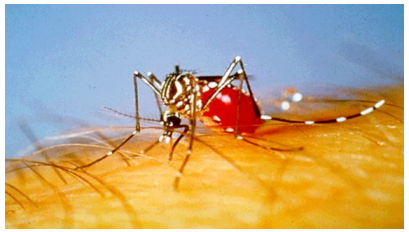
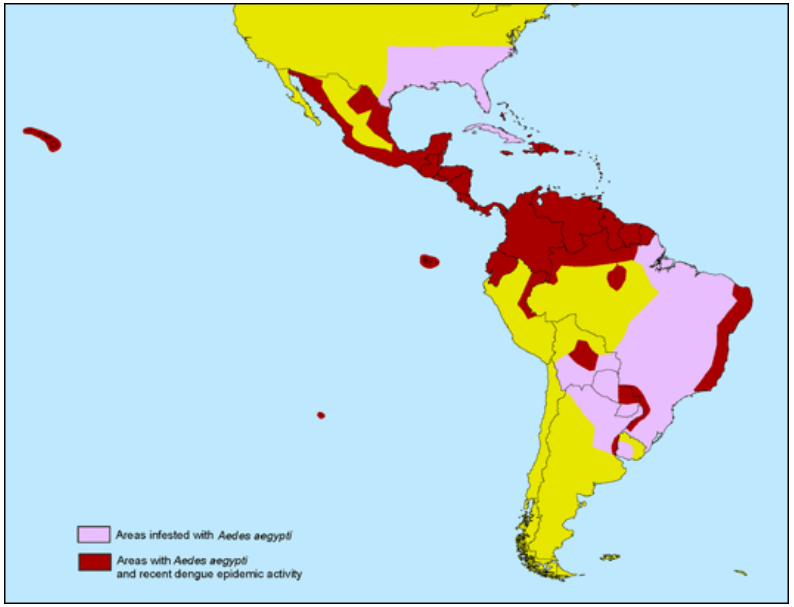
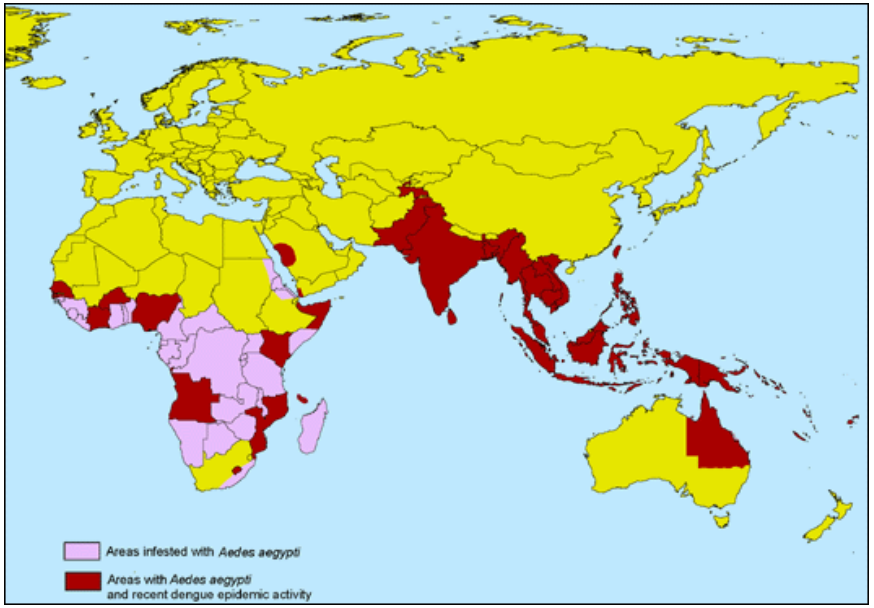
Dengue Virus

