

CHIKV Crash Lands in the Americas in 2014

Blood Safety Implications and Actions

Michael P. Busch, MD, PhD
Director, Blood Systems Research Institute
Senior Vice President for Research, BSI
Professor of Laboratory Medicine, UCSF



Chikungunya Virus

Makonde language: “to dry up or become contorted”

- Alphavirus
- 3 genotypes
 - West African
 - East/Central/Southern/East African (ESCA)
 - Asian
- Like dengue
 - Man-mosquito-man transmission cycle
 - *Aedes aegypti* is the traditional urban vector
 - Also spread by *Aedes albopictus*

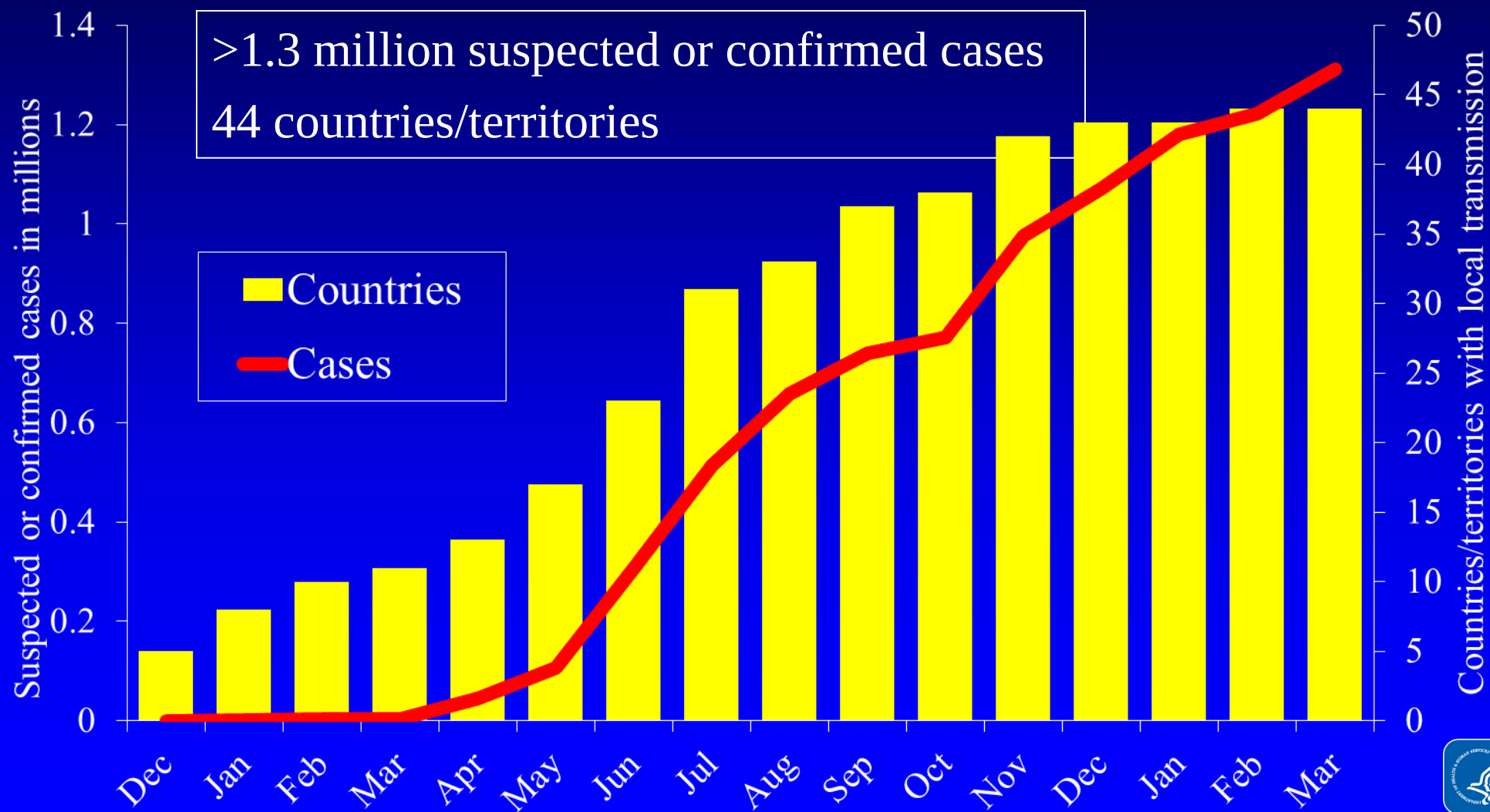
Chikungunya Virus Disease

- Acute onset of fever and severe pain in multiple joints
- Mortality low but extremely debilitating; symptoms often last months to years
- Most infected persons become symptomatic
- No antiviral therapy; treatment is symptomatic
- Lifelong immunity following infection
- No licensed vaccines; prevention relies on avoidance of mosquito bites and mosquito control (difficult)

Chikungunya Virus Outbreaks in Americas

- Since 2005, major outbreaks in tropical areas of Africa, Asia, Western Pacific
- In 2013, first locally-acquired cases in the Americas reported on islands in the Caribbean
- Large, explosive outbreaks will continue in tropical regions until enough of the population has been infected and community transmission can no longer be sustained
- In continental U.S. expect increase in travel imported cases
- Small, focal autochthonous outbreaks also expected
 - Wide use of AC, window and door screens reduce spread

Reported Chikungunya cases and Number of Countries/Territories With Local Transmission in the Americas, Dec 2013–Mar 2015



Chikungunya in the Western Hemisphere

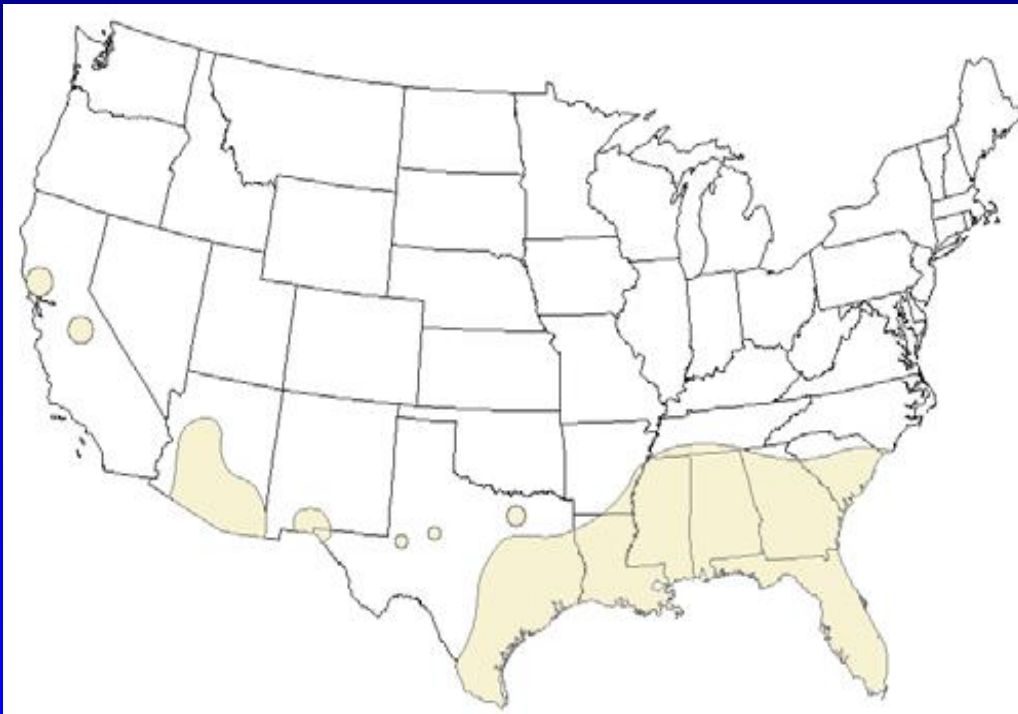


Status as of March 2015:

