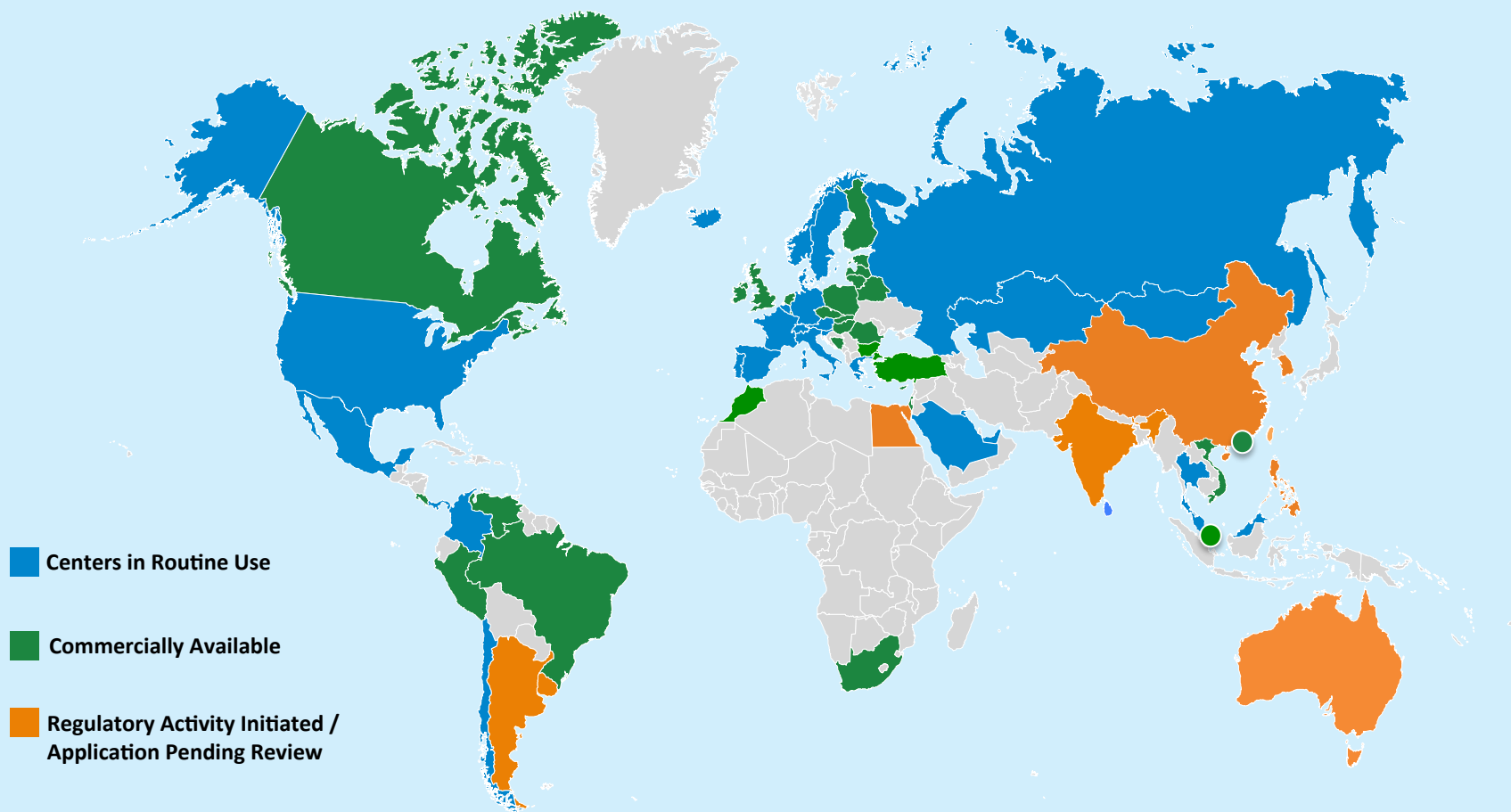
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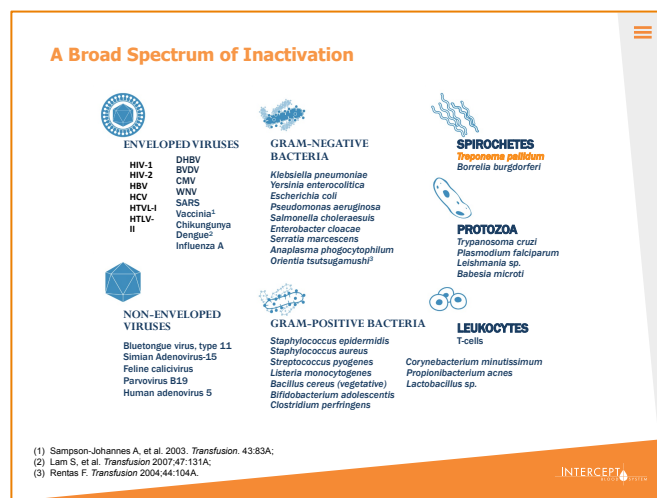
INTERCEPT Blood System: Global Status

