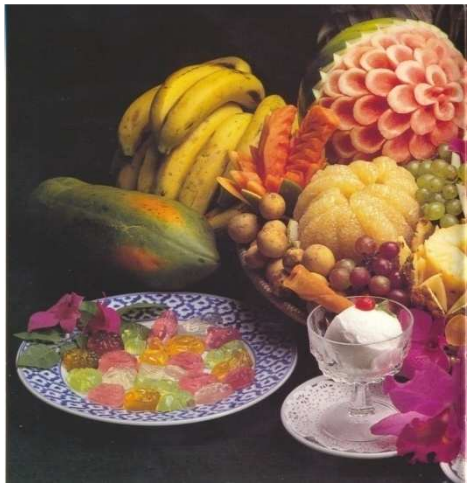
ARBOVIROSI

Federico Gobbi

Ospedale Classificato Equiparato
"Sacro Cuore – Don Calabria"
Presidio Ospedaliero Accreditato – Regione Veneto

Fondazione Don Giovanni Calabria
per la Malattie Tropicali

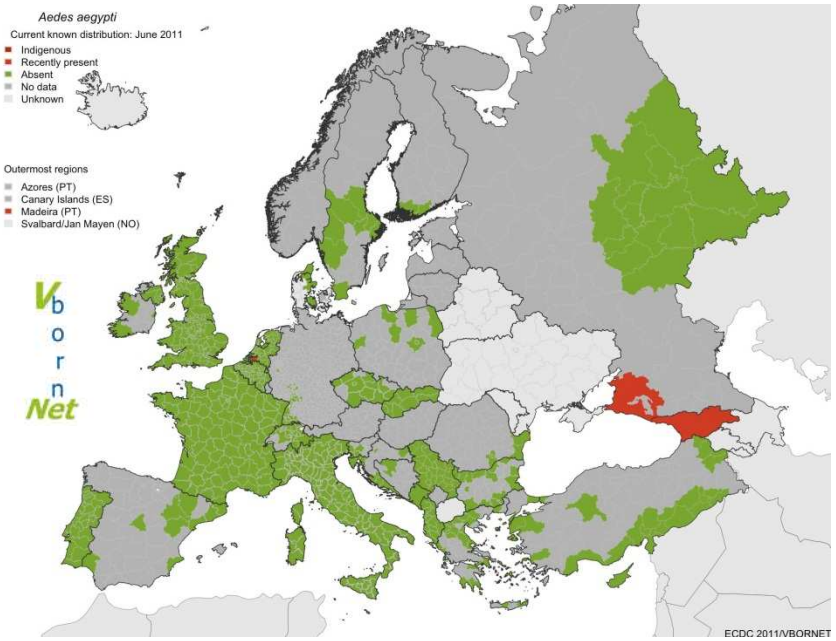



A3XX
A3XX-100

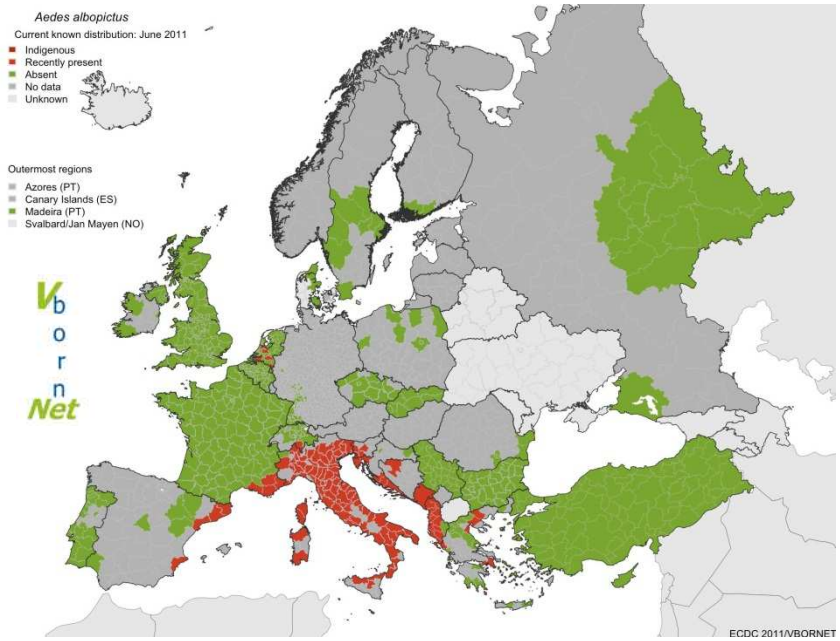

CHINA SHIPPING LINE
CSCL SEATTLE

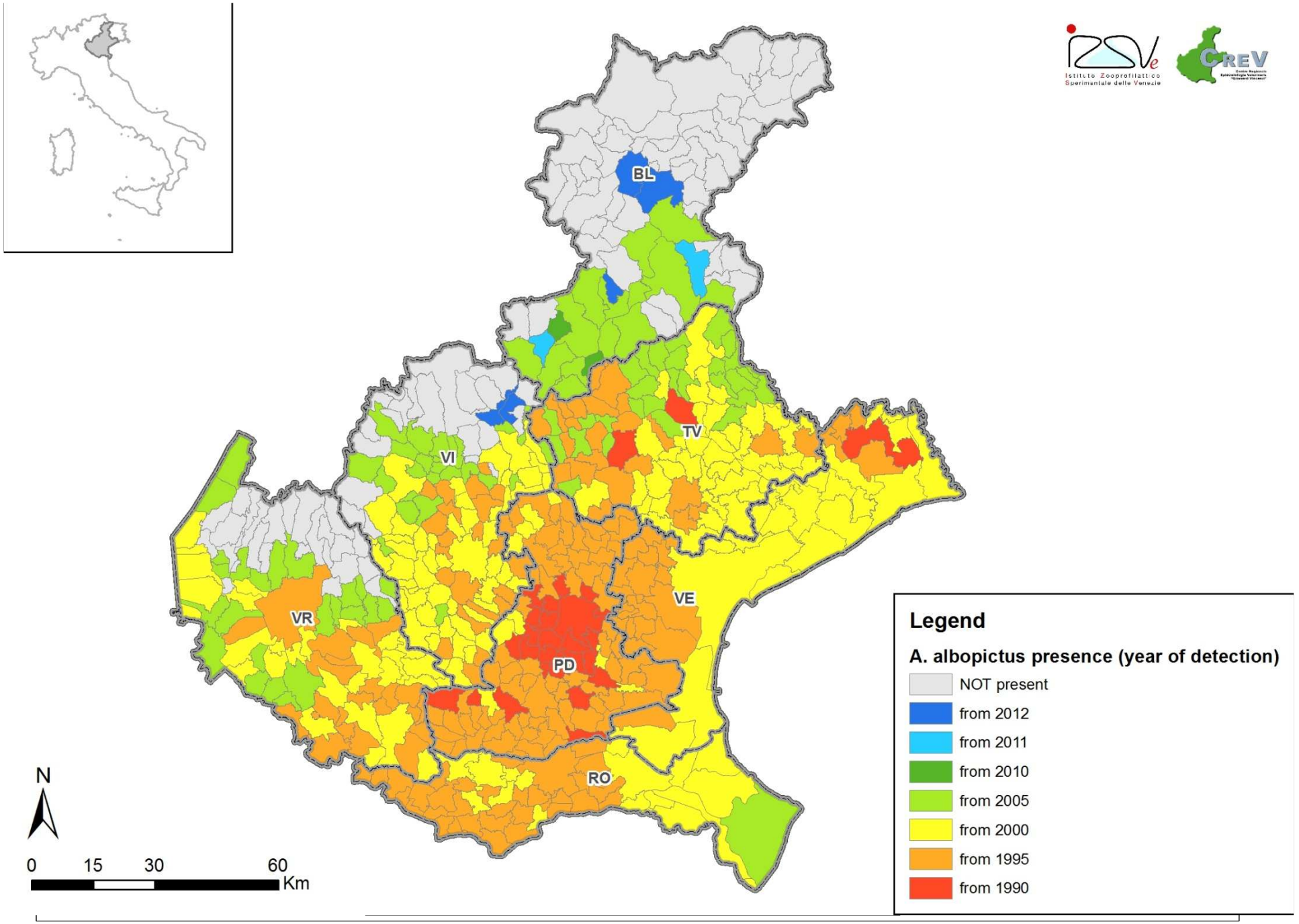
Distribuzione delle zanzare