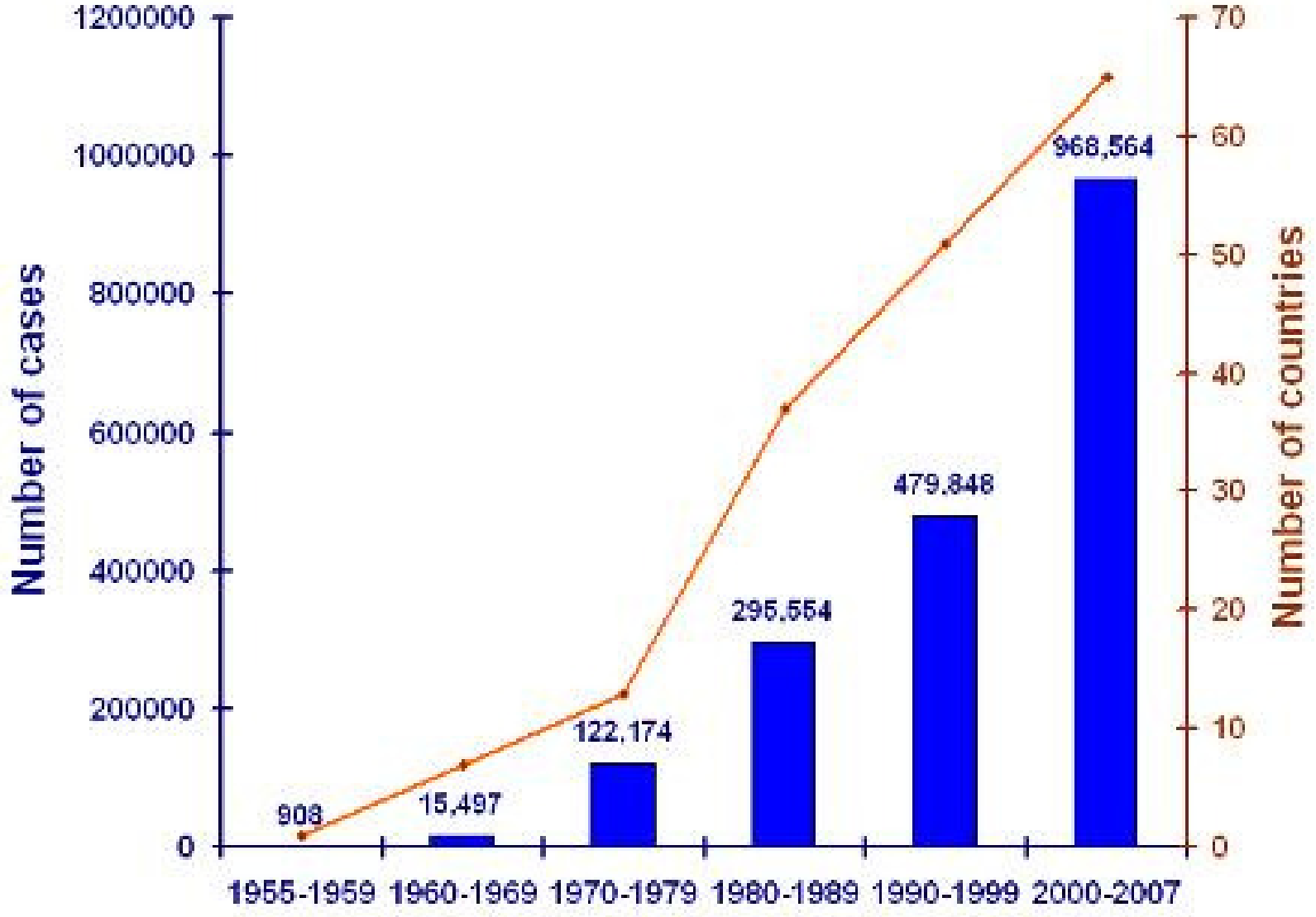


- Member of the genus *Flavivirus*
- Transmitted by the *Aedes* mosquito; mosquito => human cycle
- 4 serotypes: DENV-1, -2, -3, and -4
  - Homotypic immunity is long lasting
  - Heterotypic immunity is short lived
- Over 2.5 billion people live in risk areas for dengue infection (2/5ths of the world's population) and the epidemic appears to be expanding; most important arboviral disease of humans





Dengue Fever & Dengue Hemorrhagic Fever
Annual Reports to WHO



Dengue – Clinical Spectrum

- Asymptomatic dengue
  - 53-87% of all infections*
- Symptomatic dengue
  - 50-100 million cases worldwide annually
    - 500,000 cases require hospitalization
    - 90% pediatrics; leading cause of childhood death in >8 SE Asian countries
  - Undifferentiated fever
  - Classic dengue fever (“breakbone fever”)
  - Dengue hemorrhagic fever
  - Dengue shock syndrome
  - 25,000 fatalities annually
    - fatality rate ranges from 10-20% to 0.2% depending staff experience

*Rodriguez L *et al.* Am J Trop Med Hyg 1995, 52(6):496; Endy TP *et al.* Am J Epid 2002,156:40, Burke DS *et al.* Am J Trop Med Hyg 1988; 38:172

General Issues

- Good example of an infection that is under study as a potential transfusion risk
- Potential for importation of dengue RNA-positive blood components from endemic areas (e.g., PR)
  - Overlap of most dengue-endemic areas with malaria-endemic areas
- Potential for infected travelers with asymptomatic viremia to donate in the US
- Competent vector present in many areas of the US
- Evidence of transfusion transmission
  - 2 clusters reported (HK and Singapore)
  - 1 suspect BMT (PR)
  - 1 kidney transplant
  - 6 needlestick transmissions
- Donor viremia demonstrated during outbreaks in Puerto Rico (Caribbean), Brazil, Honduras

Transfusion-Transmitted Dengue

- Singapore (NEJM 2008;359)
  - Donor symptomatic one day after donation
  - Two recipients developed dengue-related illness
  - Third recipient asymptomatic but had IgM antibodies
  - Sera from donor and two symptomatic recipients positive for DENV-2 RNA
- Hong Kong (ProMed: Oct 11, 2002)
  - Donor symptomatic one day after donation
  - One recipient developed dengue-related illness
- Why is transfusion-transmitted dengue not more commonly reported?
  - Few studies taking the effort to document transfusion transmission against a background of dengue in endemic countries where mosquito transmission greatly exceeds any potential transfusion transmission

Dengue
Transmission by Transfusion

Hong Kong

Donor: 17 Y.O. Male

Next Day: Skin Rash

RBC Recipient: 76 Y.O. Female

Anemia (B12 Deficiency)

Fever (No Headache, etc)

IgM Seroconversion

Full Recovery

Unit: DENV-1 Positive

Chuang et al (2008) Review of dengue fever cases in Hong Kong during 1998 to 2005. Hong Kong Med J;14:170-177.

Singapore

Donor: 52 Y.O. Male

Next Day: Fever

RBC & Plasma Recipients: 64 Y.O. & 72 Y.O. Males

Fever, Pleural Effusion

PCR Positive for DENV-2

Recovery To Good Health

IgM Seroconversion (RBC)

Unit: DENV-2 Positive

Tambyah et al (2008) Dengue hemorrhagic fever transmitted by blood transfusion. N Engl J Med;359:1526-1527.

Table 1. Characteristics of the Donor and Recipients.

Patient	Age	Sex	Coexisting Conditions	Symptoms of Dengue Fever	Signs of Capillary Leak	Results of Serologic Testing	Findings on PCR Assay*	Outcome
	yr							
Donor	52	M	None	Fever and myalgia after donation (not hospitalized)	None	Not done	Dengue virus type 2	Full recovery
Recipient of fresh-frozen plasma	64	M	Diabetes mellitus, hypertension, ischemic heart disease, recent coronary-artery bypass graft, chronic renal impairment	Day 2 after transfusion (hospital day 12): fever, jaundice, malaise, and worsening thrombocytopenia	Worsening of bilateral pleural effusions	Seroconversion (on July 19, negative for IgG and IgM; on July 31, positive for both)	Dengue virus type 2	Discharged in good health
Recipient of packed red cells	72	M	Diabetes mellitus, hypertension, ischemic heart disease, peptic ulcer disease	Day 2 after transfusion (hospital day 6): fever, myalgia, malaise	Small right pleural effusion	IgG-positive on follow-up	Dengue virus type 2	Discharged in good health
Recipient of platelets	74	M	Hepatocellular carcinoma	None	None	Positive for both IgG and IgM on follow-up	Not done	Discharged in good health

* PCR denotes polymerase chain reaction.

