

Arboviral infections we are *thinking* about?



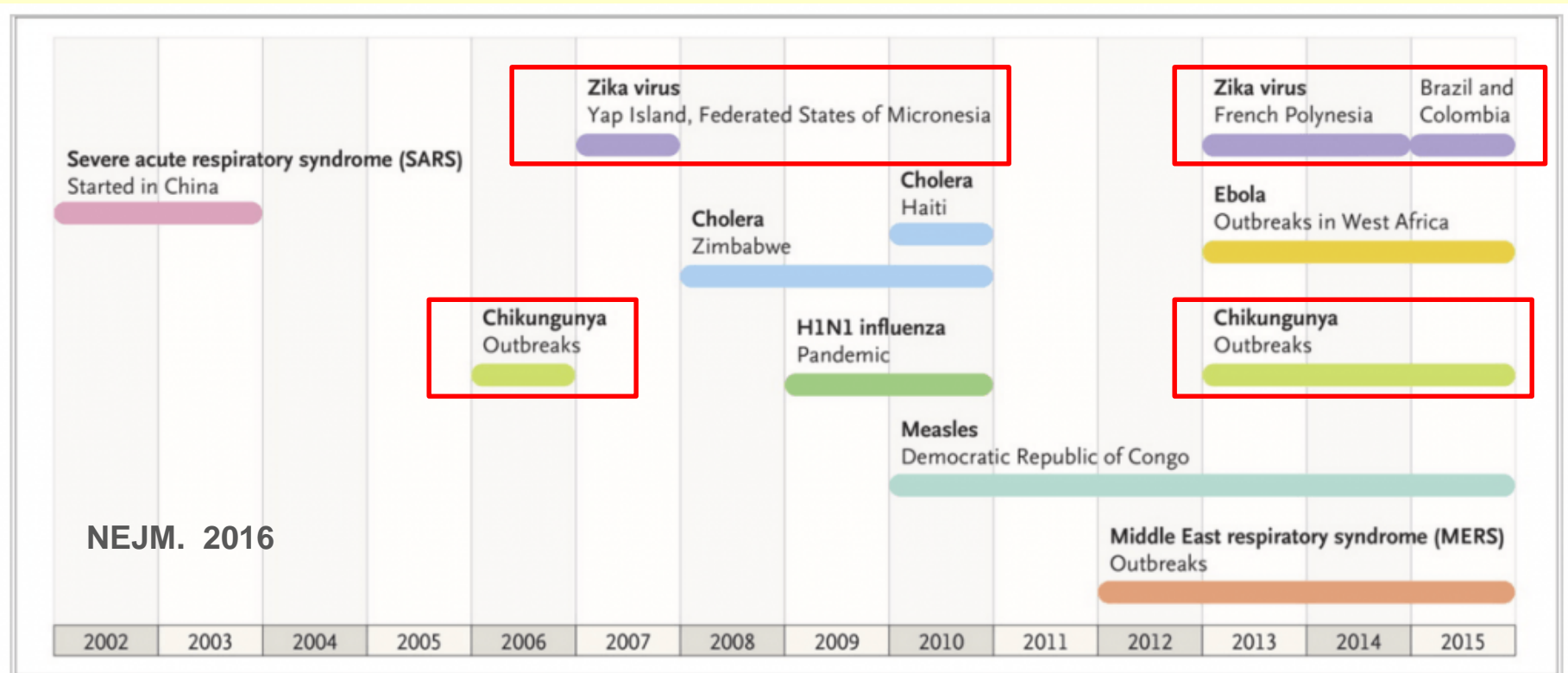
America's Blood
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Blood Centers of California
Sacramento CA
March 2016

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Adj. Clinical Professor, Infectious Diseases, Carver College of Medicine, UIHC, Iowa City

Emerging infections since 2002



Arboviruses *et al*

- Crowding
- Ecologic disturbances
- Travel
- Behavior



- Dengue
- WNV
- Chikungunya
- Zika

Who's on the "arbo" list?

(A.K.A. Full employment for Stramer, Busch, Kleinman et al)

Arboviruses

- Denguevirus
- Chikungunya
- Zika
- SLE
- Colo. Tick Fever
- Crimean-Congo HF
- EEE
- WEE
- JEV group (WNV)
- Lacrosse
- TBE (Powassan)
- SFTS
- Heartland Virus
- Bourbon Virus
- Ross River Virus

Rickettsia

- Anaplasma phagocytophilum
- Erichia ewingii
- *E. chaffeensis*
- *O. tsutsugamushi*
- *Rickettsia prowaseki*
- R. rickettsii

Bacteria

- *B. burgdorferi*
- Borrelia sp.
- T. pallidum
- *Y. pestis*
- *Brucella sp.*
- *Bartonella sp.*

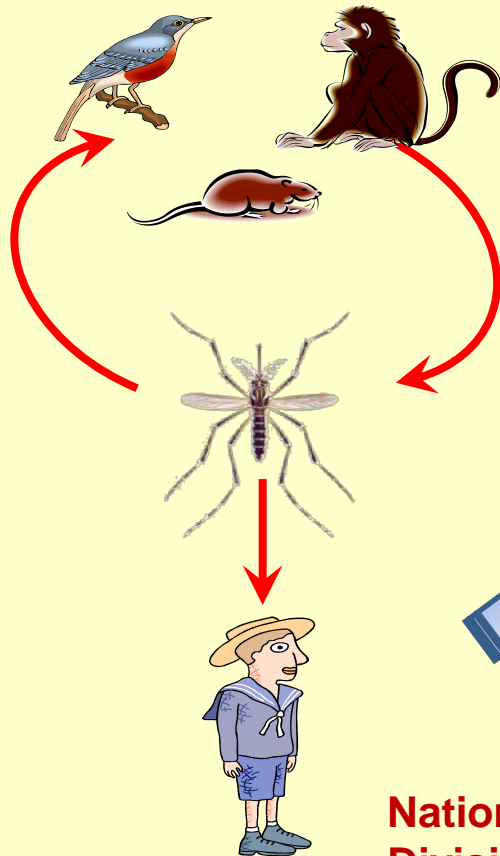
Protozoa

- Babesia sp.
- Leishmania sp.
- Malaria
- T. cruzi
- *T. brucei*

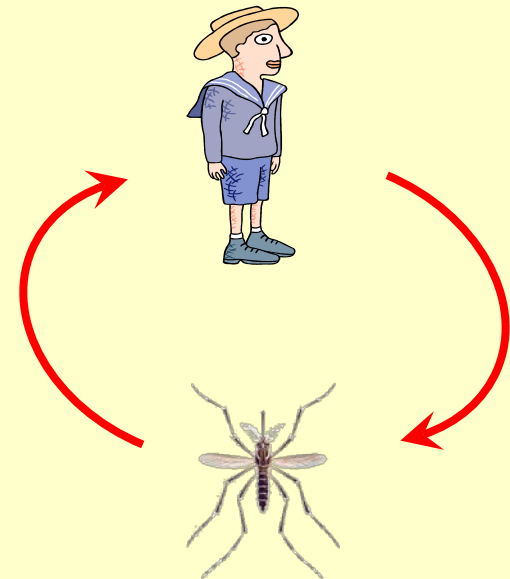
(Reasonably) documented to be TTIs.