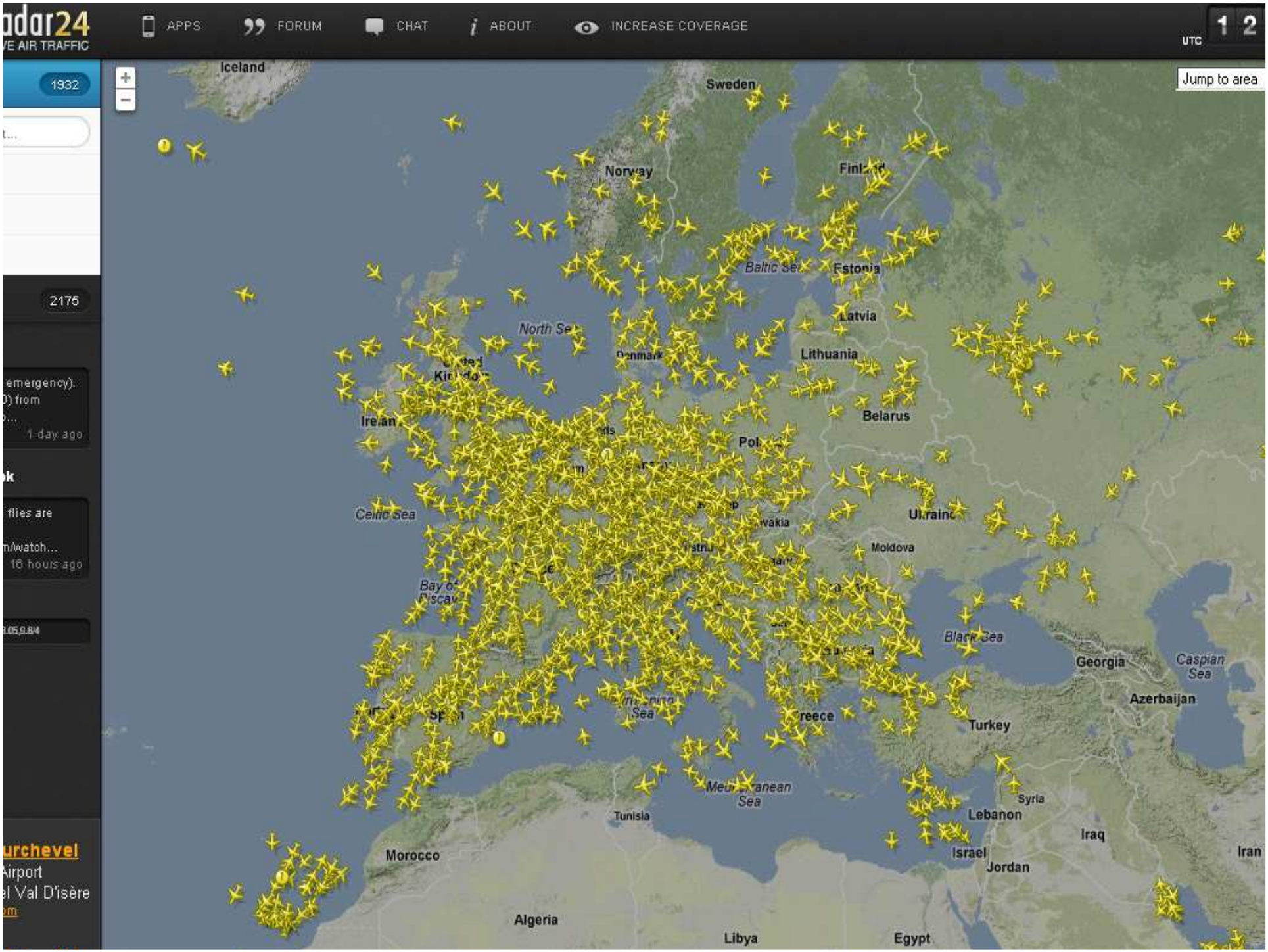
Ae. aegypti

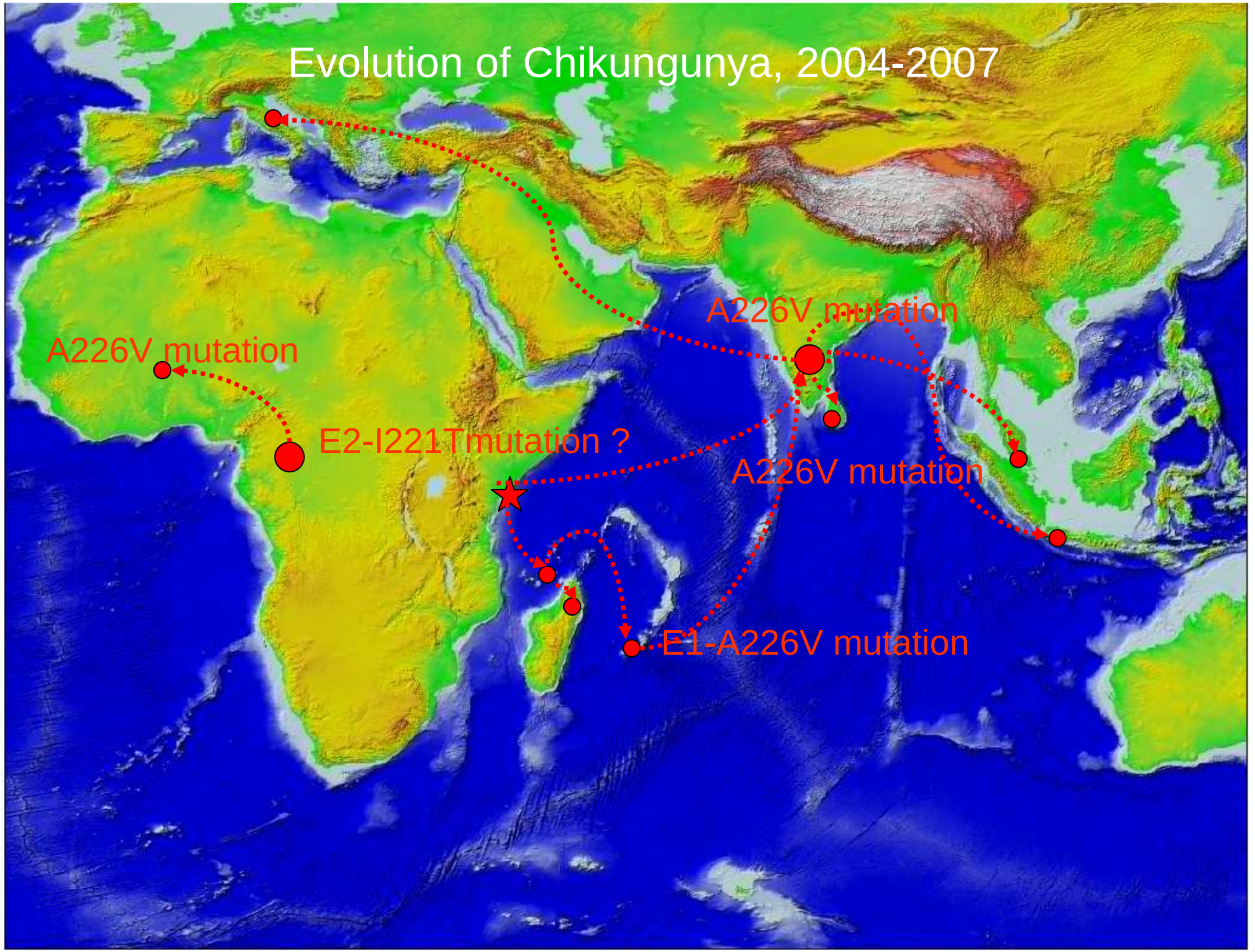


Ae. albopictus




BL
TV
VI
VE
VR
PD
RO
N
0
15
30
60
Km
Legend
A. albopictus presence (year of detection)
NOT present
from 2012
from 2011
from 2010
from 2005
from 2000
from 1995
from 1990


adar24
VE AIR TRAFFIC
APPS
FORUM
CHAT
ABOUT
INCREASE COVERAGE
UTC
1 2
Jump to area
1932
2175
emergency).
) from
1 day ago
flies are
m/watch...
16 hours ago
urchevel
Airport
el Val D'isère