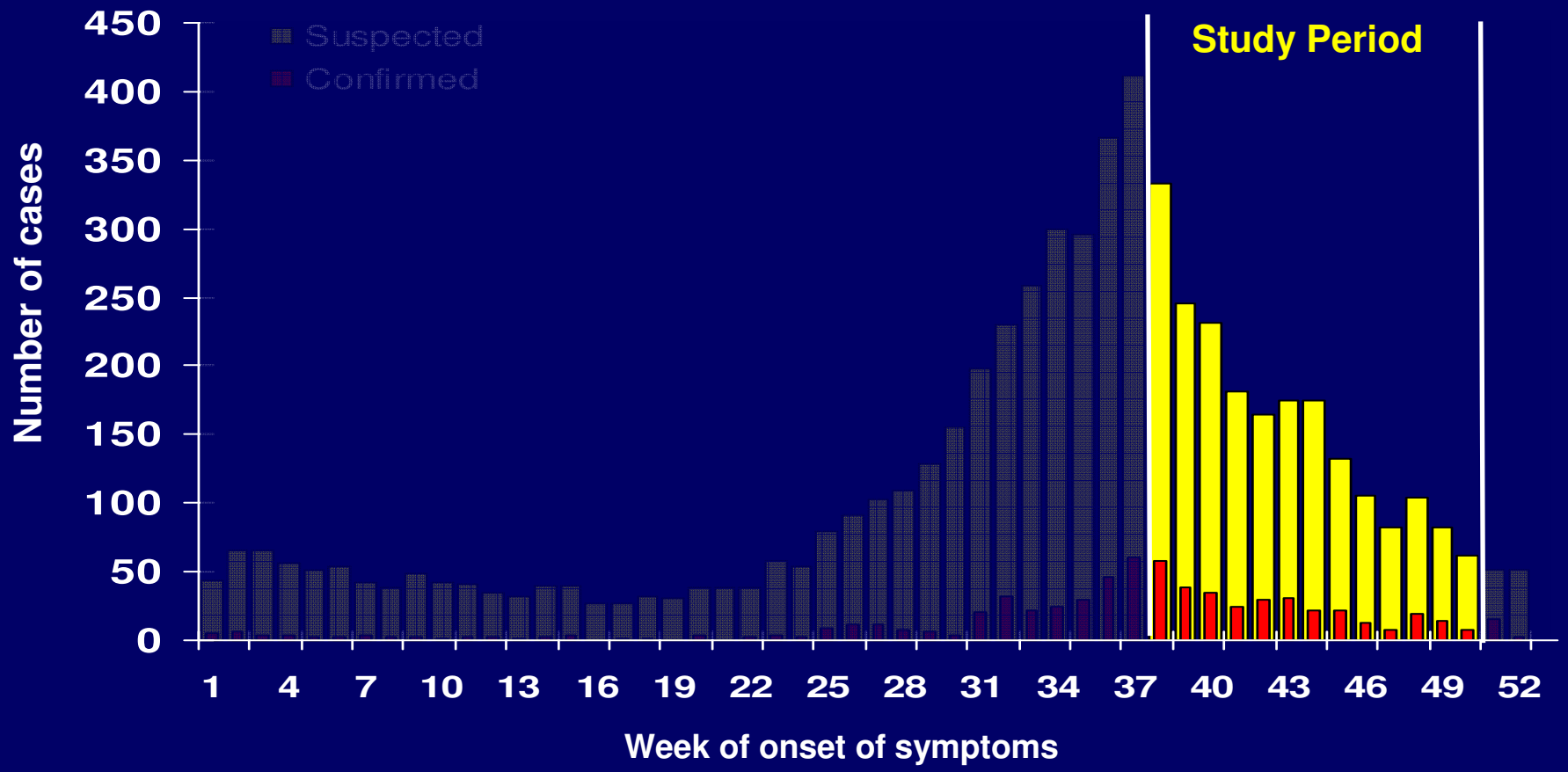
2005 Dengue Season in PR and ARC Studies; and, BSRI Studies

Donations Tested (at Gen-Probe using TMA)

- **Honduras** (Dr. Elizabeth Vinelli):
  - 9 positives of 2994 (0.37%) plasma specimens tested
    - Tegucigalpa region from August 31, 2004-January 24, 2005
    - San Pedro Sula region from September 6, 2004-January 13, 2005
- **Brazil** (Dr. Ester Sabino):
  - 3 positives of 4858 (0.06%) archived plasma specimens
    - From a dengue outbreak in the Sao Paulo area February 2003-April 2003
- **Australia** (Dr. Catherine Hyland):
  - 0 positives of 5879 archived plasma specimens from the ARCBS
    - from Townesville, Cairns and Brisbane
- **Puerto Rico** (Dr. Susan Stramer):
  - 12 positives of 16,521 (0.07%) archived plasma specimens from the ARC
    - Donations collected September 20 – December 4, 2005 (during period of increased dengue transmission in Puerto Rico)
- All 4 serotypes detected by TMA; viral detection in presence of Ab; some of which yielded infectious virus in cultured cells/mosquitoes
- Results published in Transfusion 2008;48

ARC PR Study Period

- Testing performed on all blood donations made between:
  - 20 September – 4 December, 2005



Supplementary Testing of TMA-Positive Samples

	NAT Test Gen-Probe (S/CO)[1]			Supplementary Testing CDC-Dengue Branch				
#	Initial test	2nd Test	1:16	PCR	# vRNA/mL	Live virus recovered	IgM	IgG
1	31.96	26.99	27.73	+ (D2)	$7x10^3$	+ (D2)	-	-
2	30.31	31.28	28.78	+ (D3)	$8x10^7$	+ (D3)	-	+
3	29.22	27.86	27.12	+ (D2)	$8x10^5$	+ (D2)	-	+
4	29.17	24.84	22.92	+ (D2)	$2x10^3$	-	-	-
5	23.89	20.59	8.54	-	-	-	-	+
6	21.22	5.28	0.21	-	-	-	+	+/-
7	17.78	23.10	0.15	-	-	-	-	+
8	17.41	18.44	0.31	-	-	-	-	-
9	17.24	21.05	0.33	-	-	-	-	+
10	5.97	7.73	0.15	-	-	-	-	+
11	4.08	4.15	0.13	-	-	-	-	+
12	1.53	5.56	0.60	-	-	-	-	+