Two basic patterns of *vector-borne* disease transmission

Humans: incidental hosts
e.g. WNV, Babesiosis




Humans: primary hosts
e.g. yellow fever, dengue, chikungunya, Zika



Prerequisites for a Transfusion-Transmitted Disease (TTD)

- Agent present in blood from healthy donors
- Infectious by parenteral route
- Causes clinically important morbidity by this route
- Survives modern blood processing and storage

Yay us! TT-WNV in US

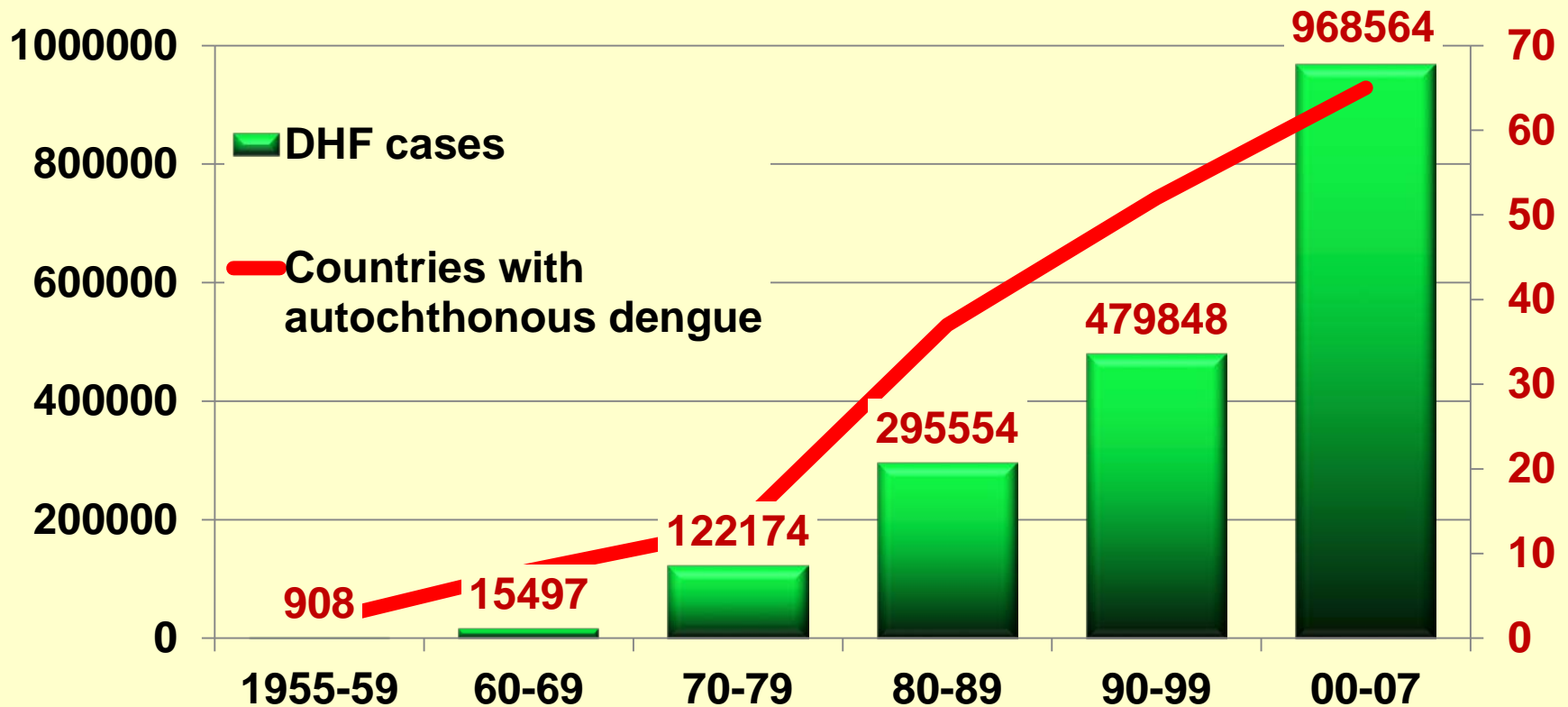
- Imported 1999 into “virgin” populations
- TTI suspected and recognized in US 2002
- Sx deferral then MP-NAT in <12 mo. (≈June 03)
- 23 transmissions 2002
- 2003 ff. evolution of MP  ID NAT conversion
- 2004-2014, 13 subsequent transmissions

Lessons learned

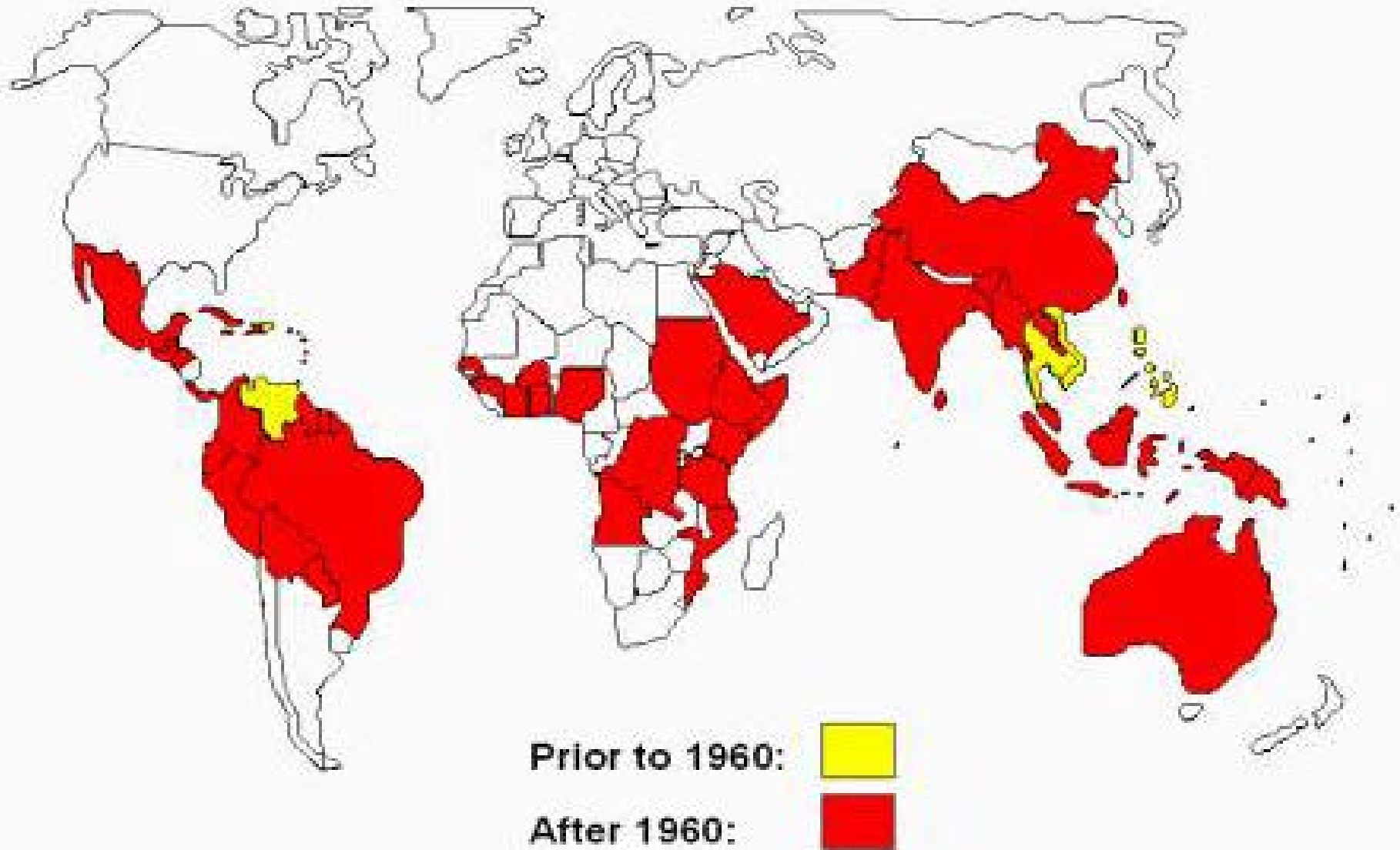
- Acute infections, including arboviruses, can be TTIs
- Importation unpredictable and can be overwhelming
- NAT is way faster than serology to implement
- Pooled NAT testing can be “insensitive” (duh!)