- 44 countries or territories in the Caribbean, Central America, South America, and North America.
- 1,310,925 suspected/confirmed cases
 - 35,000 in Puerto Rico
- Notable local transmissions in North America
 - South Florida
 - Sonora State, Mexico

Approximate Geographic Distribution of *Aedes aegypti* and *Aedes albopictus* Mosquitoes in the United States

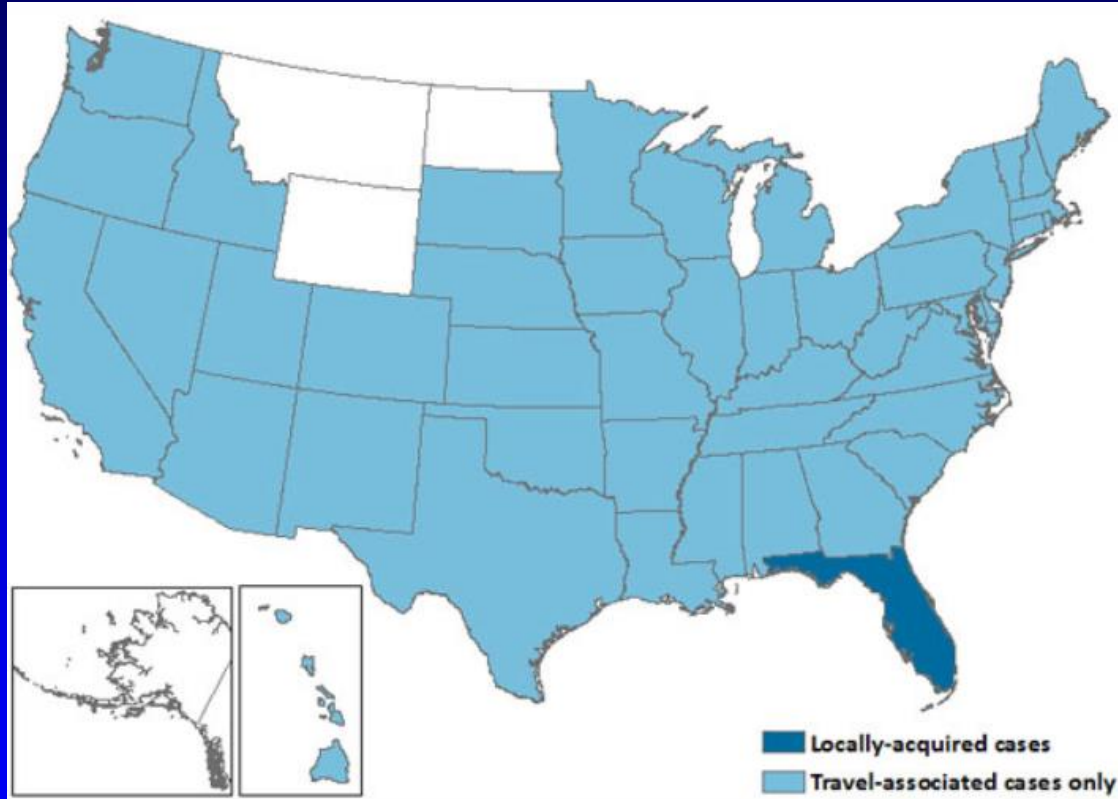
Aedes aegypti



Aedes albopictus



Chikungunya in the United States*



Historically, from 2006–2013:

- An average **28** people/year with positive tests for recent chikungunya infection
- (Range 5–65 per year)

Current Outbreak, Continental U.S.

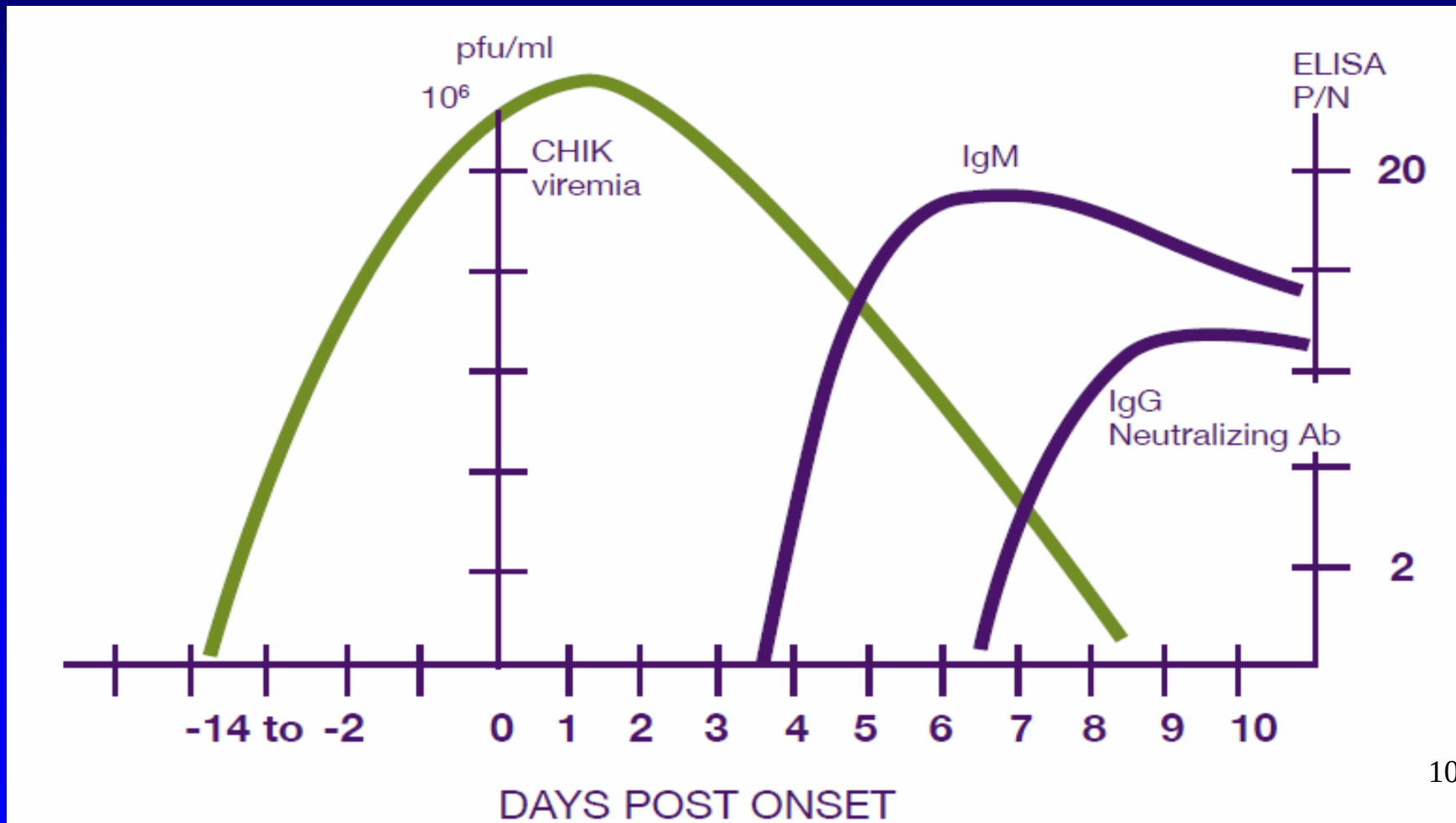
- 47 states reporting cases, and the District of Columbia
- **2,549** travel-associated cases
 - 18% from FL
 - 30% from NY
- **12** locally-acquired cases (FL)