Iceland
Sweden
Norway
Finland
Baltic Sea
Estonia
Latvia
North Sea
Denmark
Lithuania
Belarus
Ireland
Poland
Celtic Sea
Ukraine
Moldova
Bay of Biscay
Black Sea
Georgia
Caspian Sea
Azerbaijan
Spain
Mediterranean Sea
Greece
Turkey
Tunisia
Syria
Lebanon
Iraq
Iran
Israel
Jordan
Morocco
Algeria
Libya
Egypt

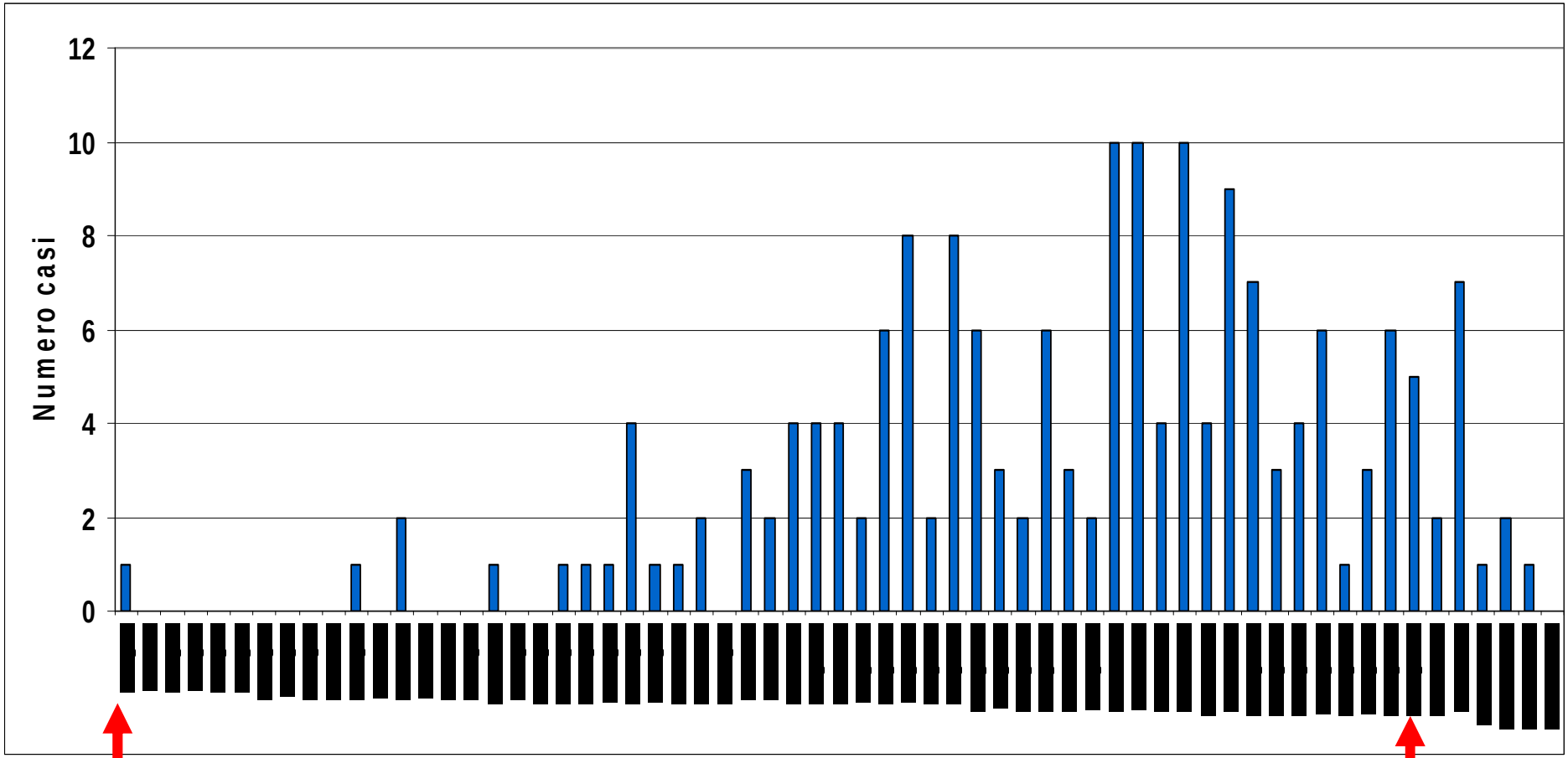

Evolution of Chikungunya, 2004-2007
A226V mutation
A226V mutation
E2-I221Tmutation ?
A226V mutation
E1-A226V mutation