>1.00 = positive result

D2 = DENV-2
D3 = DENV-3

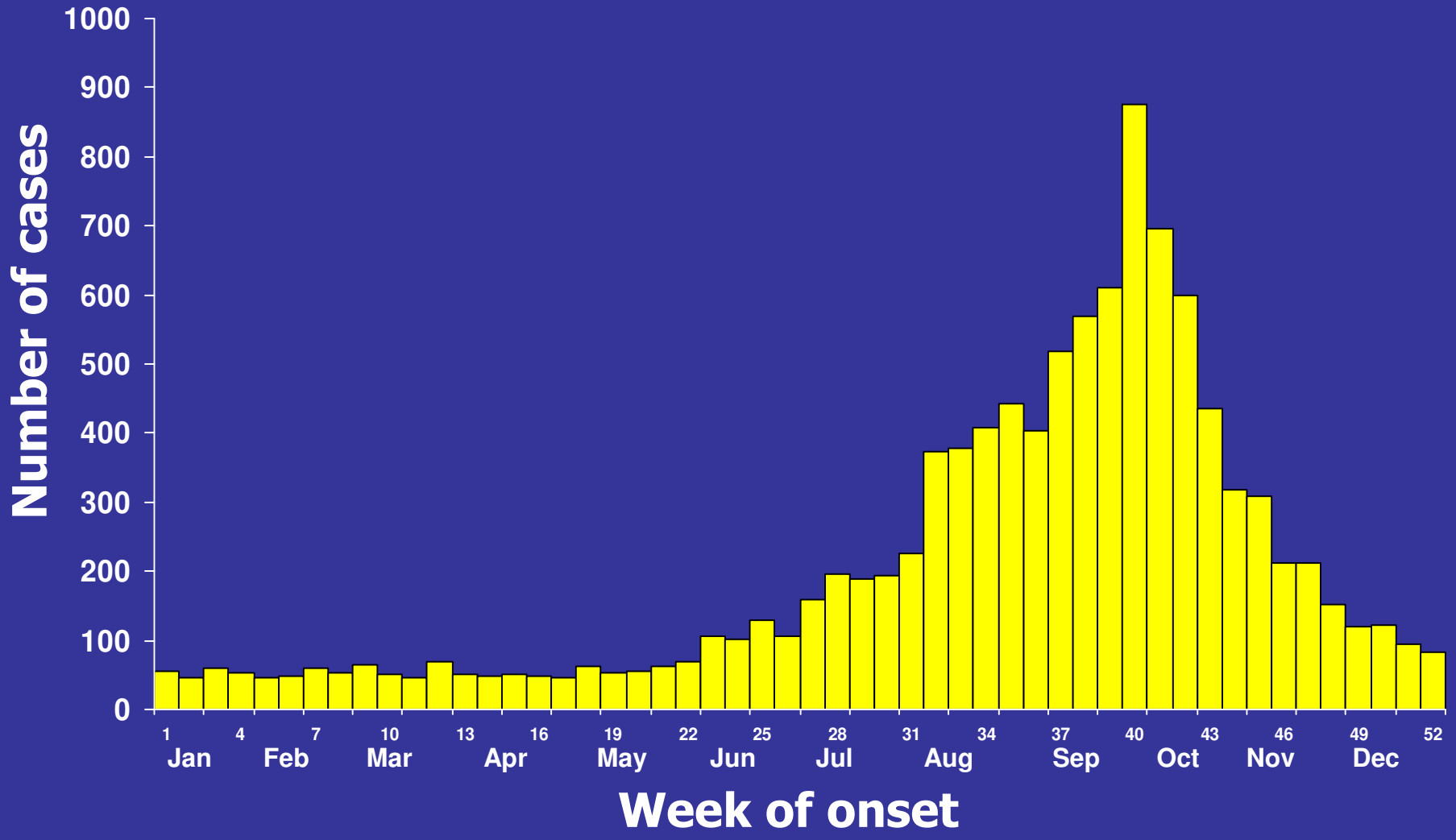
D2 = DENV-2
D3 = DENV-3

LEGEND:
1 – Signal/Cut-Off
+ = positive, - = negative

(N = 16,521)

2007 Dengue Season in PR and ARC Studies

Number of reported cases of suspected dengue by week in Puerto Rico, 2007



Summary of 2007 PR Donations

Month, 2007	Total Collections	Samples at SSO	RBCs transfused in the US corresponding to SSO samples
June	5967	425	47
July	4156	1120	131
August	6923	5624	1007
September	6581	4694	1222
October	8588	6630	1878
November	6662	5136	1130
December	5491	4598	985
TOTAL	44,368	28,227	6400