* As of March 24, 2015

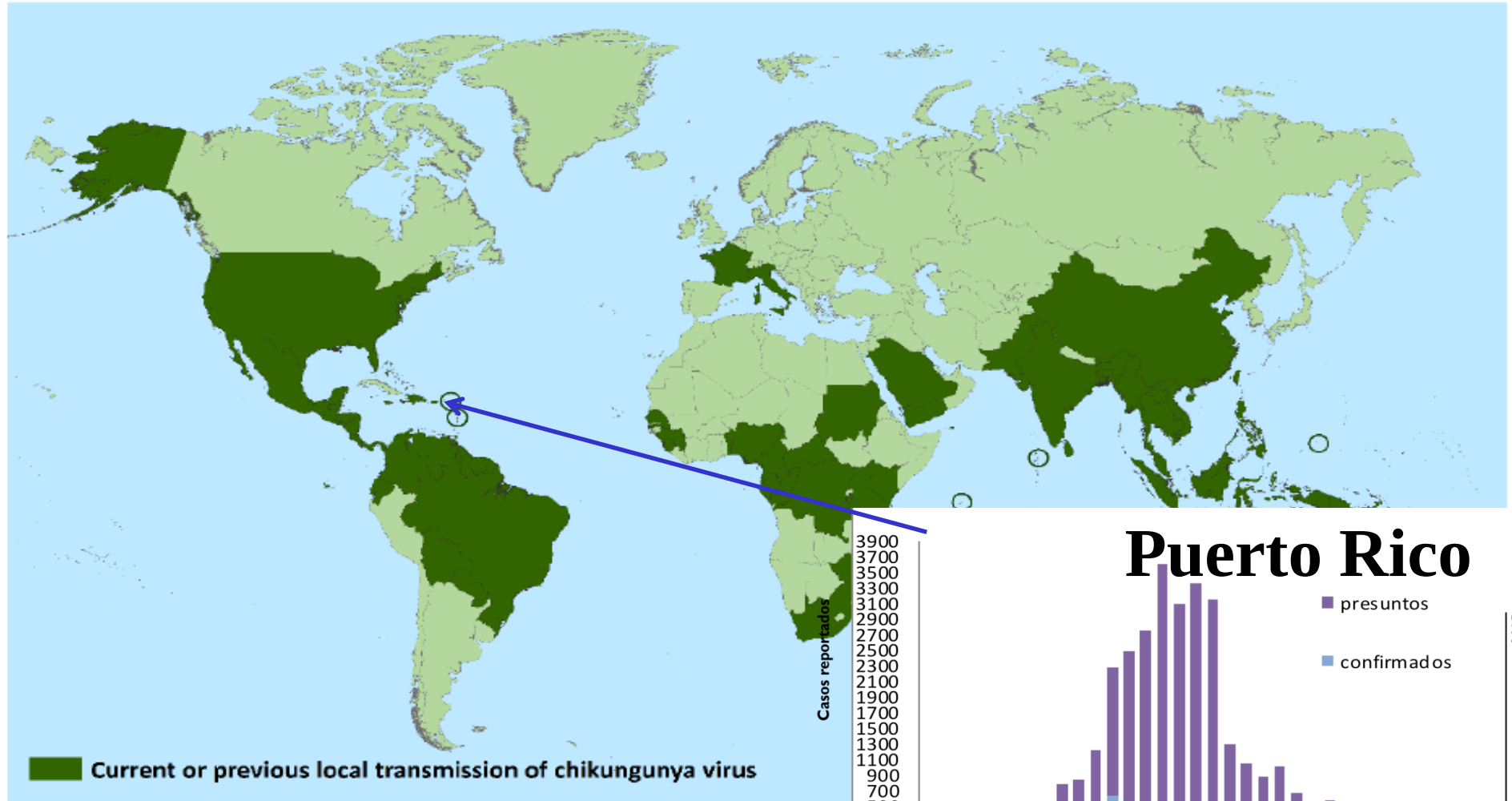
Considerations on Impact of CHIKV on Blood Safety

- No case of TT-CHIKV reported to date
- Prevalence of viremia among blood donors?
- Proportion of components derived from viremic donations that transmit infection to recipients?
- Clinical impact on infected transfusion recipients?
- Availability/efficacy of measures to reduce transfusion transmission when required?
- Cost and disruption incurred by those measures

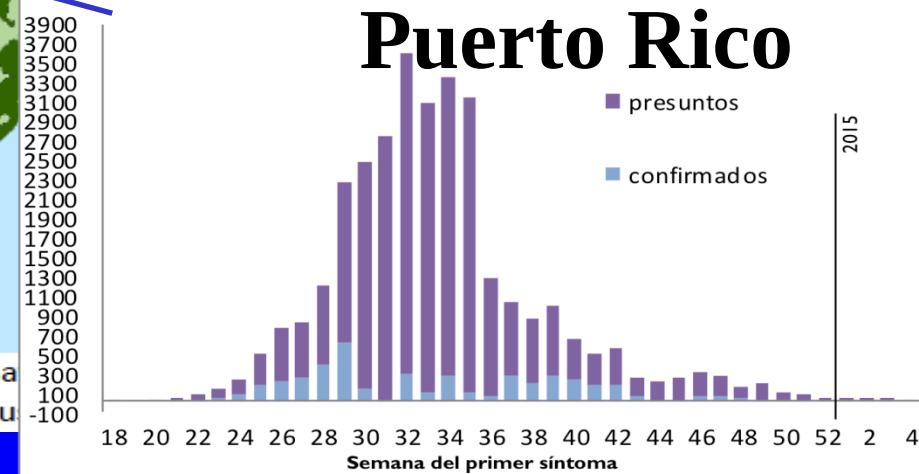
Chikungunya Viremia and Immune Response Model



Countries and territories where chikungunya cases have been reported* (as of March 10, 2015)



*Does not include countries or territories where only imported cases have been reported. There are new countries or territories that report local chikungunya virus transmission.



BSRI/CTS/CDC Study of CHIKV in PR Donors

- **Pre/Post-Epidemic CHIKV Serosurvey**
 - Anonymized plasma samples from 1000 PR donations from June 2014 and 1000 demographically linked PR donations from March 2015 frozen at CTS Tampa lab
 - Tested for CHIKV IgG Abs at BSRI using EuroImmune assay
 - IgM and PRNT performed on IgG-reactive samples
 - -> seasonal incidence and demographic correlates of infection
- **CHIKV RNA Testing**
 - Anonymized frozen aliquots of ~1700 MPs from PR donations from June-Dec 2014
 - Anonymized frozen aliquots from ~3,000 individual donations from peak epidemic
 - ID-NAT+ samples diluted 1:16 to assess yield of ID vs MP-NAT
 - IgG/IgM/PRNT testing to stage infections
 - Real-time TC-TMA CHIKV/DENV testing of MP and ID samples performed at Hologic
 - Real-time PCR CHIKV/DENV testing of MPs to be performed at Roche
- **Analyses in progress to:**
 - Correlate seasonal incidence with rates of viremic donations and clinical case reports
 - Estimate lengths of MP-NAT and ID-NAT detection periods
 - Determine infectivity of representative viremic donations in immunosuppressed mice