Competenza vettoriale

- CHIKV non mutato 24%
- CHIKV mutato **80%**
- DENV I 47%
- DENV II 72%
- DENV III 64%
- DENV IV 38%

Istituto Zooprofilattico Sperimentale delle Venezie

Epidemia di Chikungunya nel nord Italia, Anno 2007



Caso indice?
(23 giugno!!!*)

247 casi

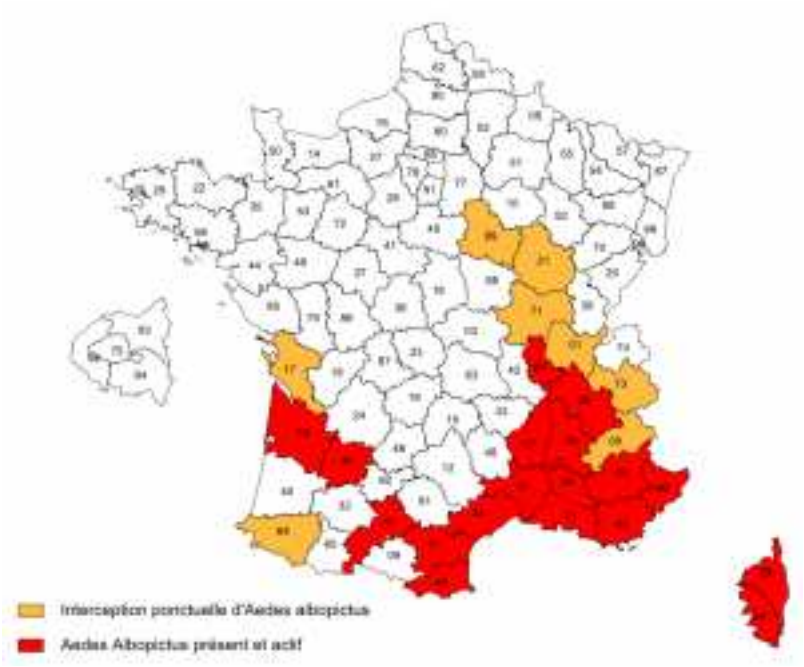
Conferma di laboratorio 29 agosto

*Rezza G, Nicoletti L, Angelici R et al. *Lancet 2007*

Gould EA, Gallian P, De Lamballerie X, Charrel RN.

First cases of autochthonous dengue fever and chikungunya fever in France: from bad dream to reality!

Clin Microbiol Infect. 2010 Dec;16(12):1702-4.



Schmidt-Chanasit J, Haditsch M, Schoneberg I, et al.
Dengue virus infection in a traveller returning from Croatia to Germany.
Euro Surveill. 2010 Oct 7;15(40).

TABLE 1

Distribution of antibodies to dengue virus in nine persons from a pool of 14 neighbours of the autochthonous case from Pelješac, Croatia, October 2010

Examinee number	DENV IgM (ratio) [a]	DENV IgG (RU/ml) [b]
1	+ (2.4)	+ (155)
2	+/- (1.04)	+ (126)
3	+ (2.2)	+ (98)
4	+ (1.2)	+ (140)
5	- (0.3)	+ (170)
6	- (0.5)	+ (155)
7	+ (2.3)	+ (138)
8	+ (2.4)	+ (94)
9	+ (2.6)	+ (170)

DENV: dengue virus.

[a] <0.8negative (-), 0.8-1.1 borderline (+/-), ≥1.1 positive (+). Results are expressed as ratio according to the manufacturer's specifications.

[b] <16 negative (-), 16-22 borderline (+/-), ≥22 positive (+). Results are expressed in RU/ml according to the manufacturer's specifications.

TABLE 2

Distribution of antibodies to dengue virus in six anonymous serum samples, Croatia, October 2010

Examinee number	1	2	3	4	5	6
DENV IgM (ratio)[a]	+/- (0.9)	+/- (0.8)	+/- (1.08)	+ (4.6)	+ (2.2)	-
DENV IgG (RU/ml)[b]	+ (72)	+ (46)	+ (40)	+ (46)	+/- (<2)	+ (153)

DENV: dengue virus.

[a] <0.8 negative (-), 0.8-1.1 borderline (+/-), ≥ 1.1 positive (+). Results are expressed as ratio according to the manufacturer's specifications.

[b] <16 negative (-), 16-22 borderline (+/-), ≥ 22 positive (+). Results are expressed in RU/ml according to the manufacturer's specifications.

9/14 sieri dei vicini positivi

6/122 sieri di pz afferenti a quel laboratorio nell'ottobre 2010 !!!!!!!

Gjenero-Margan I, Aleraj B, Krajcar D, et al.
Autochthonous dengue fever in Croatia, August-September 2010.
Euro Surveill. 2011 Mar 3;16(9).

Gould EA, Gallian P, De Lamballerie X, Charrel RN.

First cases of autochthonous dengue fever and chikungunya fever in France: from bad dream to reality!

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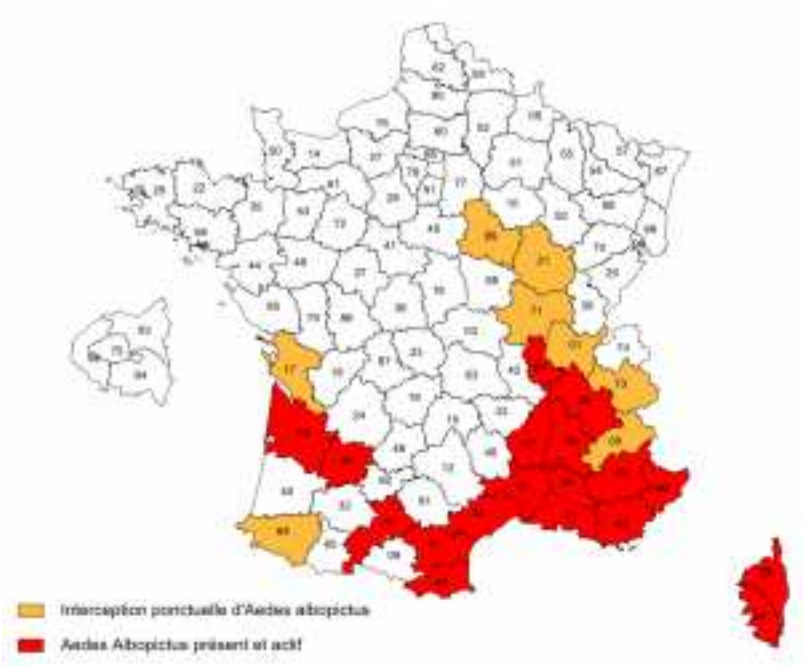