Denguevirus

- *Flavivirus* transmitted from *Aedes* mosquito to humans
- 4 serotypes: DENV-1, 2, 3, 4 (DHF/DSS = severe dengue)
- >2.5 billion at risk: most important human arbovirus
- Asymptomatic viremia and TTD documented



Dengue (re)emergence



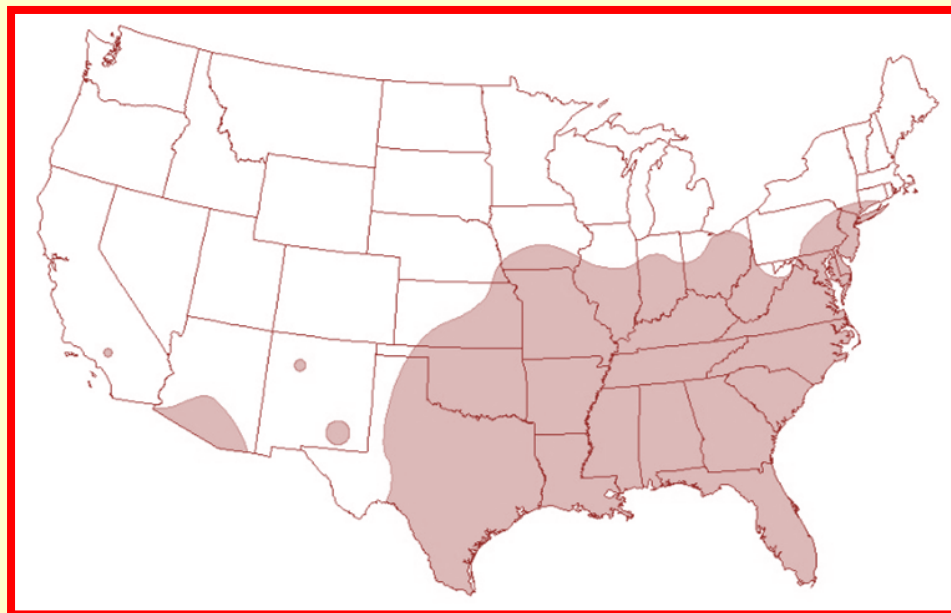
Aedes aegypti



Dengue vector distribution in the US



Aedes albopictus



If you've seen 1 season, you've seen 1 season: Dengue donor prevalence: Puerto Rico (ARC)

- **2005**
 - 12 RNA pos of 16521 tested
 - 1:1376 (0.073%)
- **2007**
 - 29 RNA positive of 15321 tested
 - 1:529 (0.19%)
- **2010-2012**
 - 2/53,451 confirmed NS-1 positive and 8/53,449 NS-1 negative/TMA positive
 - 1:5345 (.019%)

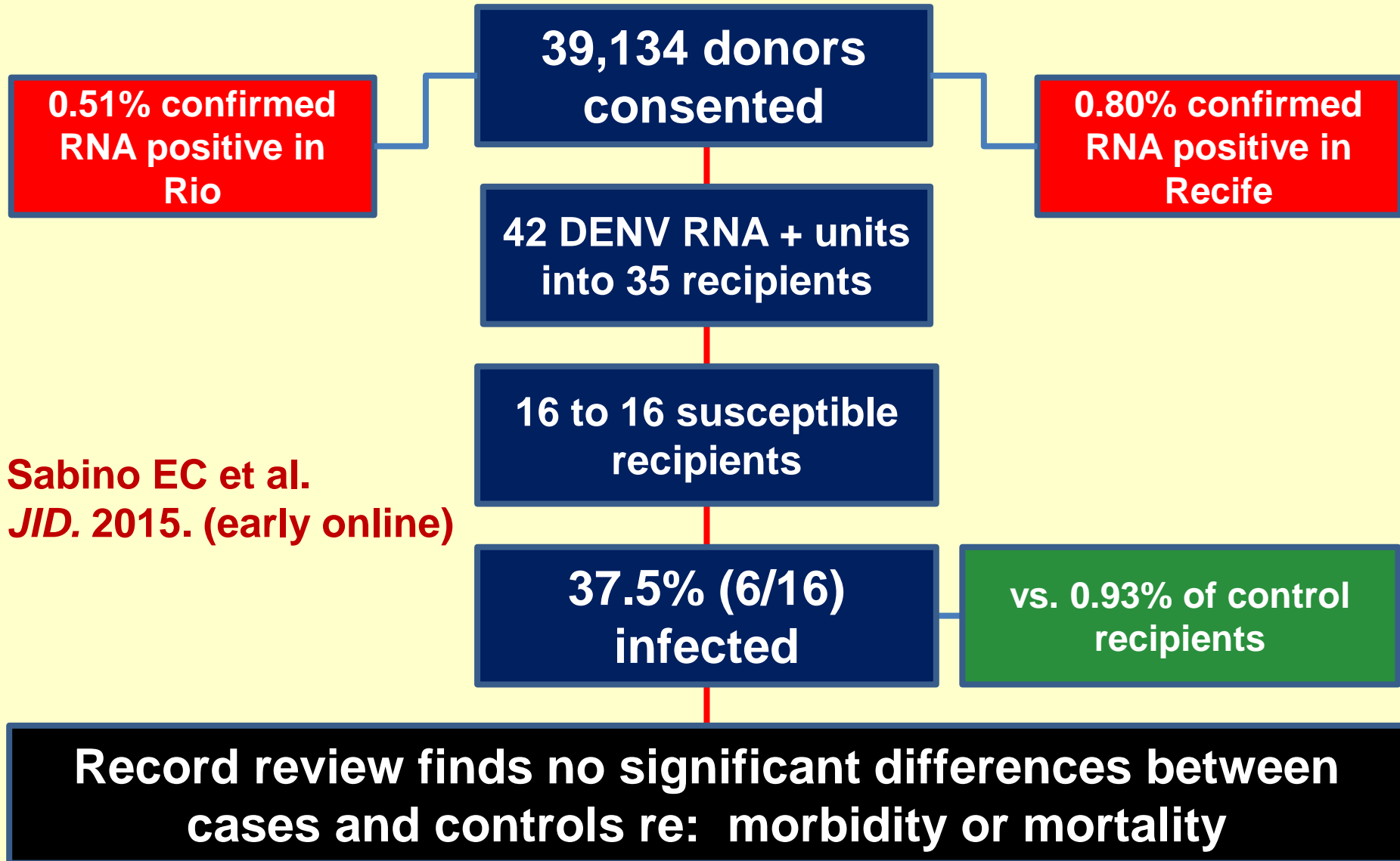
Dengue in US

- Epidemic in US decades ago
- Periodic outbreaks in FL, TX, HI
- Seroprevalence in Brownsville TX (EID 2004)
 - 2% with recent infection (IgM)
 - 40% with past (IgG)
- Key West—28 cases in 2010
- Big Island 2015-16—260 cases

TT-dengue: seven cases/clusters by yr.

- **Hong Kong, 2002: one case with PCR and serologic, no sequence confirmation**
- **Singapore, 2007: cluster of 3 cases from single donation, confirmed by envelope sequencing**
- **Puerto Rico, 2007: single case confirmed by envelope sequencing**
- **Brazil, 2012: viremic donors transmit to 6 recipients with minimal disease**
- **Puerto Rico, 2011-12: 2 (3?) transmissions from Ag negative/TMA positive donors**
- **Brazil, 2014: Single case from regular platelet donor without sequence comparison**
- **Singapore, 2014(?): single case with sequence identity with donor**

Dengue-4 in Brazilian donors: TT dengue: a sheep in wolf's clothing??