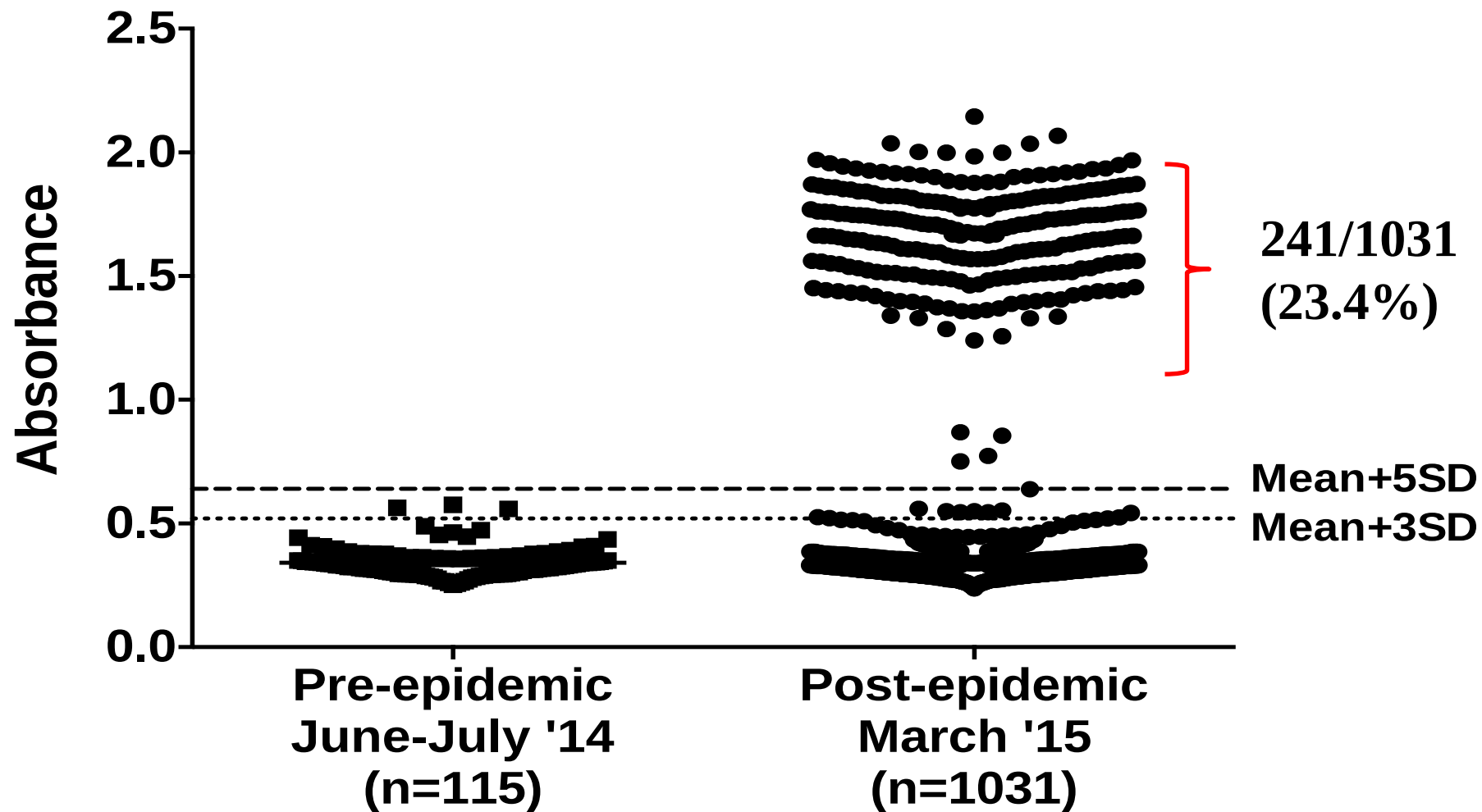
BSRI/CTS/CDC Study of CHIKV in PR Donors

- Pre/Post-Epidemic CHIKV Serosurvey
 - Anonymized plasma samples from 1000 PR donations from June 2014 and 1000 demographically linked PR donations from March 2015 frozen at CTS Tampa lab
 - Tested for CHIKV IgG Abs at BSRI using EuroImmune assay
 - IgM and PRNT performed on IgG-reactive samples
 - -> seasonal incidence and demographic correlates of infection
- CHIKV RNA Testing
 - Anonymized frozen aliquots of ~1700 MPs from PR donations from June-Dec 2014
 - Anonymized frozen aliquots from ~3,000 individual donations from peak epidemic
 - ID-NAT+ samples diluted 1:16 to assess yield of ID vs MP-NAT
 - IgG/IgM/PRNT testing to stage infections
 - Real-time TC-TMA CHIKV/DENV testing of MP and ID samples performed at Hologic
 - Real-time PCR CHIKV/DENV testing of MPs to be performed at Roche
- Analyses in progress to:
 - Correlate seasonal incidence with rates of viremic donations and clinical case reports
 - Estimate lengths of MP-NAT and ID-NAT detection periods
 - Determine infectivity of representative viremic donations in immunosuppressed mice

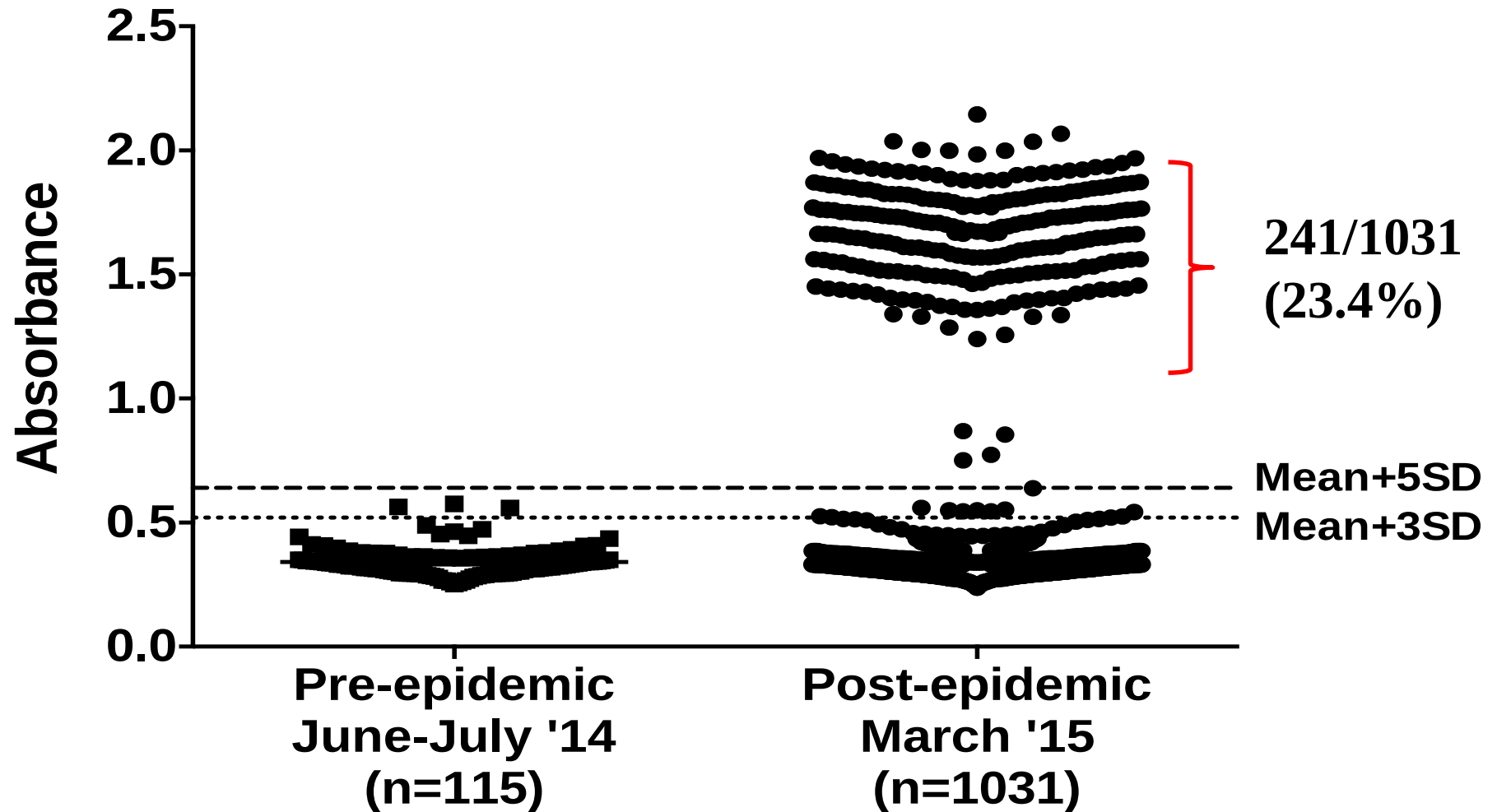
BSRI/CTS/CDC Study of CHIKV in PR Donors