- More than **10** years of routine use
- Kits sold to produce **> 4,000,000** INTERCEPT platelet and plasma units
- Used in **>150** Blood Centers in **25** countries



Last update: March 2017

The INTERCEPT Blood System: A broad Spectrum of Inactivation



Emerging Arboviruses	Log Reduction
West Nile virus ¹	≥ 6.7
Chikungunya virus ²	> 6.4
Dengue virus ³	≥ 5.6
Zika virus ⁴	≥ 6.6

1. Stramer SL, et al., (2009), *Transfusion*. 49(August 2009 Supplement): p. 1S - 29S (in plasma).
2. Tsetsarkin KA et al. *Am. J. Trop. Med. Hyg.*, 88(6), 2013, pp. 1163–1169.
3. Musso D. et al. *Transfusion*. 2014 Nov;54(11):2924-30. (Dengue in Plasma).
4. Aubry M. et al. *Transfusion*. 2016 Jan;56(1):33-40. (Zika in Plasma).

ORIGINAL RESEARCH

Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination

Maite Aubry,¹ Vaea Richard,¹ Jennifer Green,² Julien Brault,³ and Didier Musso¹

BACKGROUND: Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) transmitted by mosquitoes. The potential for ZIKV transmission through blood transfusion was demonstrated during the ZIKV outbreak that occurred in French Polynesia from October 2013 to April 2014. Pathogen inactivation of blood products is a proactive strategy that provides the potential to reduce transfusion-transmitted diseases. Inactivation of arboviruses by amotosalen and ultraviolet A (UVA) illumination was previously demonstrated for chikungunya, West Nile, and dengue viruses. We report here the efficacy of this process for ZIKV inactivation of human plasma.

STUDY DESIGN AND METHODS: Plasma units were spiked with ZIKV. Viral titers and RNA loads were measured in plasma before and after amotosalen and UVA photochemical treatment.

RESULTS: The mean ZIKV titers and RNA loads in plasma before inactivation were respectively 6.57 log TCID₅₀/mL and 10.25 log copies/mL. After inactivation, the mean ZIKV RNA loads was 9.51 log copies/mL, but cell cultures inoculated with inactivated plasma did not result in infected cells and did not produce any replicative virus after one passage, nor detectable viral RNA from the second passage.

CONCLUSION: In this study we demonstrate that amotosalen combined with UVA light inactivates ZIKV in fresh frozen plasma. This inactivation process is of particular interest to prevent plasma transfusion-transmitted ZIKV infections in areas such as French Polynesia, where several arboviruses are co-circulating.

ABBREVIATIONS: CHIKV = chikungunya virus; DENV = dengue virus; TCID₅₀ = 50% tissue culture infectious dose; WNV = West Nile virus; ZIKV = Zika virus.

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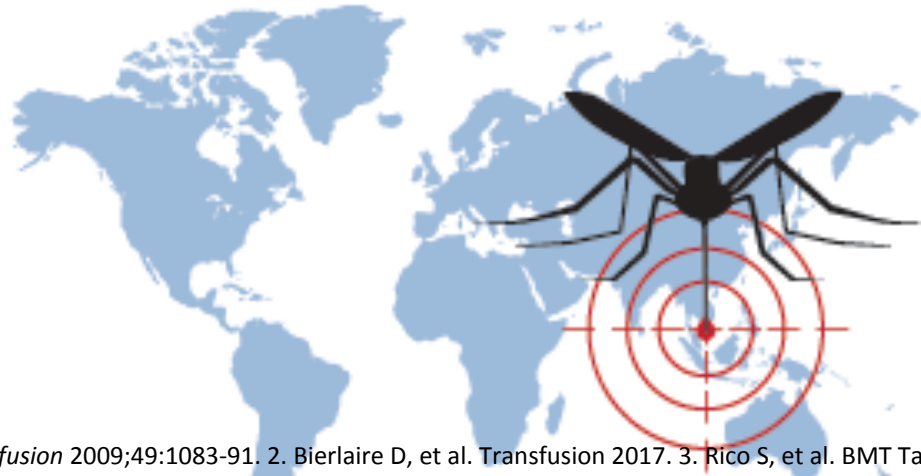
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TRANSFUSION 2015;00:00–00