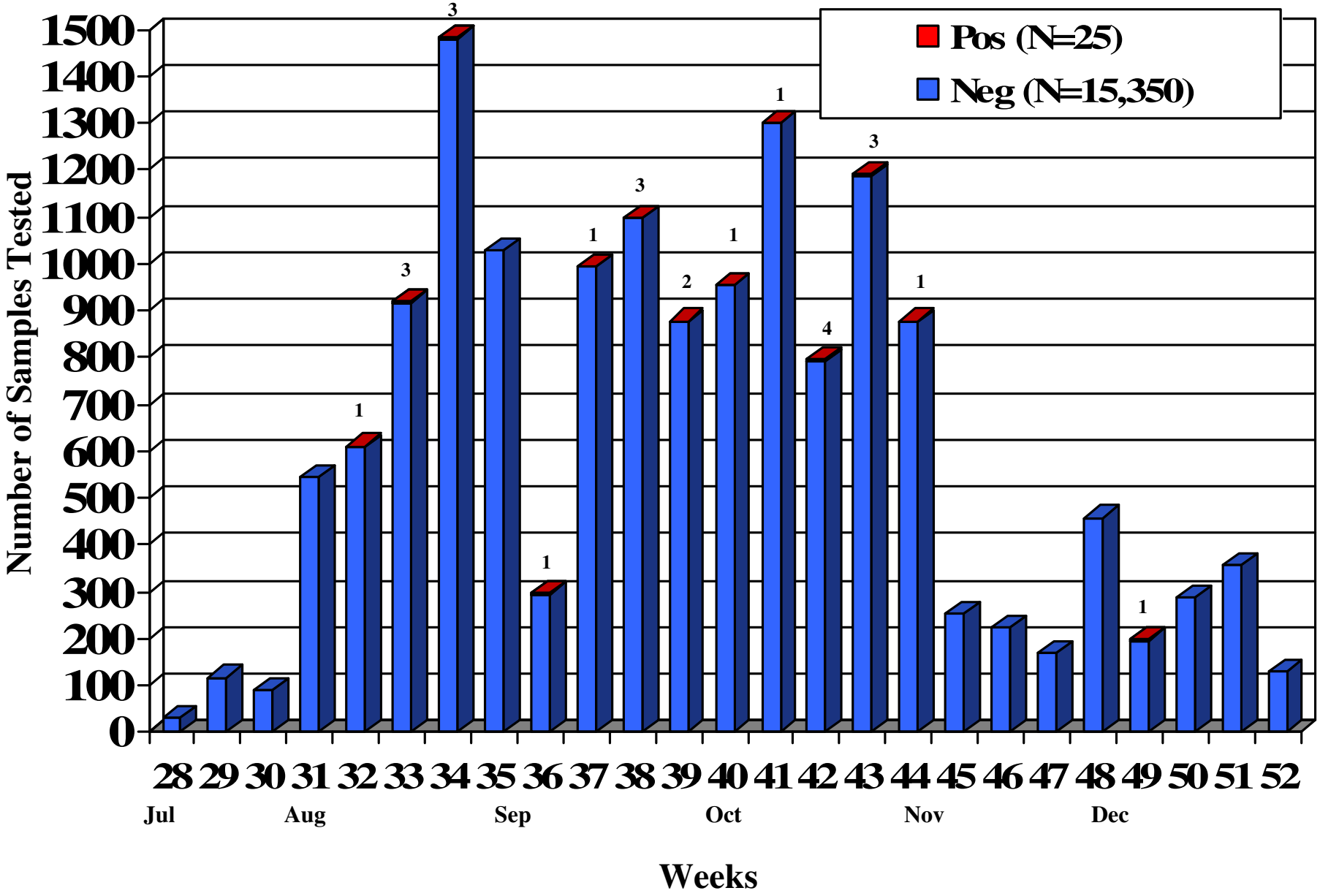
Dengue Viremic Blood Donors in PR 2007
Units Transfused in the US

#	Viral Load copies/mL	Initial	1st Re-test	1:16 Pool	CDC Testing			
		S/CO 1	S/CO 2	S/CO	RT-PCR	CT	C636	IgM
1	3.5 x 10^5	31.25	33.56	27.75	DENV-3	39.4	Pos	Neg
2	1.18 x 10^7	32.73	35.03	34.99	DENV-3	28.51	Pos	Neg
3		2.95	25.28	0.03			Neg	Pos
4		8.2	1.4	0.13			Neg	Neg
5	2.82 x 10^6	19.14	13.94	0.21	DENV-2	37.89	Pos	Pos
6	7.67 x 10^6	33.91	32.87	33.89	DENV-3	29.20	Pos	Neg
7		8.17	16.58	0.03			Neg	Neg
8		11.51	5.63	0.04			Neg	Neg
9		6.64	8.91	0.2			Neg	Pos
10		3.37	4.95	0.83			Neg	Pos
11	5.08 x 10^8	32.34	33.3	31.14	DENV-2	28.13	Pos	Pos
12	4.49 x 10^6	31.97	30.59	0.17	DENV-1	35.66	Pos	Neg
13		2.42	0.25	NA	IR	IR	IR	IR
14		1.24	0.23	NA	IR	IR	IR	IR