- Pre/Post-Epidemic CHIKV Serosurvey
 - Anonymized plasma samples from 1000 PR donations from June 2014 and 1000 demographically linked PR donations from March 2015 frozen at CTS Tampa lab
 - Tested for CHIKV IgG Abs at BSRI using EuroImmune assay
 - IgM and PRNT performed on IgG-reactive samples
 - -> seasonal incidence and demographic correlates of infection
- CHIKV RNA Testing
 - Anonymized frozen aliquots of ~1700 MPs from PR donations from June-Dec 2014
 - Anonymized frozen aliquots from ~3,000 individual donations from peak epidemic
 - ID-NAT+ samples diluted 1:16 to assess yield of ID vs MP-NAT
 - IgG/IgM/PRNT testing to state infections
 - Real-time TC-TMA CHIKV/DENV testing of MP and ID samples performed at Hologic
 - Real-time PCR CHIKV/DENV testing of MPs to be performed at Roche
- Analyses in progress to:
 - Correlate seasonal incidence from serosurvey with rates of viremic donations and clinical case reports
 - Estimate lengths of MP-NAT and ID-NAT detection periods
 - Determine infectivity of representative viremic donations in immunosuppressed and immuno-competent murine models

Puerto Rico 2014 CHIKV Serology



Puerto Rico 2014 CHIKV Serology



3.6 M residents of PR x 23.4% infection rate => 842 K infections in 2014
 35 K suspected/confirmed cases reported in PR => 4.2% infections reported

CHIKV/DENV duplex real-time assay on Panther

Mini-Pool Testing Results

Chikungunya virus					
Panels	N	#R	%R	95% LL	95% UL
SeroNAT study MP	1668	161	9.7	8.3	11.2
June	106	0	0.0	0.0	3.5
July	193	8	4.1	2.1	8.0
August	293	26	8.9	6.1	12.7
September	262	51	19.5	15.1	24.7
October	299	57	19.1	15.0	23.9
November	243	12	4.9	2.8	8.4
December	272	7	2.6	1.3	5.2

1 MP tested DENV reactive sample that was also CHIKV reactive

CHIKV/DENV duplex real-time assay on Panther Mini-Pool Testing Results

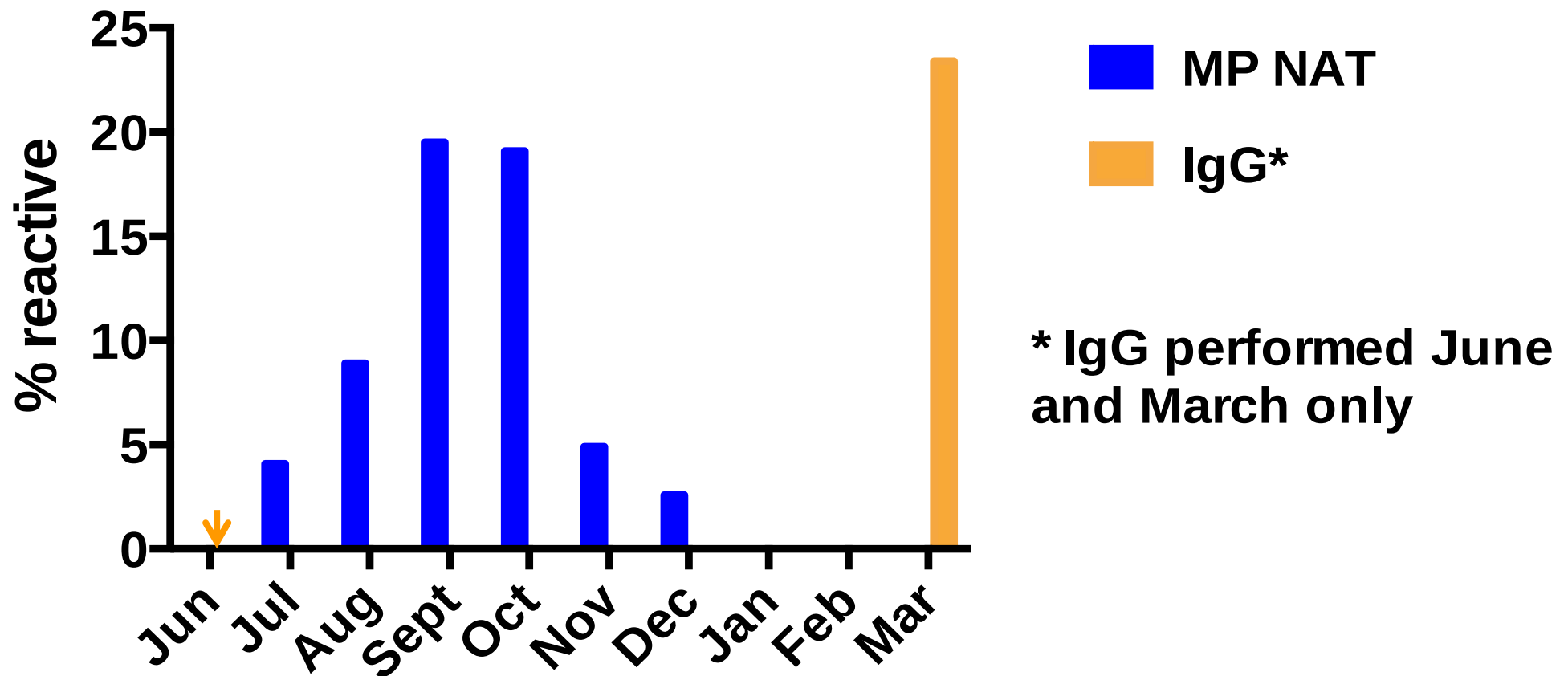
Chikungunya virus					
Panels	N	#R	%R	95% LL	95% UL
SeroNAT study MP	1668	161	9.7	8.3	11.2
June	106	0	0.0	0.0	3.5
July	193	8	4.1	2.1	8.0
August	293	26	8.9	6.1	12.7
September	262	51	19.5	15.1	24.7
October	299	57	19.1	15.0	23.9
November	243	12	4.9	2.8	8.4
December	272	7	2.6	1.3	5.2