An aside: can we get what we need?

Letter from Oct 2009, re: developing a dengue NAT

- The significant funding required to support the manufacture, QA and validation of the prototype assay to support studies was recognized as an early barrier...
- ...failed to confirm the commercial viability of a dengue blood screening assay due to the lack of a regulatory framework, reimbursement and competing priorities for healthcare dollars...

Public health vs. business imperatives

Chikungunya 101

- Alphavirus from Africa to Indian Ocean & beyond
- *Aedes* mosquitos are the vector
- Incubation 3-7 days (range 1-12)
- Abrupt high fever, headache, back pain
- **Polyarthralgia:** hands, wrists, ankles, large joints less likely
- Maculopapular rash in half or more
- 7-10 days acute clinical course: but joint pain can persist or relapse for months or longer

Chikungunya 101 cont.

1. Up to 80% of patients *symptomatic*
2. Clinical diagnosis based on local epidemiology and prominent *arthralgias*
3. Virus isolation during first 3d. of illness
4. Viral RNA detectable during first 8d. of illness
5. IgM antibody at ≥ 5 d. of illness



Chikungunya in the Americas

Dec. 2013-Oct. 16, 2015

Total >1,700,000*

Confirmed 49,338

Deaths 257

***Autochthonous (confirmed, suspected) & imported.**

Source: PAHO

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 IR ARO

* Note: Entire countries have been shaded on the map though there is no evidence of country-wide virus presence. © Pan American Health Organization (PAHO) - 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. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

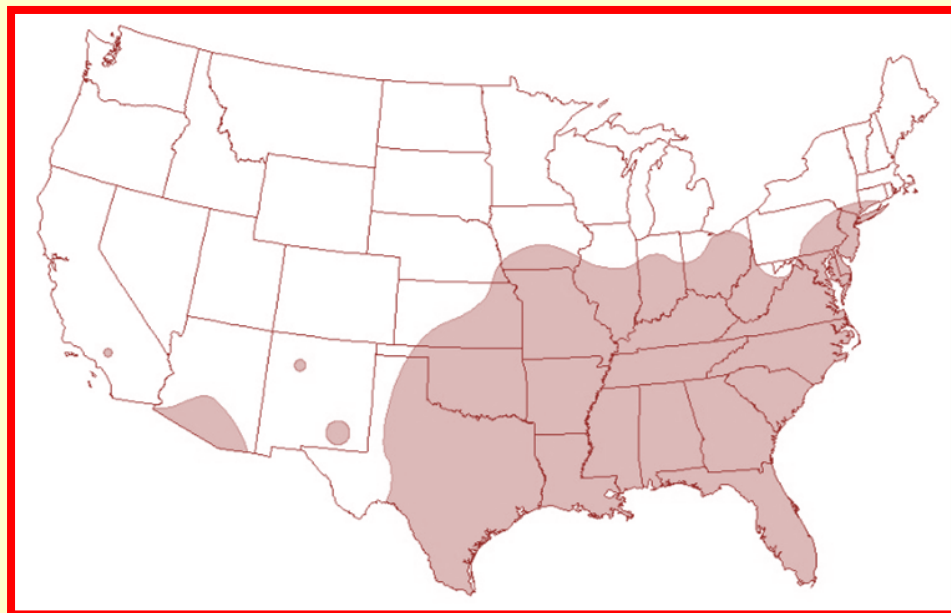
Aedes aegypti



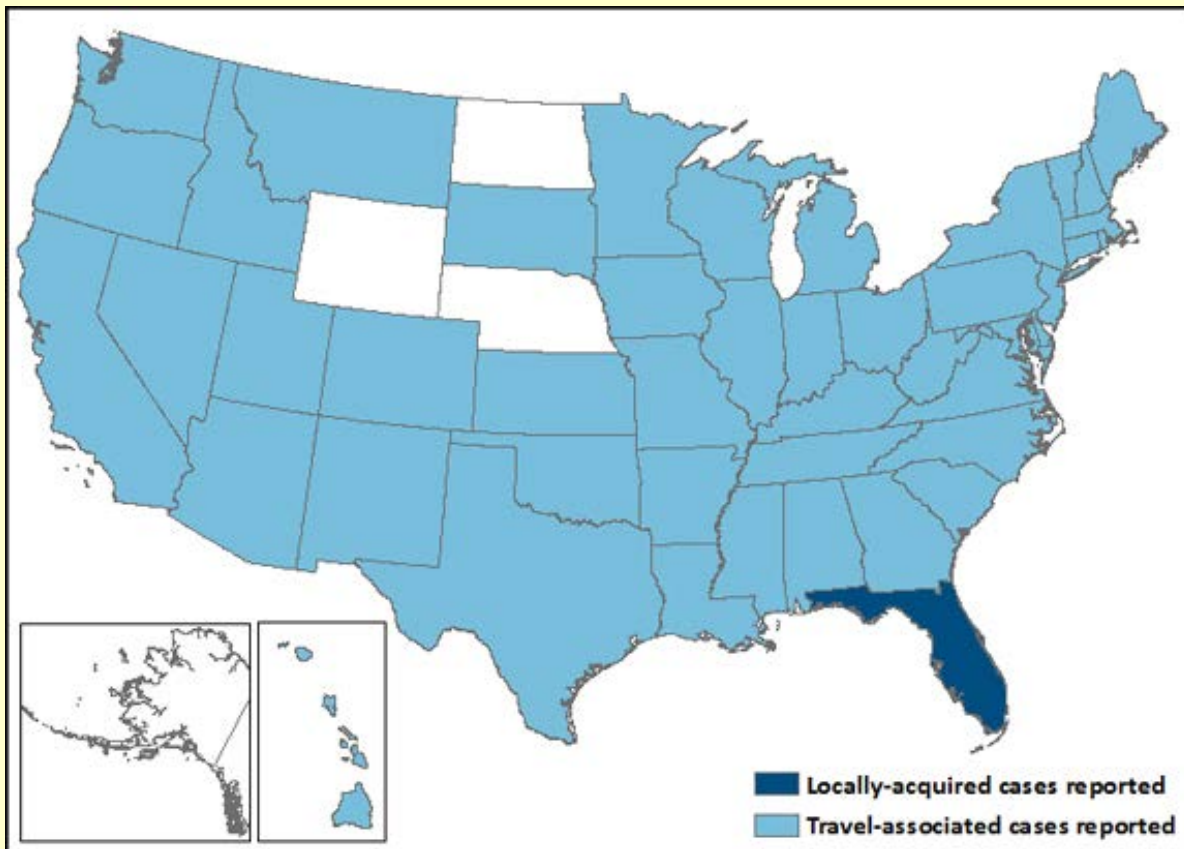
Chik vector Distribution in the US



Aedes albopictus



ChikV in the United States



States reporting chikungunya: US **2014**

- **2006-13**
 - 28 positive tests/yr (range 5-65)
 - All travelers
- **2014**
 - 2799 total cases
 - 46 states
 - ~1/2 in NY/NJ & FL
 - 14 local cases in FL
- **2015**
 - 679 total cases
 - 44 states
 - No local cases