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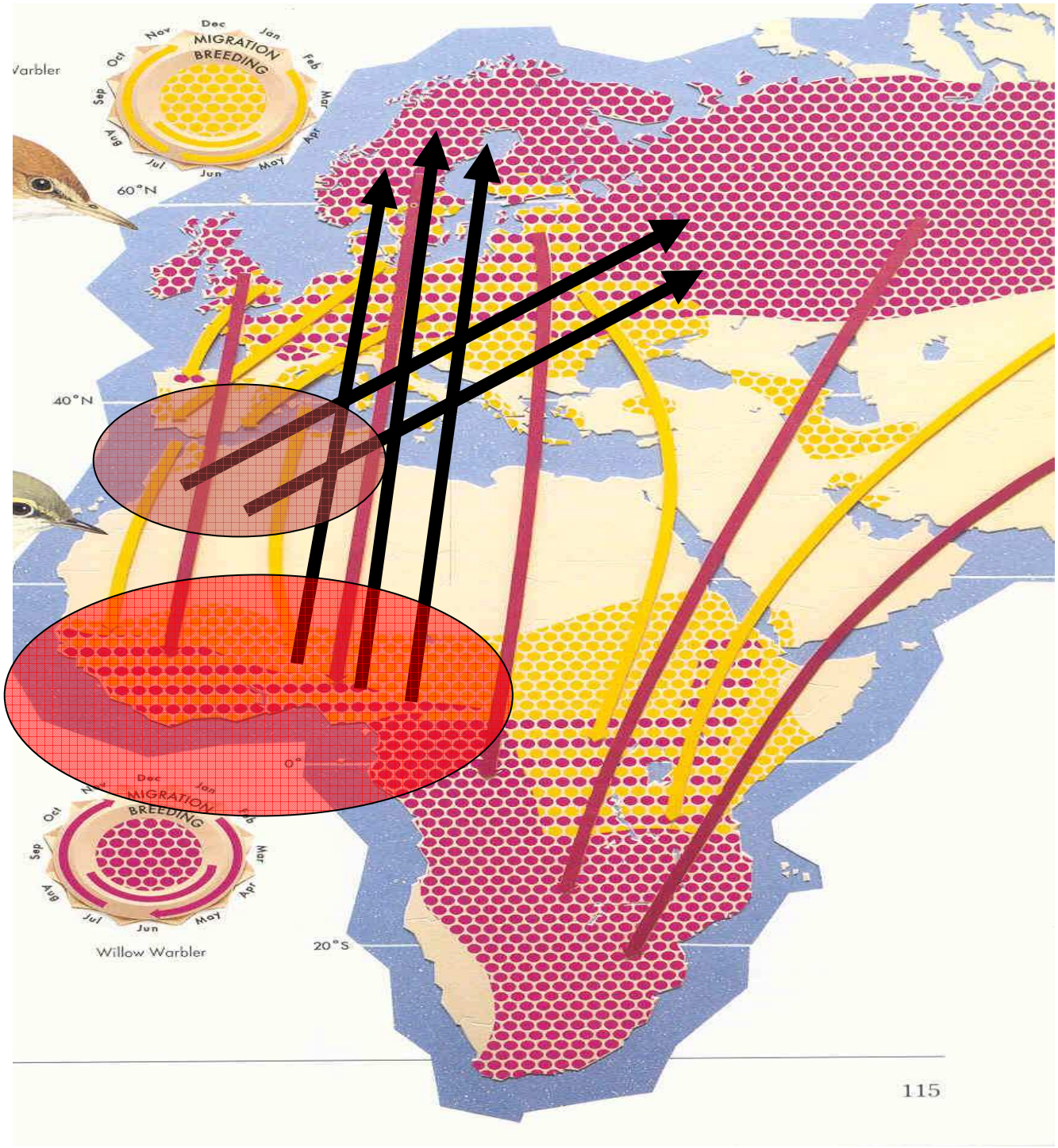
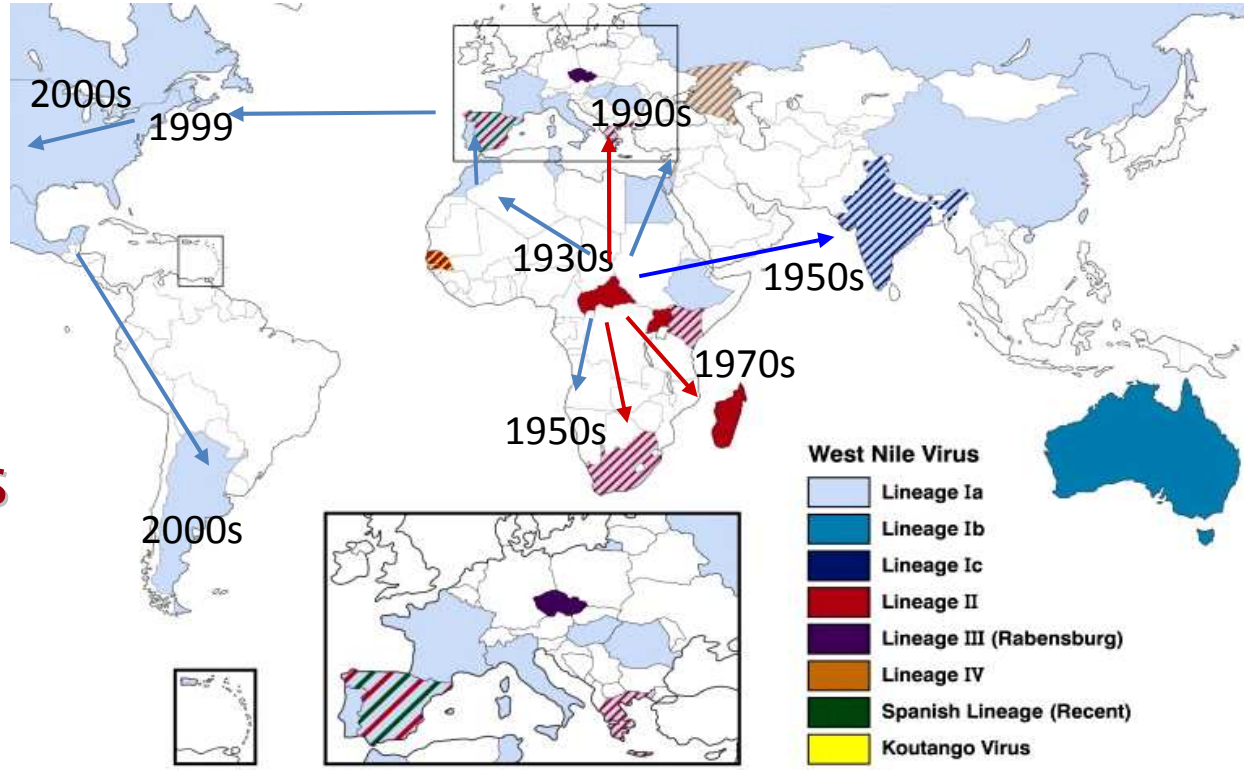
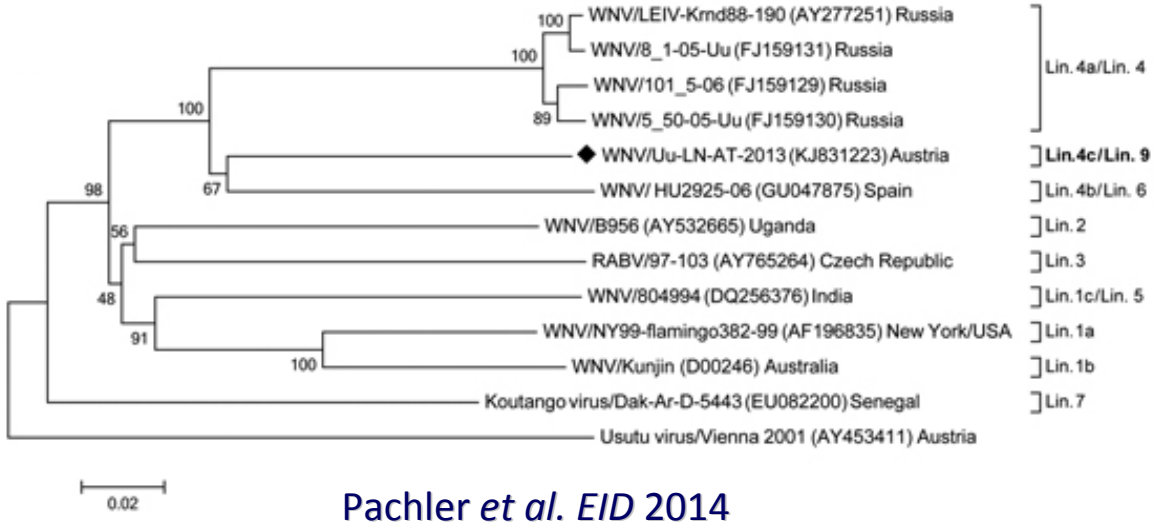