Viral Load Distributions of MP+ samples

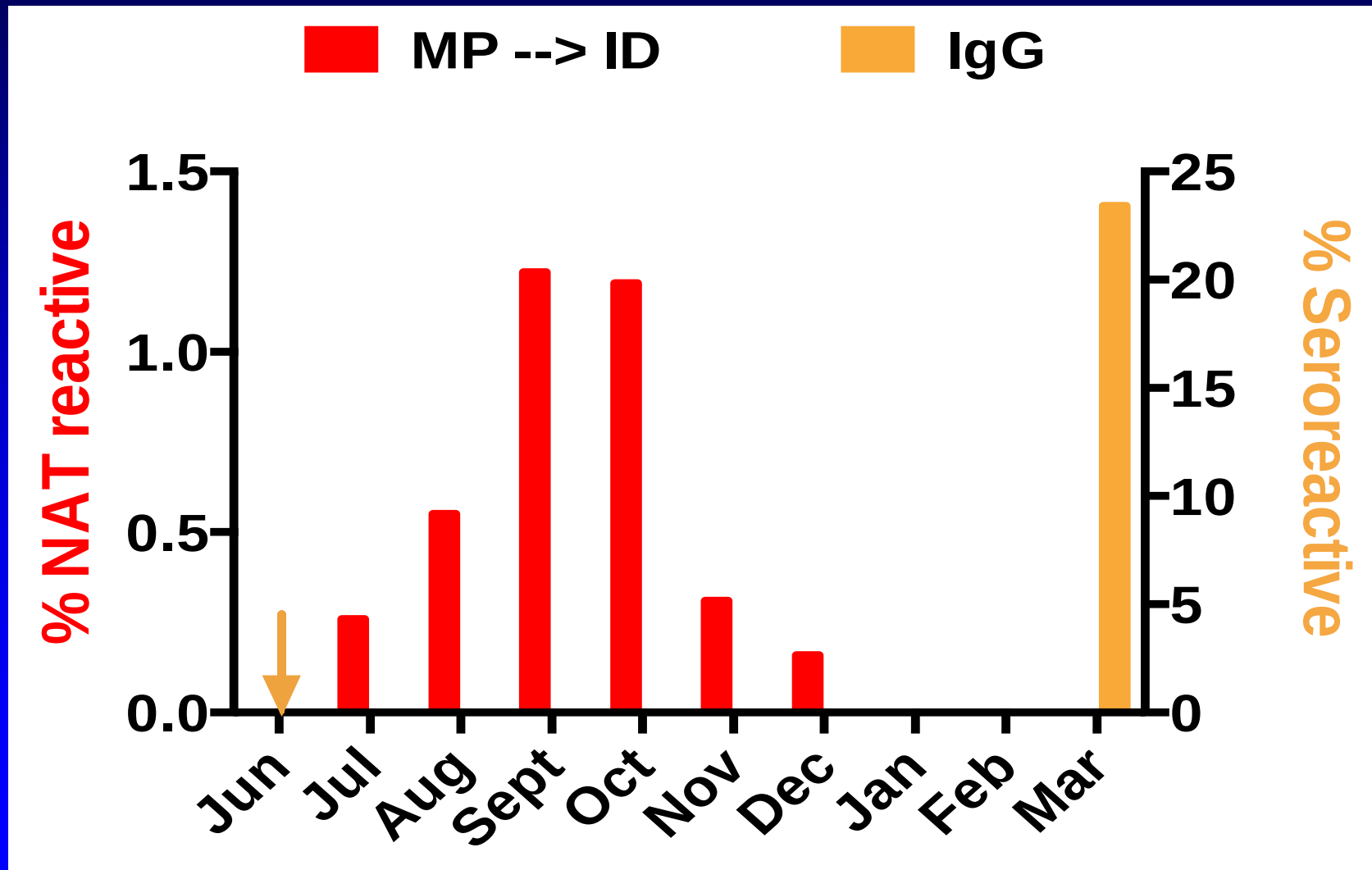
estimated Log c/mL	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Unquantifiable	0	7	11	11	6	1	36
0.5 - 1.9	1	4	10	8	2	3	28
2.0 - 2.9	3	3	3	8	0	2	19
3.0 - 3.9	1	2	6	11	2	0	22
4.0 - 4.9	1	4	7	6	2	1	21
≥ 5.0	2	6	14	13	0	0	35
Total	8	26	51	57	12	7	161

1 MP tested DENV reactive sample that was also CHIKV reactive

Rates of RNA+ MPs during 2014 CHIKV epidemic in PR relative to seasonal incidence



Imputed rates of RNA+ IDs using assay with sensitivity of MP NAT



CHIKV/DENV duplex real-time assay on Panther

Individual Donor Testing Results

Chikungunya virus					
Panels	N*	#R	%R	95% LL	95% UL
SeroNAT study IDT	3007	56	1.9	1.4	2.4
September	987	18	1.8	1.2	2.9
October	1010	21	2.1	1.4	3.2
November	1010	17	1.7	1.1	2.7

No DENV reactive sample detected

CHIKV/DENV duplex real-time assay on Panther

Individual Donor Testing Results

Chikungunya virus					
Panels	N*	#R	%R	95% LL	95% UL
SeroNAT study IDT	3007	56	1.9	1.4	2.4
September	987	18	1.8	1.2	2.9
October	1010	21	2.1	1.4	3.2
November	1010	17	1.7	1.1	2.7

Viral Load Distributions of ID+ samples

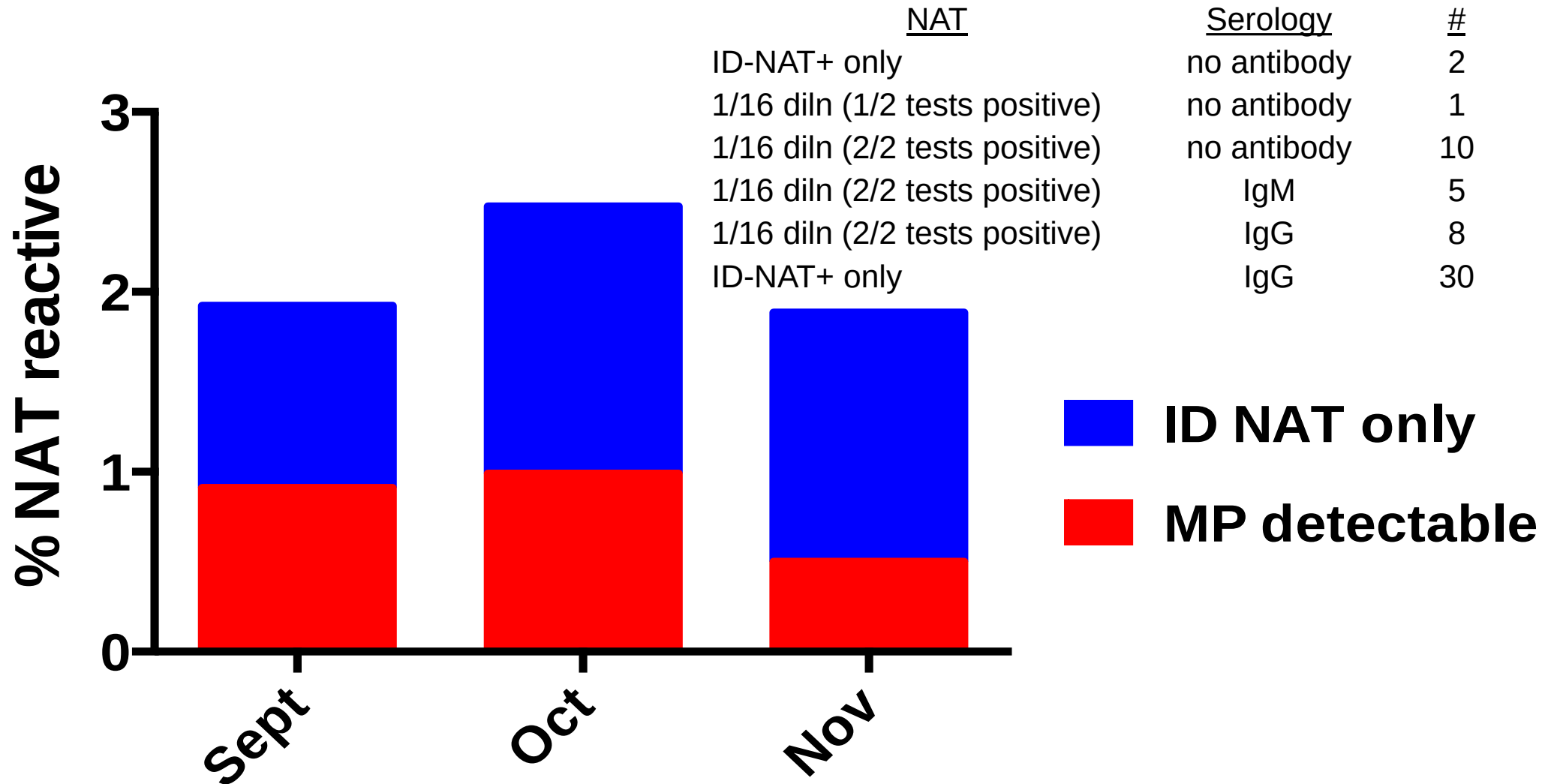
estimated Log c/mL	September	October	November	Total
Unquantifiable	7	10	11	28
0.5 - 1.9	3	4	3	10
2.0 - 2.9	1	3	1	5
3.0 - 3.9	3	0	1	4
4.0 - 4.9	1	1	1	3
≥ 5.0	3	3	0	6
Total	18	21	17	56