Volume 00, Month 2015, TRANSFUSION 1

The INTERCEPT Blood System: Maintaining Safe and Adequate Supply During Arboviral Outbreaks

INTERCEPT has been called upon to sustain platelet availability during arboviral outbreaks:

- 2005 CHIKV epidemic on Ile de La Réunion, France.¹
- 2010 DENV/CHIKV outbreaks in Guadeloupe and Martinique, French Polynesia.²
- 2013/2014 French Polynesia able to proactively address Zika outbreak with PI.²
- 2014 CHIKV and DENV outbreaks in the Caribbean region.³
- 2016 ZIKV outbreak in Puerto Rico.⁴



1. Rasongles P, et al. *Transfusion* 2009;49:1083-91. 2. Bierlaire D, et al. *Transfusion* 2017. 3. Rico S, et al. BMT Tandem Meeting; February 2016. 4. Weiner E, et al. AABB 2016, SP454.

4. WHO Interim guidance WHO/ZIKV/HS/16.1 February 2016. 5. FDA Guidance for Industry August 2016.

Zika Virus Epidemic, 2015 - 2016: Puerto Rico – Banco de Sangre de Servicios Mutuos

- Per initial FDA Guidance (Feb 2016), all collections halted, components imported from US. Testing was not available.
- Importation posed challenges.
- Shortened platelet shelf-life, cost, logistical burden, issues with donor recruitment and sustaining local availability.
- In March 2016, adopted PI for all apheresis platelet products collected at BSSM.



“Rapid implementation of the INTERCEPT Blood System helped us maintain platelet availability during a Zika outbreak.”

- Jose Alsina, VP & COO,
Banco de Sangre de Servicios Mutuos

1. Weiner E. et al. AABB 2016, SP454.

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INTERCEPT for Red Blood Cells – Status



- **Primary endpoints met successfully:**
 - In EU Phase III in acute anemia patients (n=50).
 - In US Phase II recovery & survival study in healthy subjects.
- **Completed enrollment:**
 - EU Phase III RBC study in chronic anemia patients (n=75).
- **CE mark submission upon completion of CMC studies**
 - Scheduling of TUV submission date.



- **National funding by BARDA** permits to accelerate a comprehensive RBC program
 - Base Period and Additional Options (~\$180M).
 - Major Phase 3 & Phase 4 clinical development effort.
 - Manufacturing scale-up and disposable advances.
 - PI & in-vitro studies
 - PMA submission



The INTERCEPT Blood System: Dengue Virus Inactivation in All 3 Components

Robust Dengue inactivation in plasma, platelets, and red blood cells

Blood Component	Infectivity (Log ₁₀ TCID ₅₀ /mL) or PFU/mL	RNA Load (Log ₁₀ GEq/mL)	Equivalent GEq/mL
Plasma (DENV -1) ¹	5.61	10.21	1.6x10 ¹⁰
Platelets in PAS (DENV-2) ²	>5.3	NA	NA
Red Blood Cells (DENV-1) ³	6.61	8.42	2.6x10 ⁸

1. Musso et al. Transfusion. 2014;54:2924–30
2. Dupuis et al. Transfusion. 2012;52 (3S)(3S:225A):225A
3. Unpublished; Data on-file at Cerus.

PFU : plaque forming unit

NA : not available

The INTERCEPT Blood System: Zika Virus Inactivation in All 3 Components



Robust Zika inactivation in plasma, platelets, and red blood cells

Blood Component	Average Inactivation		Equivalent
	Infectivity (Log ₁₀ TCID ₅₀ /mL)	RNA Load (Log ₁₀ GEq/mL)	GEq/mL
Plasma ¹	>6.57	10.25	1.8x10 ¹⁰
Platelets in PAS ²	>4.42	7.46	2.9x10 ⁷
Red Blood Cells ³	>5.99	7.75	5.6x10 ⁷
Asymptomatic Donor Sera ¹	NA	4.85±1.0	7.1x10 ⁴

- The level of infectious virus inactivated is higher than the levels detected in asymptomatic viremic donors.

¹ Aubry et al., Transfusion 2016 epub. ² Santa Maria et al. Unpublished, ³ Laughunn A et al. Transfusion 2016.