Warbler
MIGRATION
BREEDING
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
60°N
40°N
0°
20°S
Willow Warbler

Geographical clustering of WNV lineages and clades



Modified from Pesco & Ebel, *Infect Genet Evol* 2011



Pachler *et al. EID* 2014

5-25% nucleotide diversity among lineages

(17-20% pairwise nucleotide distance between WNV lin 1 and lin2)

Ciclo biologico

Amplifying hosts
Birds (serbatoio)

Culex sp., Aedes sp.,
Ochlerotatus sp. (vettori)

Incidental hosts
Humans, horses,
and other animals

Toscana: casi in equini,
1998

Vettore: culex pipiens

Compare in estate-autunno
(maggio- dicembre)

Eurosurveillance, Volume 13, Issue 41, 09 October 2008

Rapid communications

FIRST HUMAN CASE OF WEST NILE VIRUS NEUROINVASIVE INFECTION IN ITALY, SEPTEMBER 2008 – CASE REPORT

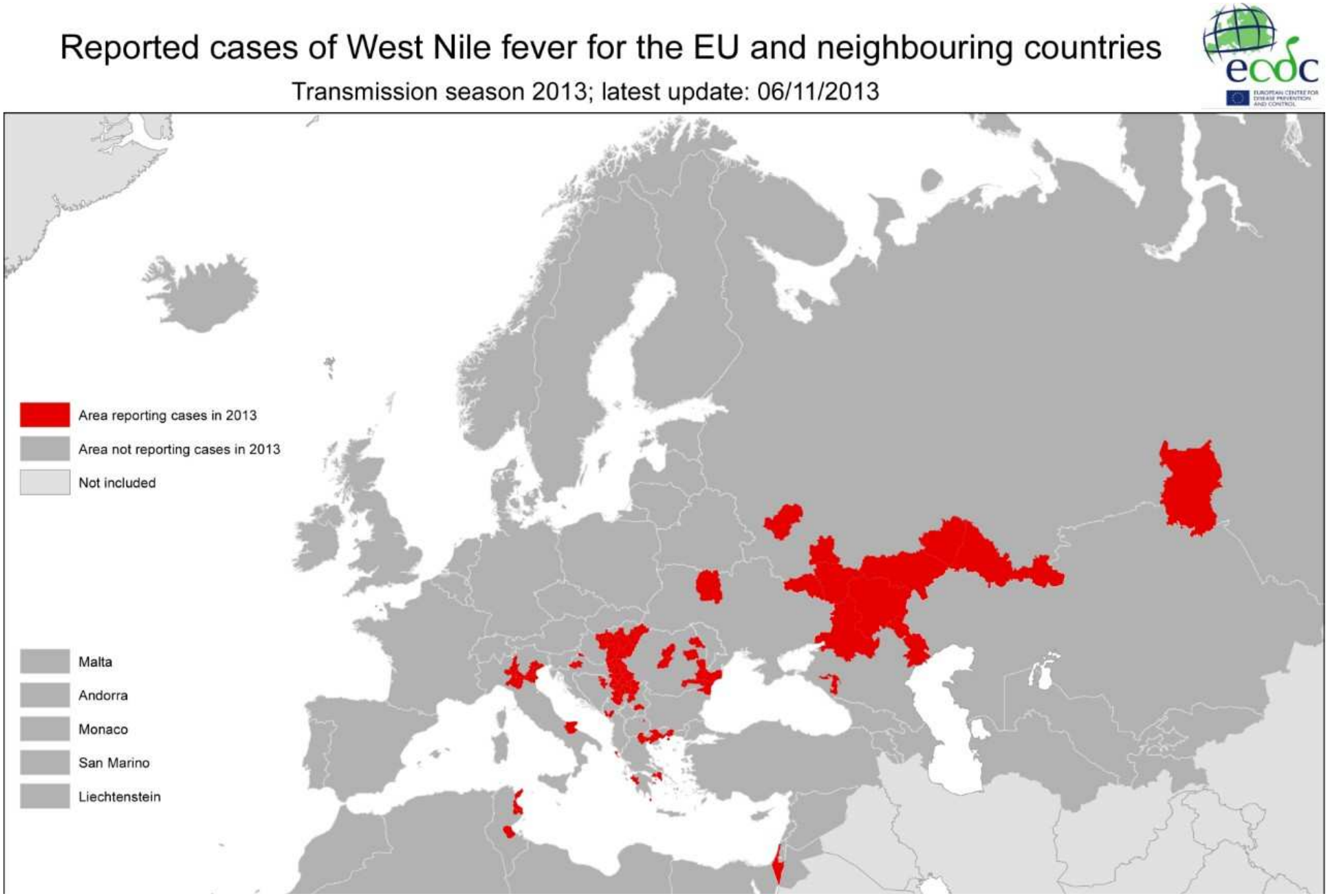
G Rossini[1], F Cavrini[1], A Pierro[1], P Macini[2], A. C. Finarelli[2], C Po[2], G Peroni[3], A Di Caro[4], M Capobianchi[4], L Nicoletti[5], M P Landini[1], V Sambri (vittorio.sambri@unibo.it)[1]