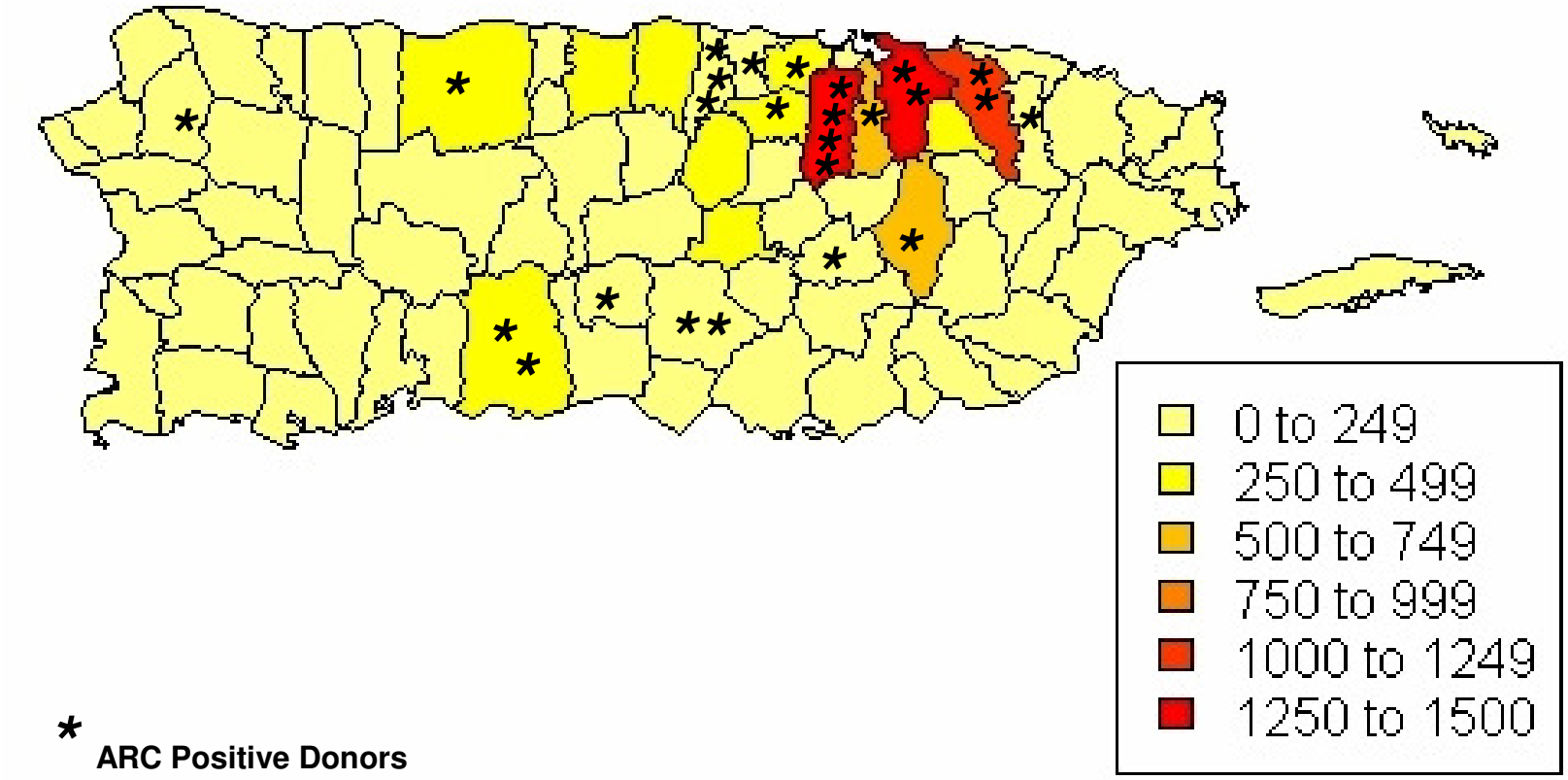
Dengue Viremic Blood Donors in PR 2007
Units Transfused in PR

#	Viral load copies/mL	S/CO					CDC Testing			
		Initial	1st Retest	1:16 Pool	Alt TMA	1:16 Pool	RT-PCR	CT	C636	IgM
1	6.39 x 10^5	33.10	38.68	40.31	87.86	89.91	DENV-3	22.34	Pos	
2	1.12 x 10^9	27.75	38.99	38.91	87.16	88.52	DENV-2	26.39	Pos	
3		5.06	4.12	1.37	26.96	8.61				
4		14.23	23.26	7.32	28.59	3.28				
5		5.68	20.55	1.16	29.48	21.59				
6		1.02	2.29	0.13	28.01	0.01				
7		34.81	37.21	32.97	76.16	32.72				
8		13.14	25.77	0.07	29.26	12.51				
9	7.25 x 10^7	37.66	39.16	40.26	87.13	89.32	DENV-3	25.61	Pos	
10	1.35 x 10^8	33.30	37.38	35.39	91.10	83.09	DENV-2	29.67	Pos	
11		23.38	31.07	13.29	31.25	31.18				
12	1.37 x 10^7	40.29	27.03	36.10	82.29	92.04	DENV-3	28.11	Pos	
13		4.46	0.01	0.21	24.80	0.06				
14		1.15	0.03	0.06	0.06	0.02				

2007 Dengue RNA Test Results by Week of Collection
Prevalence 1:614



Distribution of Blood Donors by *Municipio* of Residence –ARC Positive Donors



Recipient Investigation

- Complete US recipient tracing
- Complete PR recipient tracing
- Review records
  - Symptoms consistent with dengue infection?
- Collect blood samples from recipients
  - Evidence of dengue infection (IgG, IgM; testing at CDC)?
- Complete Questionnaire
  - Detailed list of potential symptoms
  - Demographic information
- Recipient consent form
  - Benefit: Learn if exposed to dengue in the past
  - Risk: Dengue Hemorrhagic Fever if reinfected