Prerequisites for a TTD: ChikV

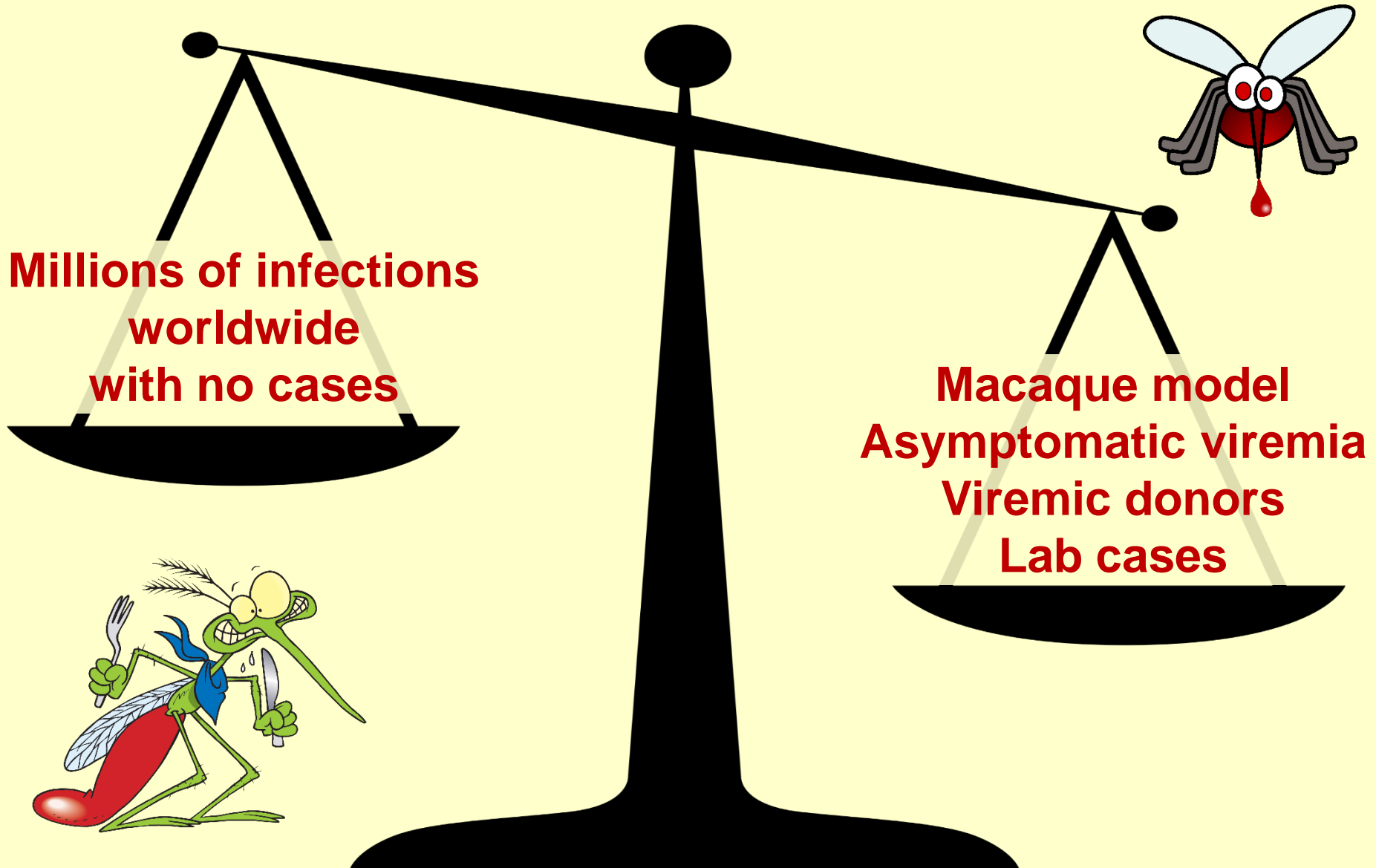
- **Presence of agent in blood of well donors**
 - ChikV symptomatic in ~80% of infections, c.f. Zika and WNV, but ~2d. viremia before symptoms
 - 4/2149 well donors PCR +: French West Indies 2014 (Gallian P et al. Blood. 2014.)
 - 3/557 well donors TMA +: Puerto Rico (ARC) 2014 (Chiu et al. EID. 2015)
- **Agent infectious by parenteral inoculation**
 - Lab accidents & macaque model (Labadie et al. JCI. 2010)
- **Survives modern blood processing and storage**
 - Limited understanding
- **Clinically recognizable morbidity by this route**
 - Limited understanding

Why haven't we seen ChikV TTIs?

- The “needle in the haystack” in large, explosive epidemics
- We haven't really looked
- How do you exclude vector-borne infection?
- “Asymptomatic” donors may not feel well and stay away
- Something different about mosquito-borne and parenteral infection?



Transfusion-transmitted ChikV?



Model results from 3 studies

Location	Incidence	Duration viremia (days)		Percent asymptomatic	Viremia prevalence/100,000 donations	
		Before symptoms	After symptoms		At epidemic peak	Mean
Thailand ¹	5.3%	1.5	8.0	10%	237.0	38.2
	Worst case	1.5	17.0	10%	267.1	52.3
Reunion ²	35%	1.5	6.0	15%	1500	132
No. Italy ³	0.03%	2.0	6.0	15%	1.05	N/A

¹Appassakij, *Transfusion*. 2014.

²Brouard, *Transfusion*. 2008.

³Liumbruno, *Blood Transfusion*. 2008. (Region wide modelling).

Est. peak weekly ChikV transfusion risk

Lyle Petersen, CDC/DVBD, for TTD 09-15-14

Assumptions: viremia 2d before symptoms, 15% of infections are asymptomatic and 100% transmission from viremic donor

Peak incidence/wk Peak risk/10⁵ donations

Palm Beach 1 case	0.0000007	0.03
Palm Beach 2 cases	0.0000015	0.06
Palm Beach 5 cases	0.0000037	0.16
Palm Beach 10 cases	0.0000074	0.32
Palm Beach 100 cases	0.0000737	3.21