1. Centro di Riferimento Regionale per le Emergenze Microbiologiche (Regional Reference Centre for Microbiological Emergencies - CRREM), Microbiology Unit, Azienda Ospedaliero-Universitaria di Bologna, Policlinico S.Orsola-Malpighi, Bologna, Italy
2. Servizio di Sanità Pubblica (Public Health Service), Regione Emilia Romagna, Bologna, Italy
3. Department of Public Health, Azienda Unità Sanitaria Locale di Imola, Imola, Italy
4. Istituto Nazionale Malattie Infettive (National Institute of Infectious Diseases) "L. Spallanzani", Rome, Italy
5. Istituto Superiore di Sanità (National Institute of Health, ISS), Rome, Italy

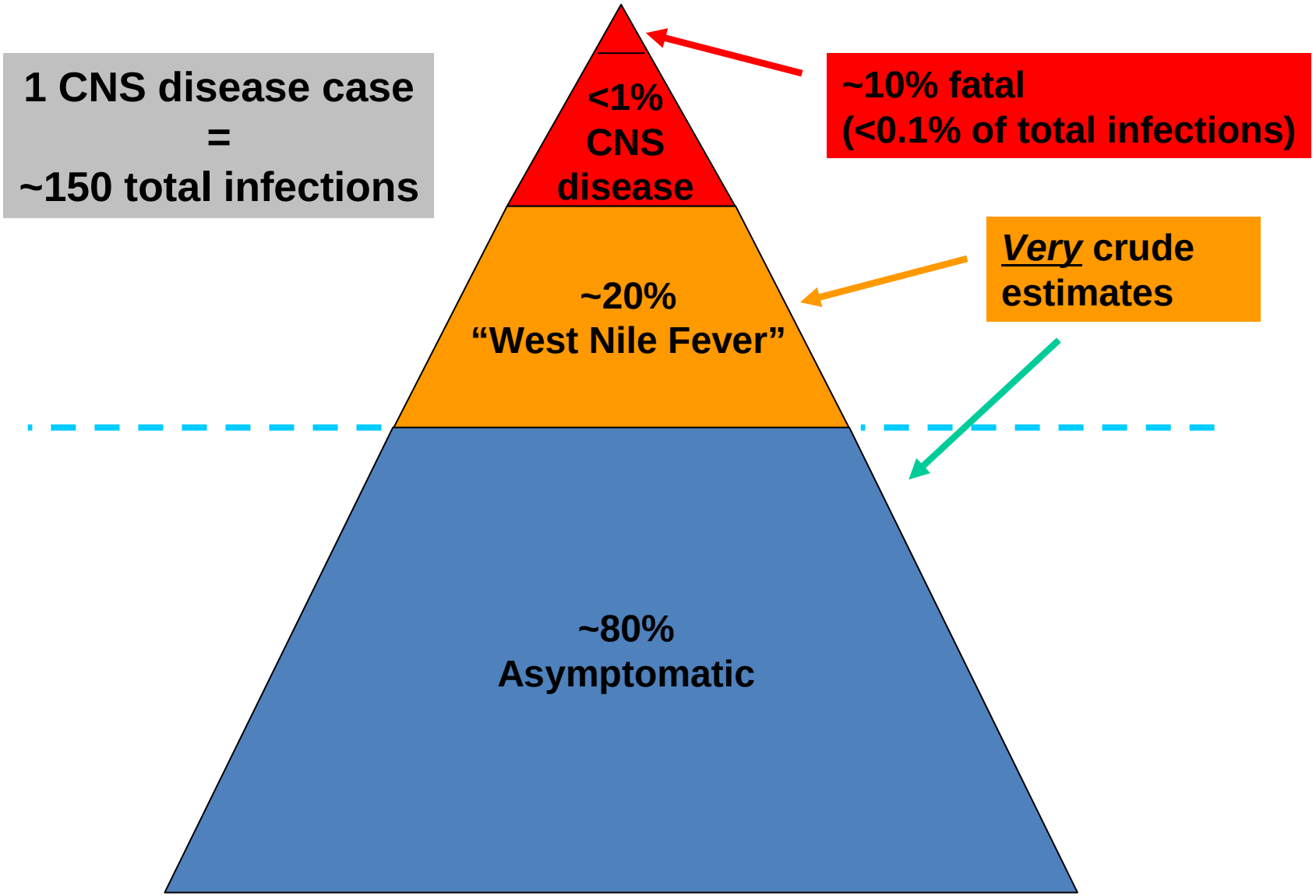
Citation style for this article: Rossini G, Cavrini F, Pierro A, Macini P, Finarelli AC, Po C, Peroni G, Di Caro A, Capobianchi M, Nicoletti L, Landini MP, Sambri V. First human case of West Nile virus neuroinvasive infection in Italy, September 2008 – case report. Euro Surveill. 2008;13(41):pii=19002. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19002

Date of submission: 02 October 2008

West-Nile Europa (2013)