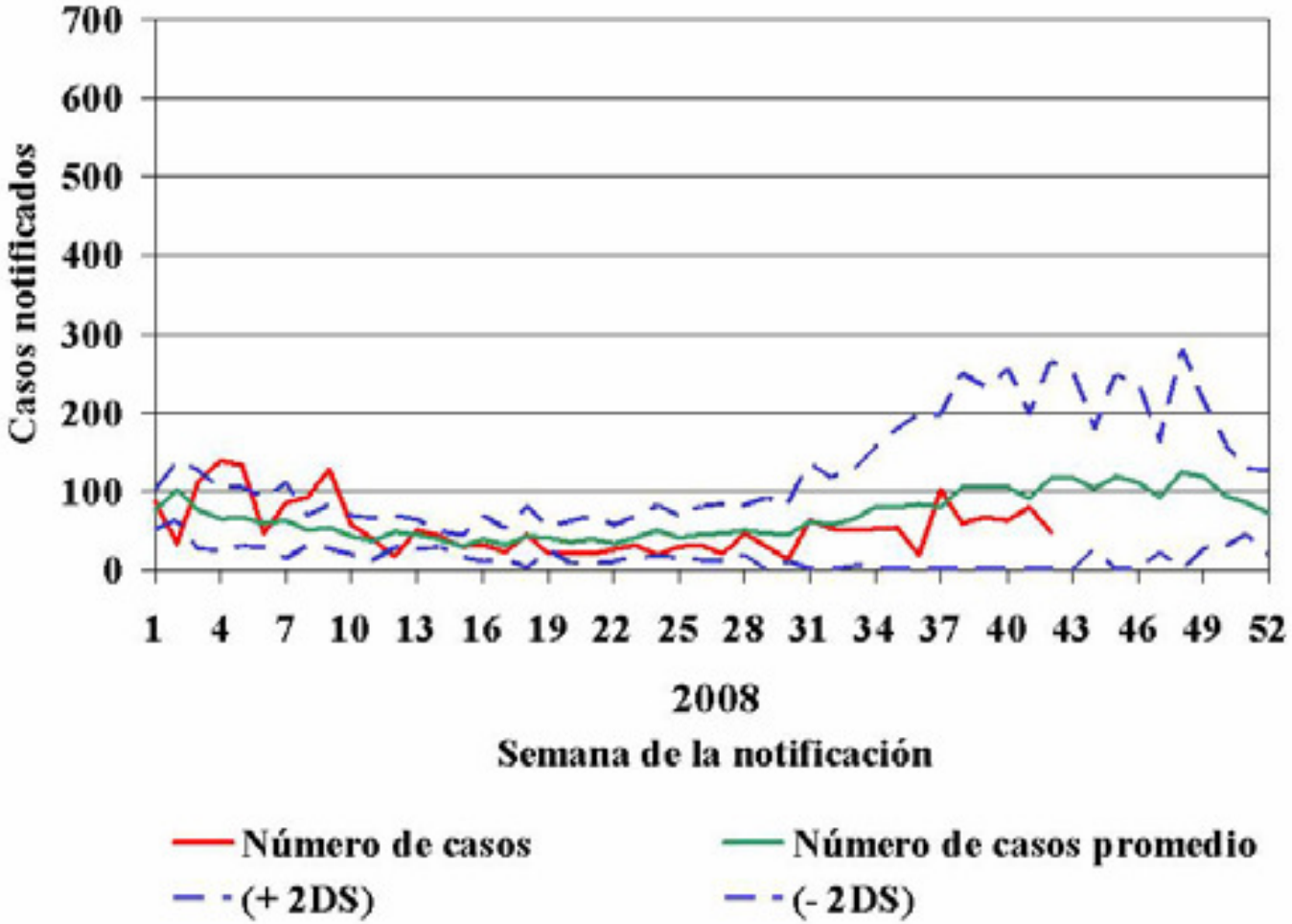
2005 and 2007 Prevalence Rates

- 12 dengue RNA pos of 6400 donations tested that shipped into the US
  - 1:533 (0.19%)
  - 12/14 samples tested RR/conf'd pos = 99.95% specificity
- 13 dengue RNA pos of 8950 donations tested that remained in PR
  - 1:689 (0.15%)
  - 13/14 samples tested RR/conf'd pos = 99.99% specificity
- **2007 prevalence**
  - **25 total dengue RNA pos of 15,350 tested**
  - **1:614 (0.16%)**
  - **25/28 samples tested RR = 99.99% specificity**
  - **14/28 (50%) reactive in a MP of 16**
- **2005 prevalence**
  - **12 total dengue RNA pos of 16,521 tested**
  - **1:1376 (0.073%)**
  - **12/14 samples tested RR = 99.99% specificity**
  - **5/12 (42%) reactive in a MP of 16**

2008 Dengue Season in PR

Number of cases notified per week, 2008

Número de casos notificados por semana, 2008



By week number 42, the notification level is below the Average for the 5 years of reference. Average for years 2000-2004, *± 2SD*

A la semana número 42 el nivel de notificación está por debajo del promedio para los cinco años de referencia. (Promedio en los años 2000-2004, ± 2DS).

Dengue in the Continental US and Hawaii

- Dengue epidemics occurred in the US in the late 1700s to the first half of the 1900s
- 7 outbreaks in TX since 1980
- 1 outbreak in Hawaii in 2001

Dengue Seroprevalence in South Texas

1986: STD random patient samples in South TX

0.9% IgM+

1999: Laredo, TX serosurvey

1.3% IgM+, 23% IgG+

2004: Brownsville, TX

1.3% IgM+, 40% IgG+

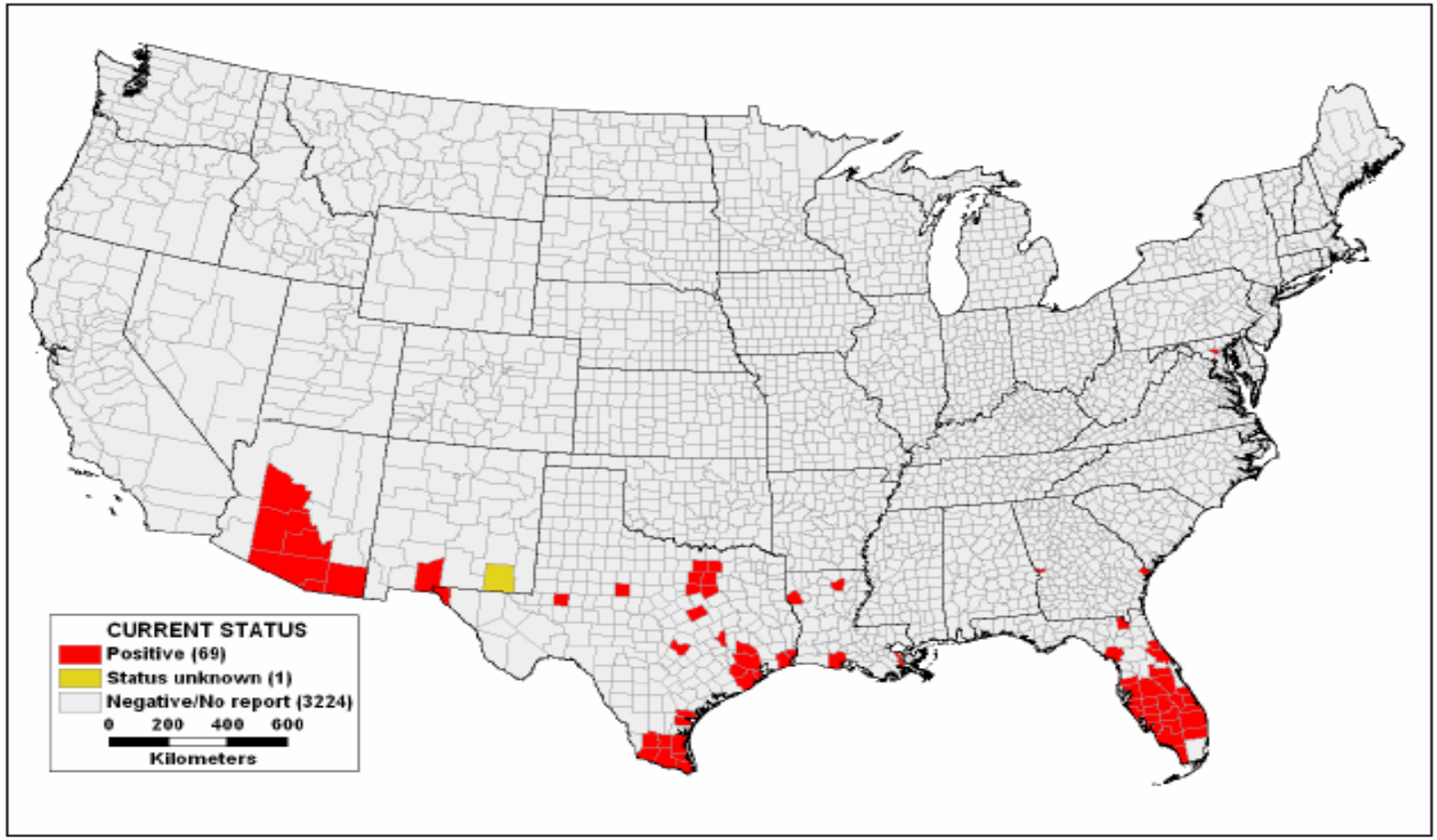
2005: Maramoros and Brownsville serosurvey