No DENV reactive sample detected

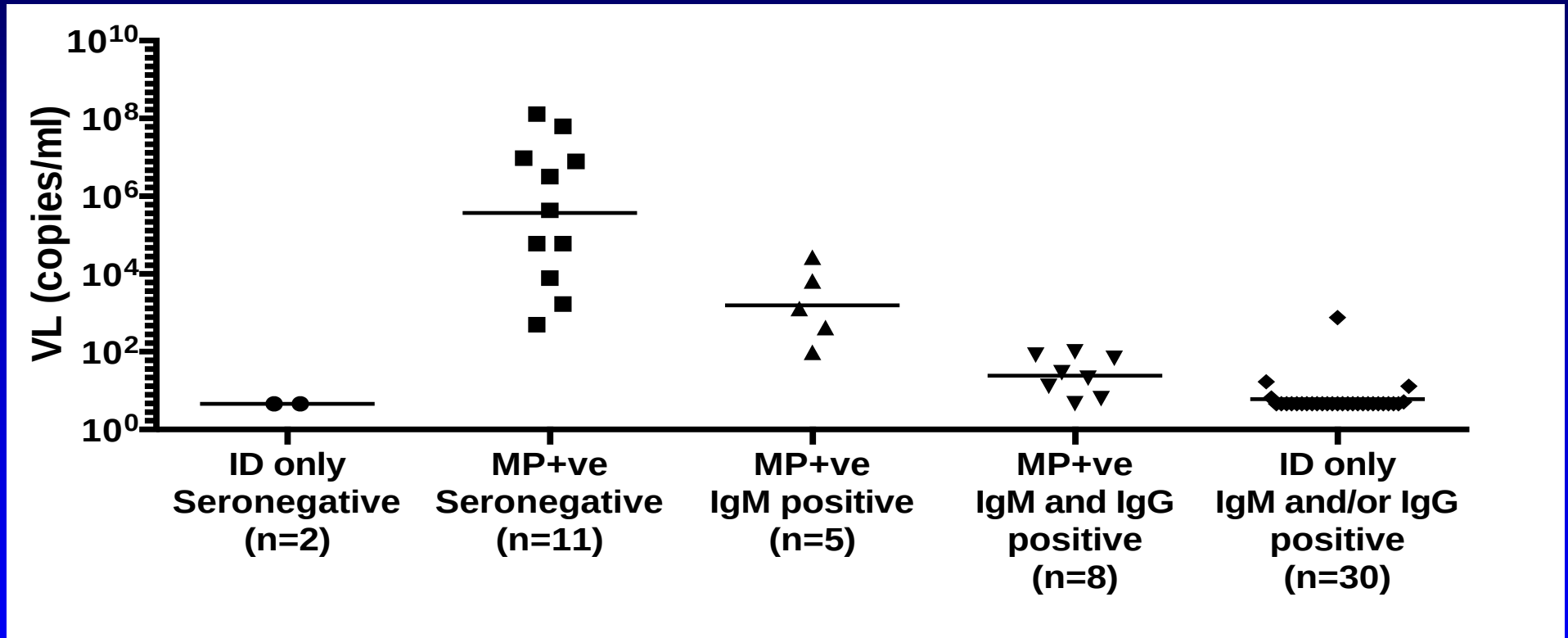
Individual donation CHIKV+ samples diluted to 1:16 to mimic MP NAT

		Tested Neat		Tested 1:16 (duplicate)								
				At least 1 replicate is Reactive			Both replicates are Reactive			Only the first replicate is Reactive		
	N	# R	%R CHIKV	# R	%R CHIKV	% CHIKV Neat Reactive detected	# R	%R CHIKV	% CHIKV Neat Reactive detected	# R	%R CHIKV	% CHIKV Neat Reactive detected
September	987	18	1.82%	9	0.91%	50%	8	0.81%	44%	8	0.81%	44%
October	1010	21	2.08%	10	0.99%	48%	6	0.59%	29%	9	0.89%	43%
November	1010	17	1.68%	5	0.50%	29%	3	0.30%	18%	4	0.40%	24%
Total IDT	3007	56	1.86%	24	0.80%	43%	17	0.57%	30%	21	0.70%	38%

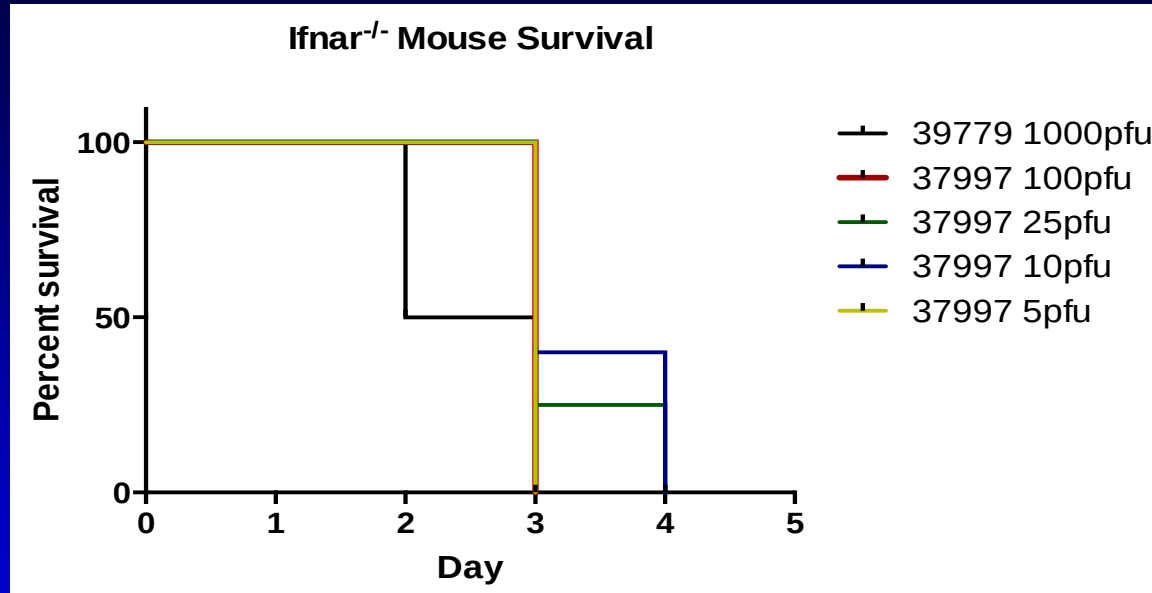
Detection of CHIKV+ donations by ID vs MP-NAT



CHIKV viral loads based on real-time TMA of 56 RNA+ ID-NAT reactive PR donations, by stage of infection



CHIKV infectivity in immunocompromised mice lacking the type I IFN receptor ($Ifnar^{-/-}$)



Other murine models

- Wild-type neonate mice
 - Day 8-9 C57BL/6 mice, high titer virus (10^5 pfu) intradermally. Lethal infection 4-6 p.i. Infection inhibited by mAbs.
- Acute arthritic model
 - 6 week old wild-type C57BL/6 mice, 10^4 pfu subcutaneously in footpad. Develop foot swelling 6-8 days p.i. Symptoms inhibited by mAbs.