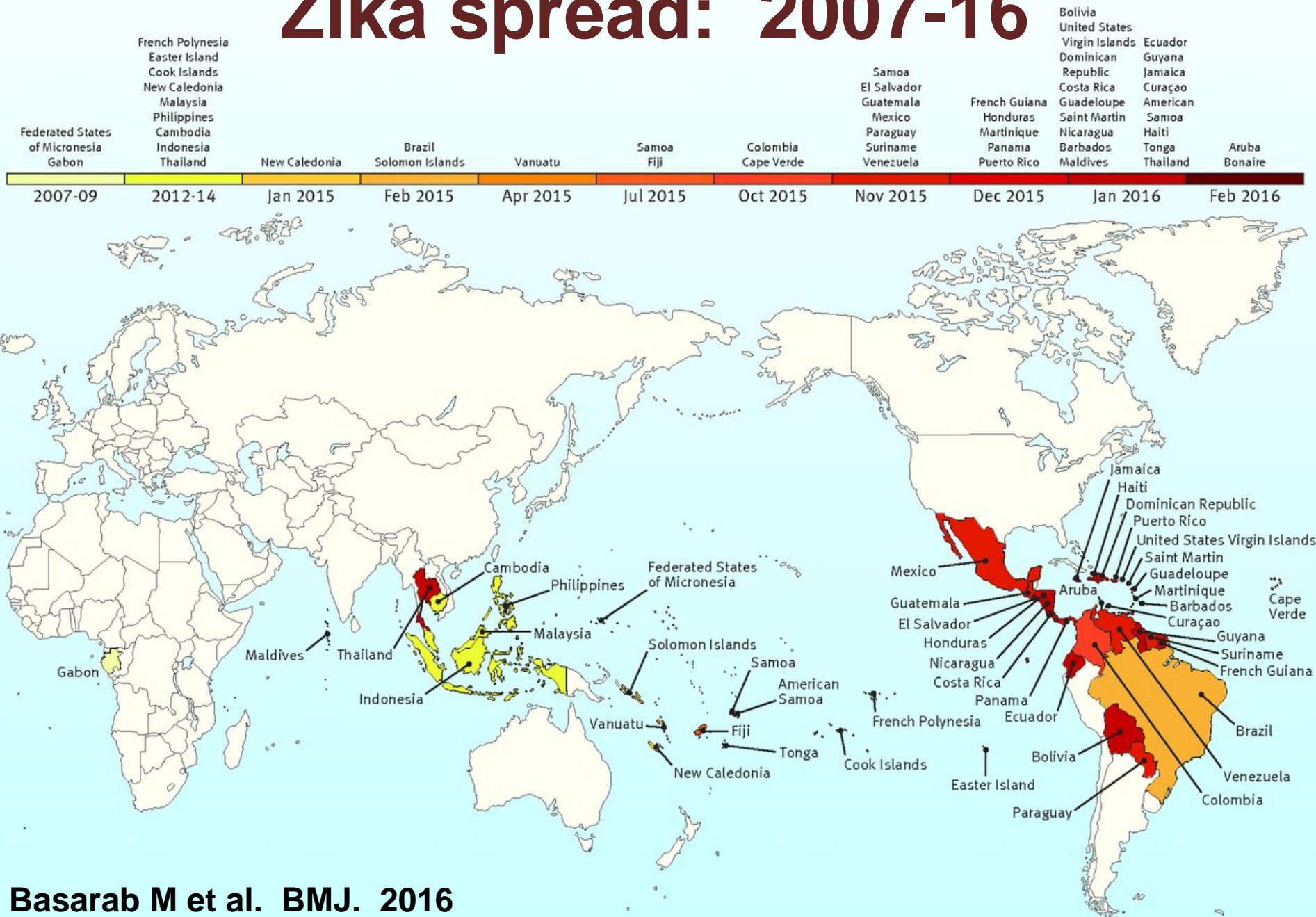
Zika: what it is

- Flavivirus from non-human primates during YF work in Uganda in 1949 (in the Ziika Forest). Related to dengue, YF, WNV, JEV
- Recognized as human pathogen in Africa in 1960s: trivial dengue-like syndrome
- Yap Island 2007 and the rest is “history on the fly”
 - $\approx 75\%$ attack rate
 - 80% of infections without symptoms
- Guillain-Barre in French Polynesia 2013-14
- Microcephaly et al, Americas 2015

Zika Virus: Yap Island 2007



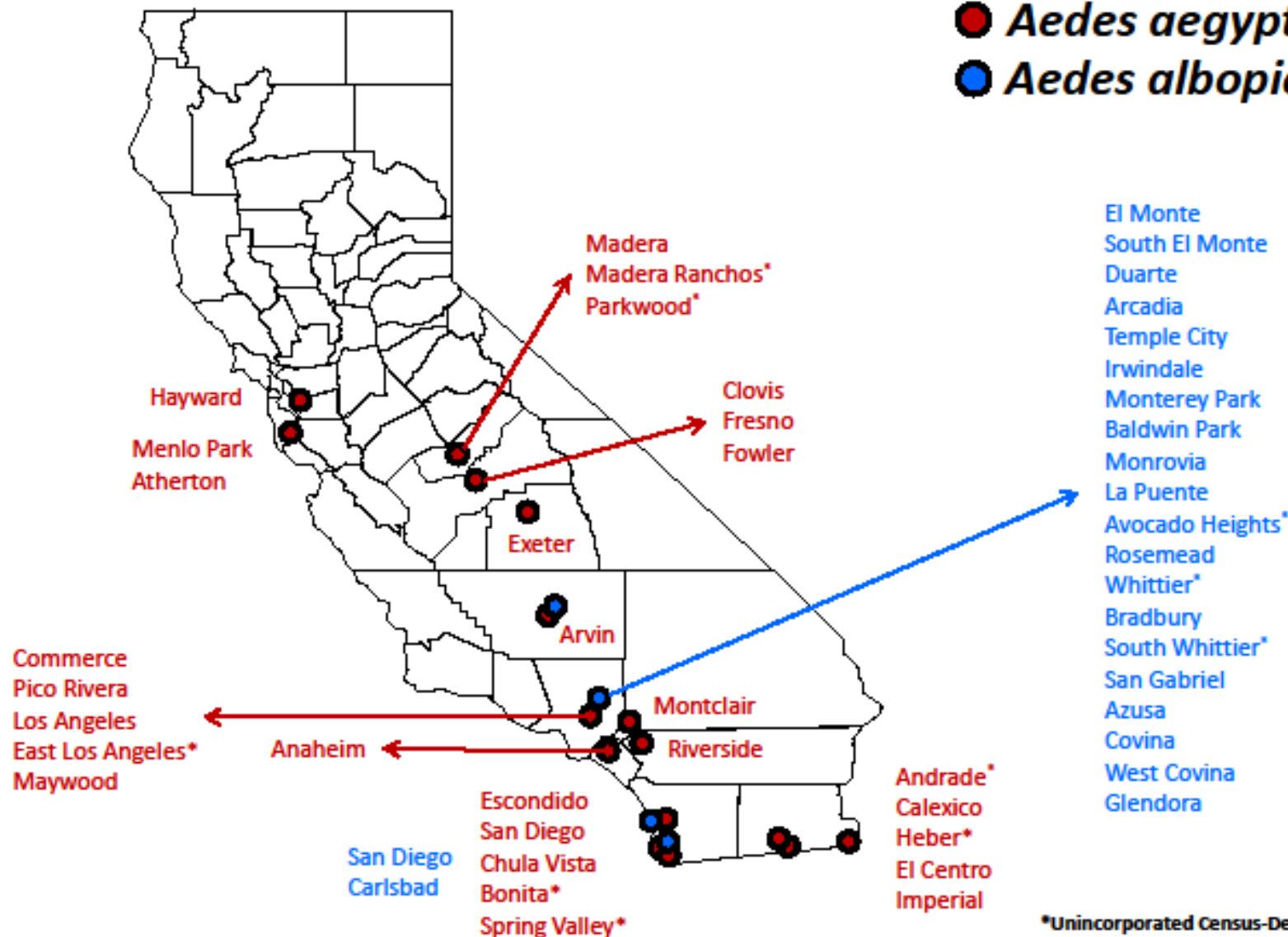
Zika spread: 2007-16



Aedes aegypti and *Aedes albopictus* Mosquitoes Detection Sites in California, 2011-2015