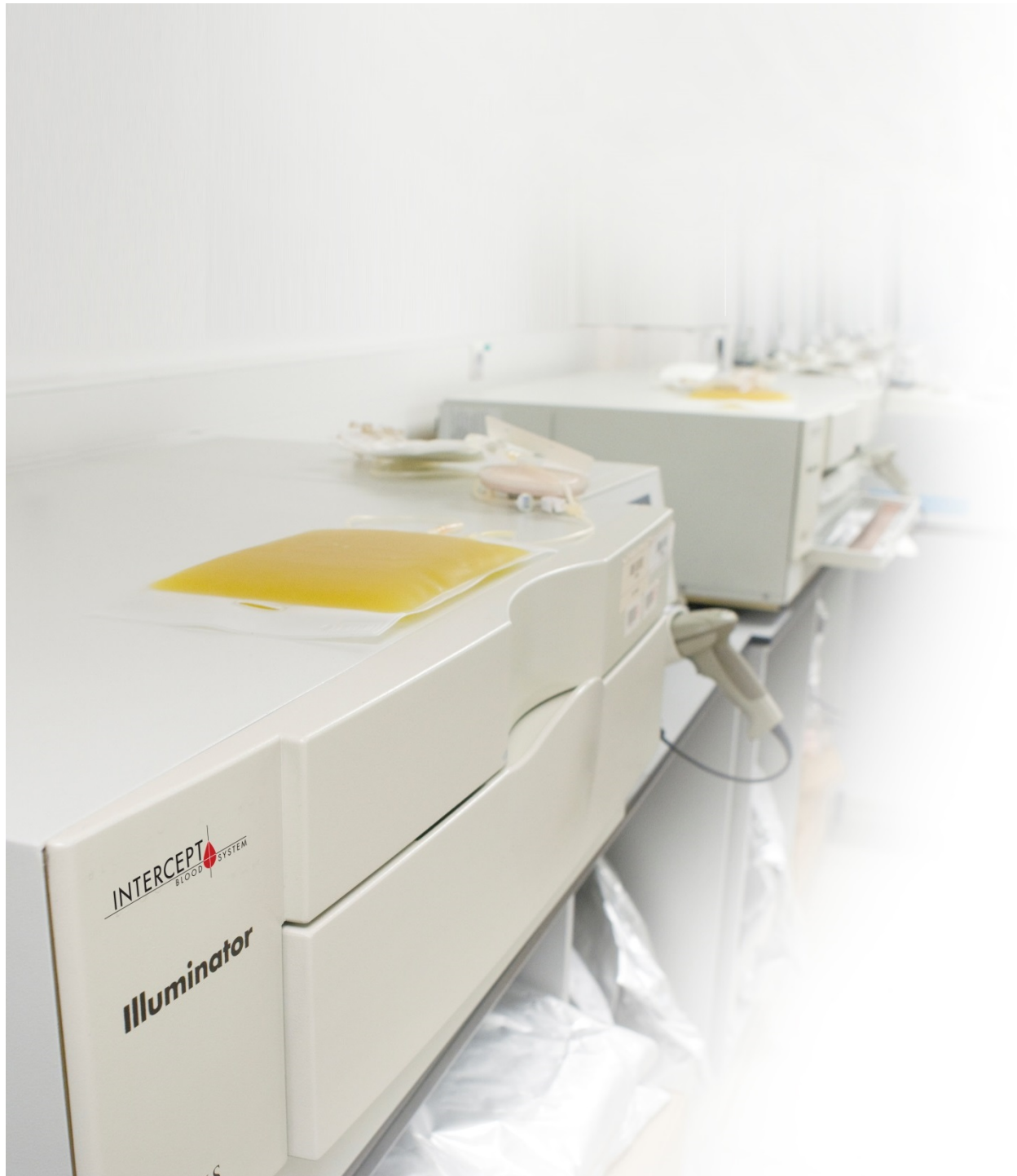
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In Conclusion...

- Blood shortages in Asia are a chronic issue that can be exacerbated by emerging pathogens (i.e. via deferrals, new tests).
- Emerging pathogens and their unpredictability call for a proactive measure to effectively mitigate TTI risk, and to maintain blood availability.
- ***The use of a robust PI system provides a comprehensive solution, that will help maintain blood safety and availability.***
 - Today, INTERCEPT Platelets and Plasma are available to help ensure blood sustainability.
 - Platelets supply is particularly at risk in event of outbreak; susceptible to expiry, logistics issues, and blood shortage.
 - Single donor collections can be safeguarded efficiently.
 - INTERCEPT RBC System is in active development; provides an opportunity to simplify TTI mitigation strategies (e.g. testing, deferrals).



Thank you