22% IgM+, 76.6% IgG+ (MX)

2.5% IgM+, 38.2% IgG+ (TX)

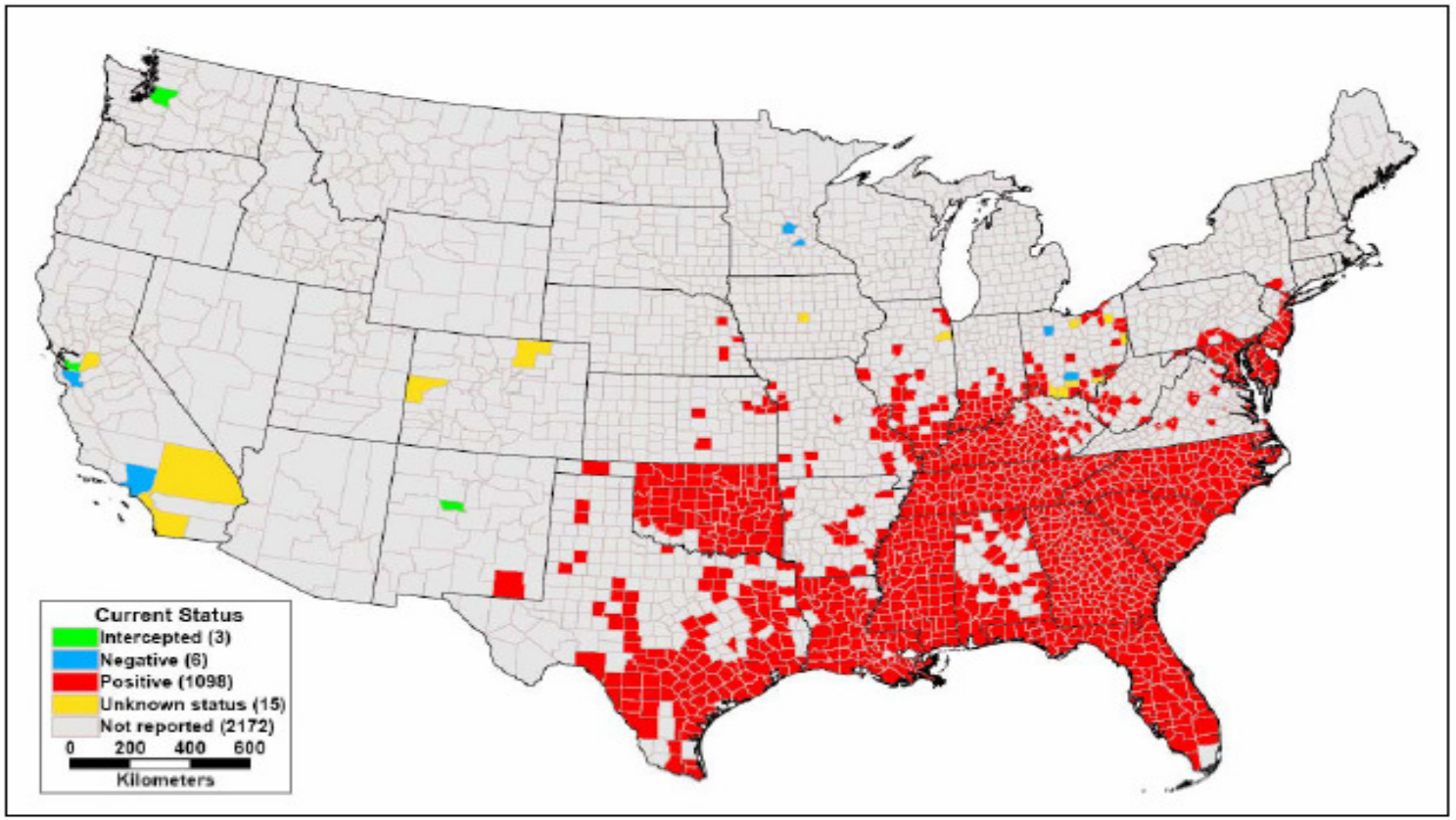
MMWR 1987; 36(33):551-4; 2007; 56(31):785-9. Reiter P, EID 2003; 9(1):86-89. Burnkard J, 2006 (UMI)

Distribution of *A. aegypti*



Source: Chester G. Moore, Ph.D., Colorado State University

Distribution of *A. albopictus*



Source: Chester G. Moore, Ph.D., Colorado State University

WNV Neuroinvasive Disease Incidence, by County, US, 1999-2007