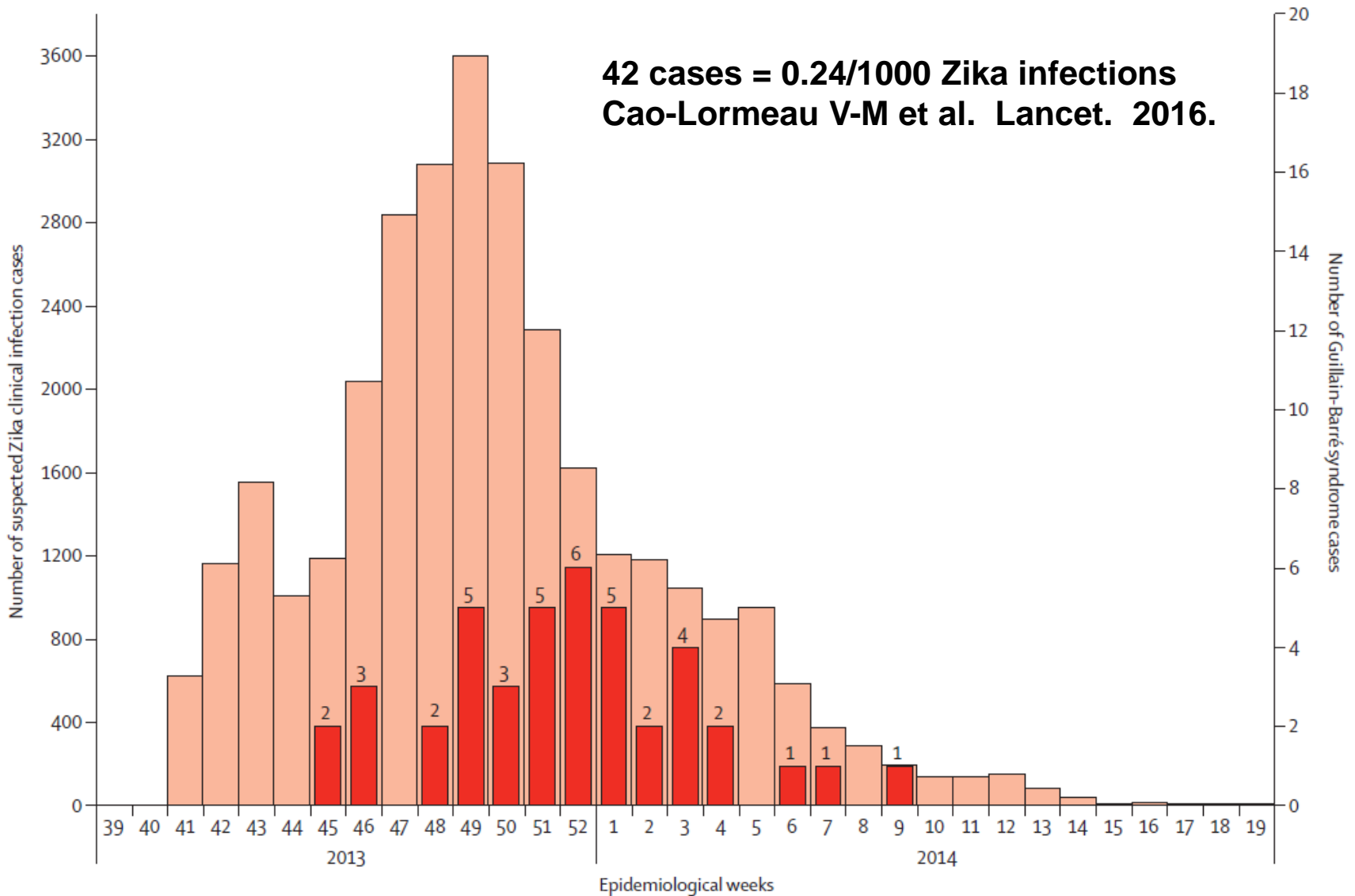
Updated October 6, 2015

- *Aedes aegypti*
- *Aedes albopictus*



*Unincorporated Census-Designated Places

Zika and GBS: French Polynesia



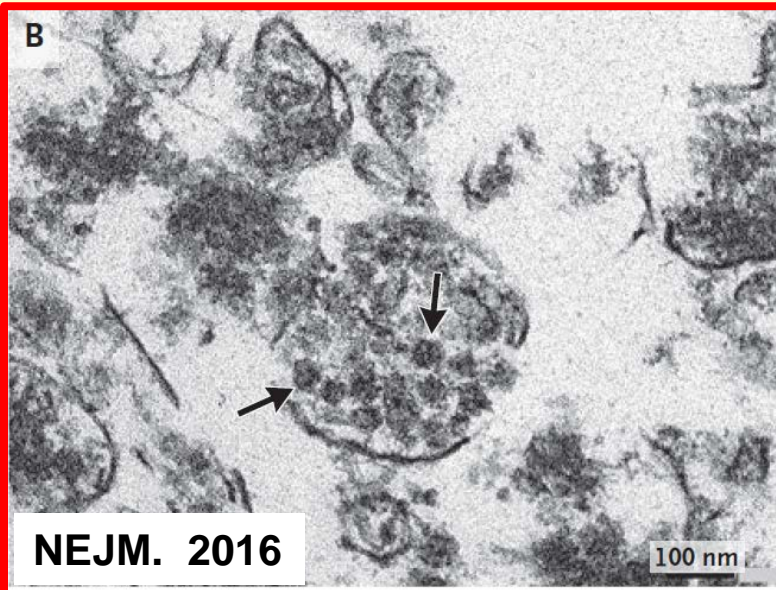
Have I gotten your attention?

“Association” of Zika infection with microcephaly: Brazil

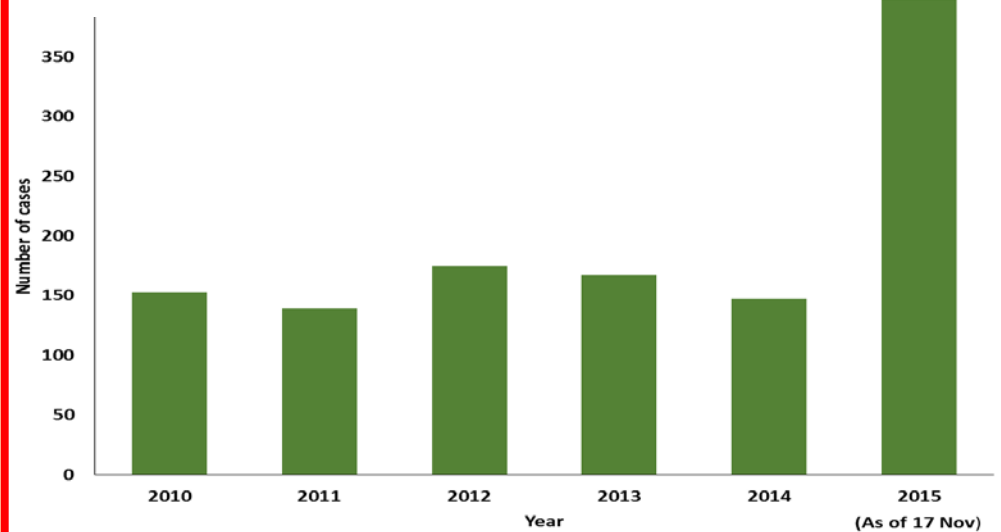
USA Today. 2016



B



ECDC. 2016



Arboviruses : what can/should we do

(absent universal, highly effective vaccines &/or....)

- **Travel-associated cases**

- Enhance PDI + quarantine

- **Defer for travel to epidemic foci**

- Testing

- Pathogen reduction

**First
assess
impact on
donor base**

- **Autochthonous transmission**

- Enhance PDI + quarantine

- **Suspend collections in “affected” areas**

- Testing

- Pathogen reduction (platelets+plasma)

Travel deferrals?

- **Simple**
- **React with moderation to existing threats**
- **Proactive against new acute infections in the future**
- **Impact not “great”, and can be reduced substantially by staging donor education and deferral implementation over a year or so.**
- **Katz “votes” yes**

Travel surveys to assess non-malaria travel

	Summer	Winter
Blood Centers	ARC & ABC	ARC & ABC
	Fixed sites	Fixed sites and mobiles
Distribution*	Paper, at canteen	Web-based
Content	Americas & Caribbean, country-level detail	Global, macro-regional detail
Dates of administration	Aug – Sept 2014	March 2015
Languages	English & Spanish	English only
N responses	33,408	19,879

*Only successful donors were invited to allow assessment of the marginal impact of temporary travel deferrals

What's the worst that could happen?

combined results, summer & winter surveys

Percent donor "loss" with alternate deferral approaches*

	Summer-14d	Summer-28d	Winter-14d	Winter-28d
Mexico	0.19%	0.52%	0.40%	0.92%
Caribbean	0.16	0.48	0.48	1.16
C. America	0.02	0.06	0.13	0.26
S. America	0.03	0.07	0.07	0.20
Total "Americas"	0.39	1.17	0.96	2.23
Total ex-US & Canada	NA	2.64	1.35	4.02

*Rows 1-4 may not sum to row 5 due to incomplete reporting of travel destination and travel to multiple places.