Mitigation Strategies for TT-CHIKV

- NAT screening
- Photochemical inactivation of platelets/plasma
- Curtail donations in outbreak areas
- Defer donors from areas experiencing outbreaks
- Enhanced donor deferral
- Enhanced post-donation notification
- Temporary quarantine of donations with proactive post-donation call back

Conclusions Regarding Impact of CHIKV on Blood Safety

- Prevalence of viremia among blood donors
 - Can be very high for short periods of time during large epidemics
- Proportion of components from viremic donations that transmit infection to recipients
 - Unknown, but likely high at least until IgG antibody develops
 - NAT positivity $\neq$ Infectivity; need for animal and human TT studies
- Clinical impact on infected transfusion recipients
 - Unknown, but likely some morbidity and low mortality
- Availability of measures to reduce TT when required
 - Sourcing blood from low risk regions and enhanced deferral or post-donations call-back challenging
 - NAT screening and PR feasible, but concern over affordability
- Cost and disruption incurred by these measures
 - Can be high and may not be feasible in high epidemic regions

Acknowledgements

Creative Testing Solutions

Phillip Williamson

PR blood banks

CTS Tampa lab staff

BSRI

Graham Simmons

Kai Lu

Nathan Liss

Marcus Muench

Michelle Quintos

Hologic/Grifols

Jeff Linnen

Vanessa Bres

Maesa Hanhan

Derrek Ocampo

Roche

Tony Hardiman

Subita Sudershana,

CDC

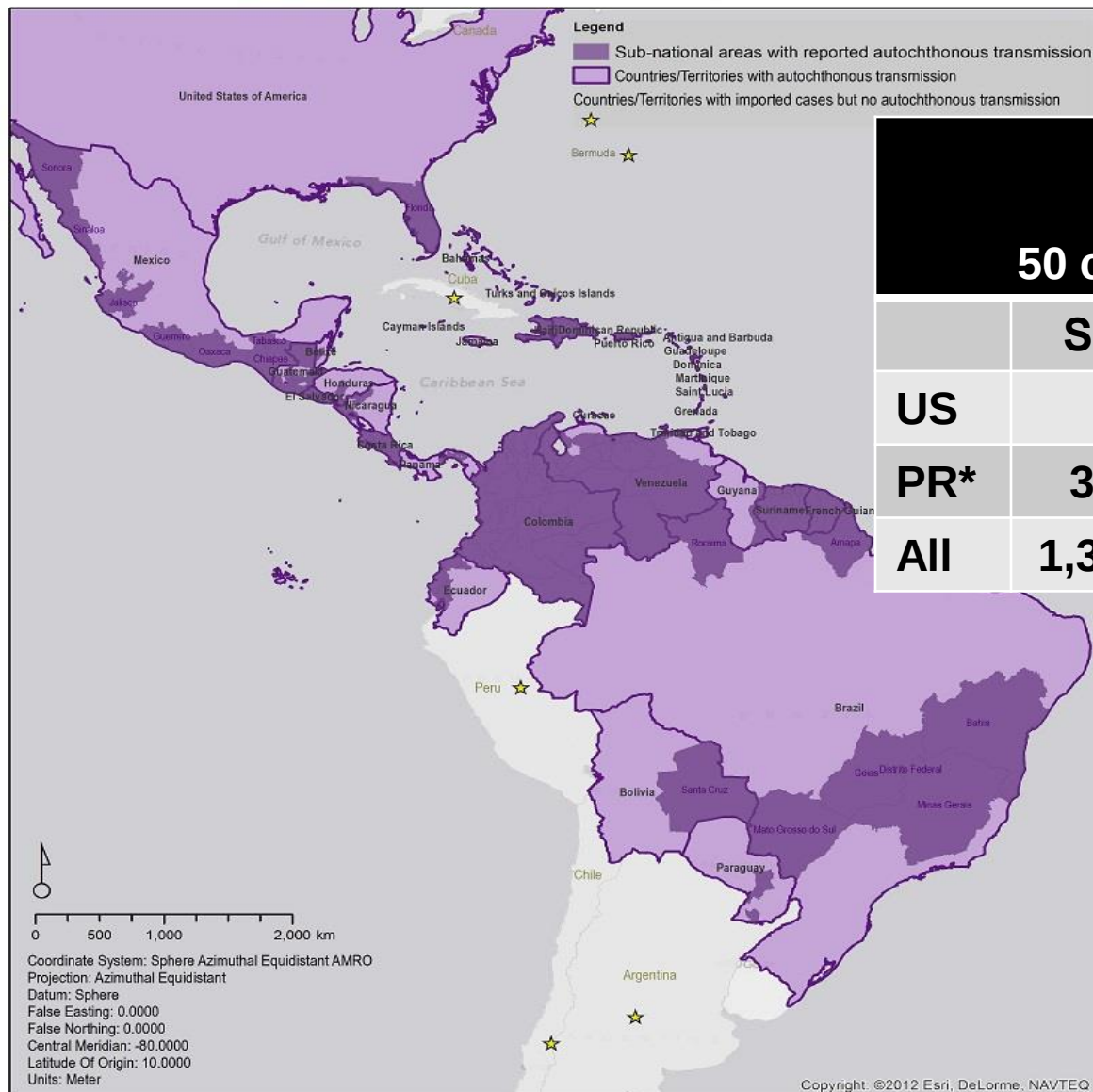
Lyle Petersen

Reappearance of Chikungunya, Formerly Called Dengue, in the Americas

Scott B. Halstead

After an absence of ≈ 200 years, chikungunya returned to the American tropics in 2013. The virus is maintained in a complex African zoonotic cycle but escapes into an urban cycle at 40- to 50-year intervals, causing global pandemics. In 1823, classical chikungunya, a viral exanthem in humans, occurred on Zanzibar, and in 1827, it arrived in the Caribbean and spread to North and South America. In Zanzibar, the disease was known as kidenga pepo, Swahili for a sudden cramp-like seizure caused by an evil spirit; in Cuba, it was known as dengue, a Spanish homonym of denga. During the eighteenth century, dengue (present-day chikungunya) was distinguished from breakbone fever (present-day dengue), another febrile exanthem. In the twentieth century, experiments resulted in the recovery and naming of present-day dengue viruses. In 1952, chikungunya virus was recovered during an outbreak in Tanzania, but by then, the virus had lost its original name to present-day dengue viruses.

Countries/territories with autochthonous transmission or imported cases of Chikungunya in the Americas, EW 49, 2013 - EW 10, 2015



Data source:
 PAHO/WHO. Number of reported cases of Chikungunya Fever in the Americas
<http://www.paho.org/chikungunya>
 Map production:
 PAHO-WHO AD CHA IRARO

* Note: Entire countries have been shaded on the map though there is no evidence of country-wide virus presence.
 © Pan American Health Organization - World Health Organization (WHO) 2015.
 All rights reserved. This map is intended for general representation of geography and to be used as an exploration tool. Not for alteration, reproduction, publishing or distribution outside of PAHO-WHO and member states, without permission. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of PAHO-WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Cases reported to PAHO to April 24 (week 16 2015)
50 countries/territories in the Americas

	Susp'd	Lab conf'd	Imprt'd	Deaths
US	0	11	2574	0
PR*	31,433	4349	31	21
All	1,367,343	30,580	3637	191