Interventions for dengue/chik (now Zika)

- **Puerto Rico: local and ARC collections**

- Donor query re: symptoms/exposure in “neighborhood”
 - Passive PDI for symptoms: RBC
 - Call platelet donors, discard if not reached
 - PR for apheresis platelets (*all the ARC collects there*)
- Local banks

- **US: OneBlood during 2014***

- One donor deferred based on the additional donor question
- No units discarded as a result of donor call backs
- No detectable impact on the blood supply

*Leparc and Reik. S27-020B. AABB. 2015.

AB-16-03

- **Self-deferral for travel/residence in the Americas outside of the US and Canada for 28 days**
- **Post-donation information x 14 days with ≥ 2 compatible symptoms from those who failed to self-defer**
 - **Recall untransfused product**
 - **Confirmed Zika, Dengue, Chikungunya recall any in date product collected in the 14 days before onset and defer for 28 days after well**
- **Did not address local transmission**
- **Did not address sexual transmission**

FDA (final) Guidance

Areas without local transmission

- Update educational materials to facilitate self-deferral of symptomatic donors for 4 weeks after recovery
- Formal 28 day deferral for travel/residence to areas with local Zika transmission per CDC website
- 28 day deferral after recovery for dx or symptoms of Zika arising within 2 weeks of departure from Zika area
- Self-deferral for 4 weeks after sex with a male diagnosed with or who traveled or resided in an area with active Zika in 3 months before the sexual contact
- Instruct donors with recent travel or residence re: PDI for diagnosis or symptoms of Zika for donors within 2 weeks of donation

FDA (final) Guidance

Areas with local transmission (*undefined for the purposes of blood collection*)

- Get blood from areas without local transmission unless...
 - PRT (licensed or IND—platelets and plasma only)
 - Tested with licensed donor screening assay (licensed or IDE)

...If still collecting using PRT or test

- Donor ed. materials to instruct on signs and sx of Zika and self-deferral for 28 days after well
- 28 day deferral for sex with male with dx or sx of Zika in 3 months before sexual contact
- PDI for dx, signs or sx within 2 weeks after donation

FDA (final) Guidance

PDI and product management

- **Products from donors who should have been deferred or with dx, signs or sx within 2 weeks:**
 - **Quarantine and destroy undistributed products**
 - **Notify transfusion service to quarantine and destroy distributed, untransfused products**
 - **Notify physician for transfused products to monitor patient for Zika infection**



...and Zika virus

- 1. Probable non–vector-borne transmission of Zika virus, Colorado, USA. Foy et al. EID. 2011.**
- 2. Potential sexual transmission of Zika virus. Musso et al. EID. 2013**
- 3. Detection of Zika virus in urine. Gourinat et al. EID. 2015.**
- 4. Detection of Zika virus in semen. Atkinson et al. EID. 2016. (RNA, not infectious virus, at *62 days*)**
- 5. Multiple cases under investigation at CDC.**

Suggested to FDA

13 yrs. of WNV testing, evolving effective measures

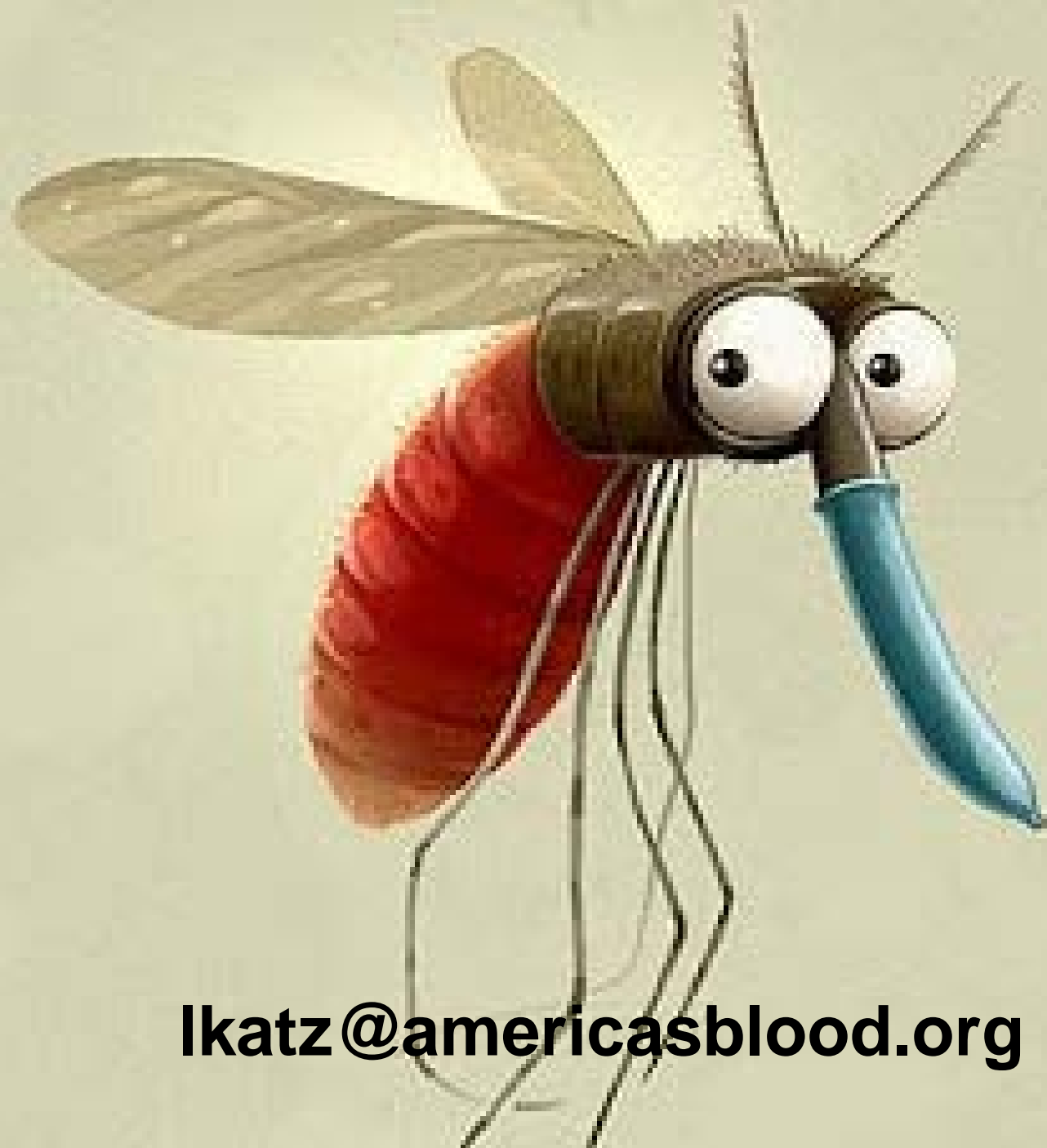
- **Centers with state/local public health officials**
- **Data-triggered minipool to ID testing switching**
 - **23 transmissions before testing**
 - **15 transmissions since 2003**
 - **No transmissions since 2014**
- **Collectors & public health can determine & respond to risk,**
- **Have done largely at residential zip code level.**

This is paradigm that should be applied now

Log₁₀ reductions of emerging pathogens

Pathogen	Inactivation In PC (log ₁₀)
West Nile virus	>6.0
Chikungunya virus	>6.4
H1N1 influenza virus	>4.1
H5N1 influenza virus	>5.9
Dengue viruses	>5.0
Zika virus	>6.0* (FFP only)
SARS-HCoV	>6.3
Parvovirus B19	4 to ≥5.5
<i>Trypanosoma cruzi</i>	>5.3
<i>Babesia microti</i>	>5.3

*Tissue culture infectivity abolished (>6.0 log₁₀)



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