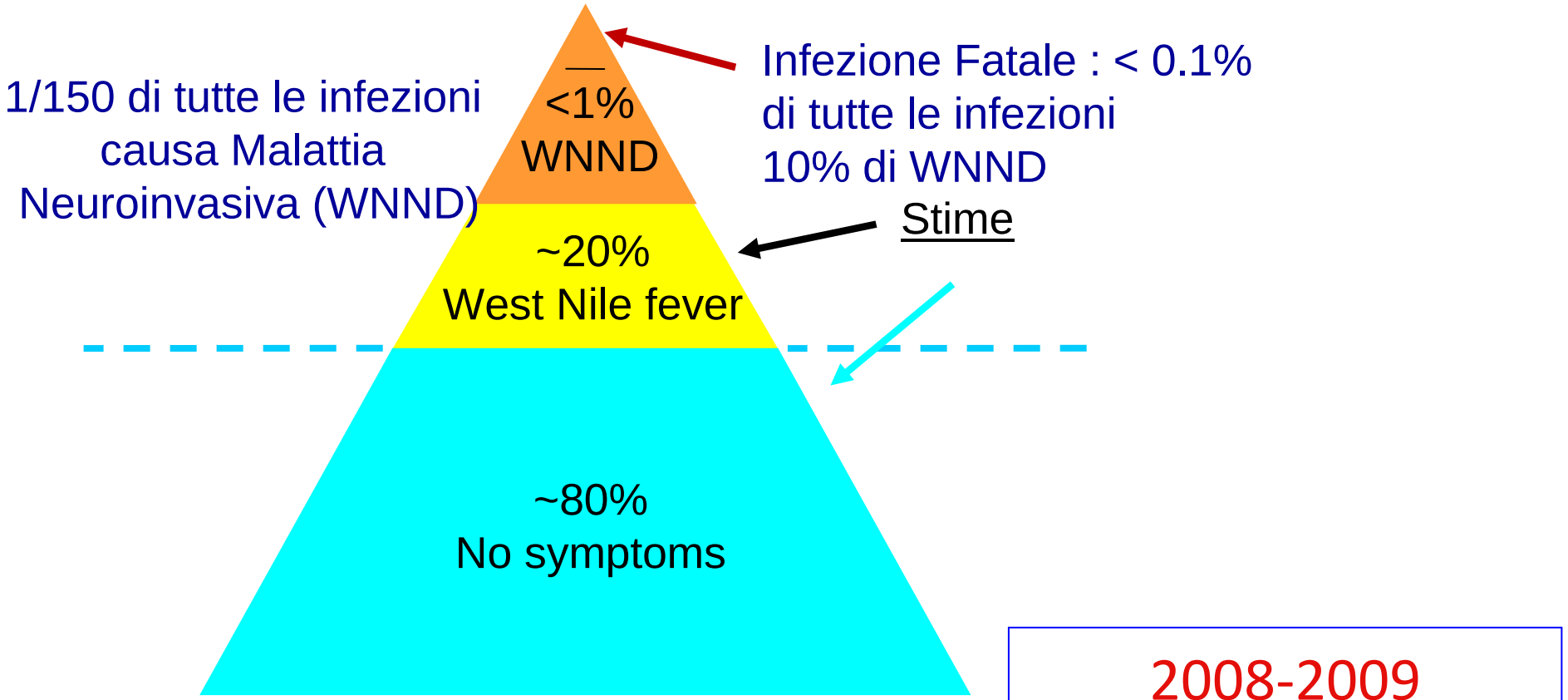
WNV infezione nell'uomo



Figure

Distribution of solid organ donors shown to be positive for West Nile virus[a], Italy, 2009 (n=15)

[a] Shown to have West Nile virus-specific antibodies (IgG and/or IgM) by enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA).



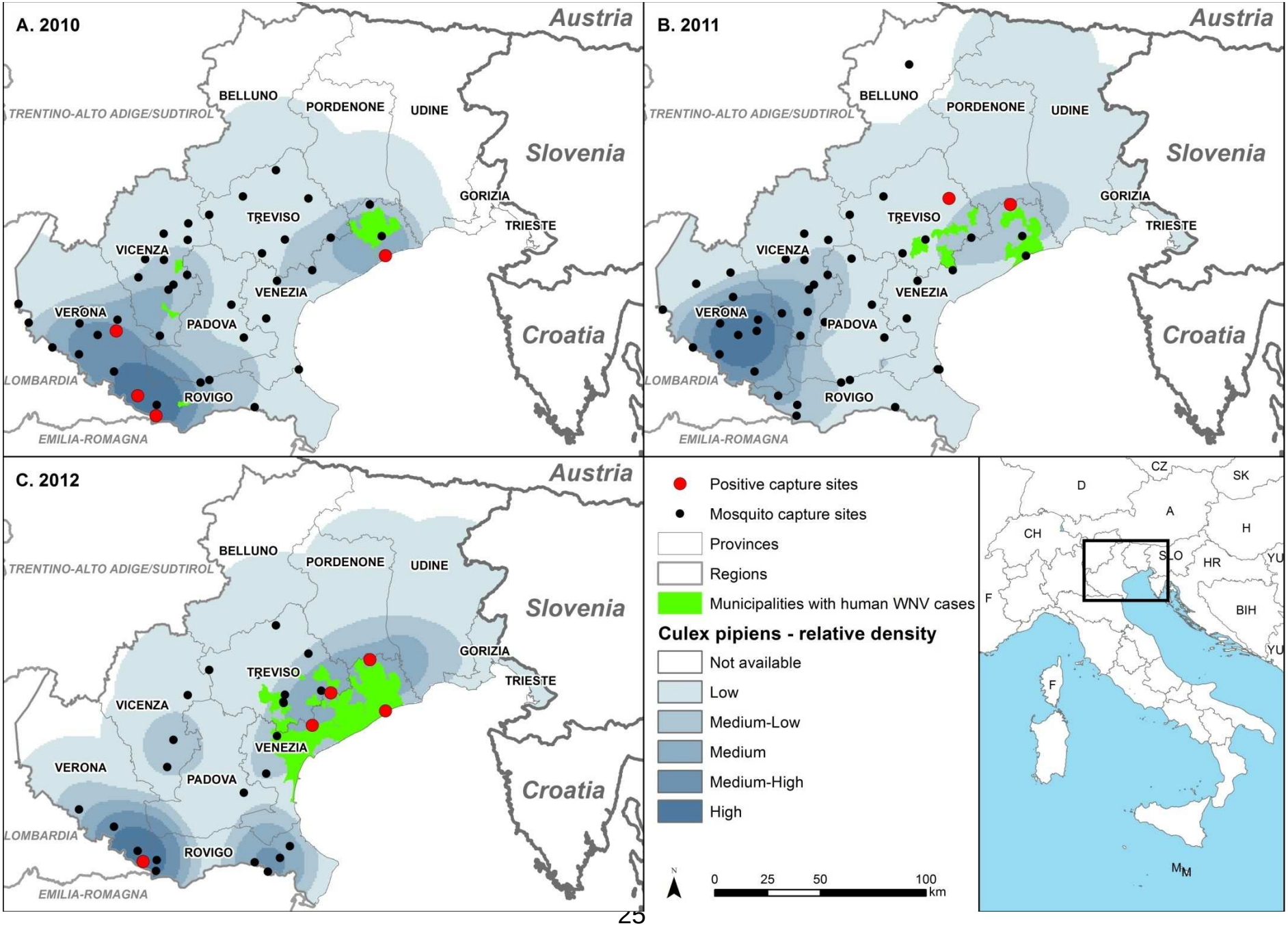
2008-2009

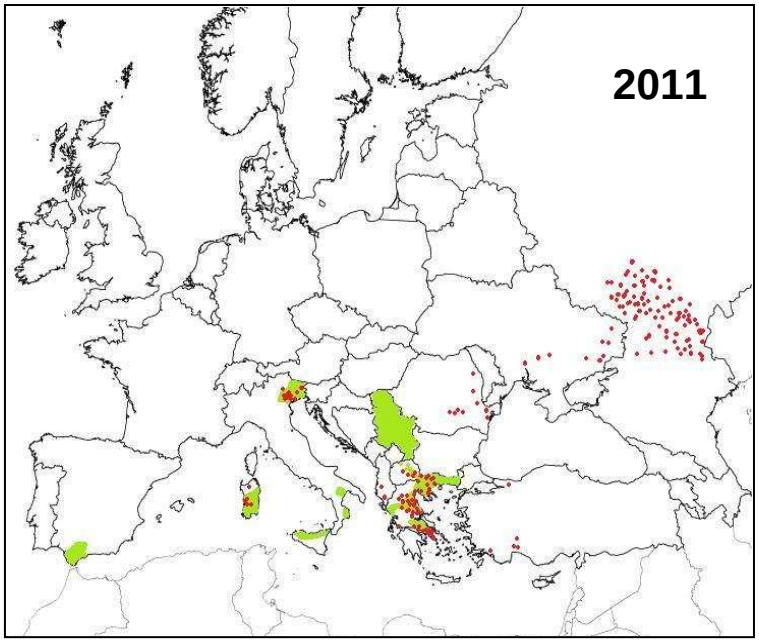
1 caso di WNF vs 22 casi di WNND !!

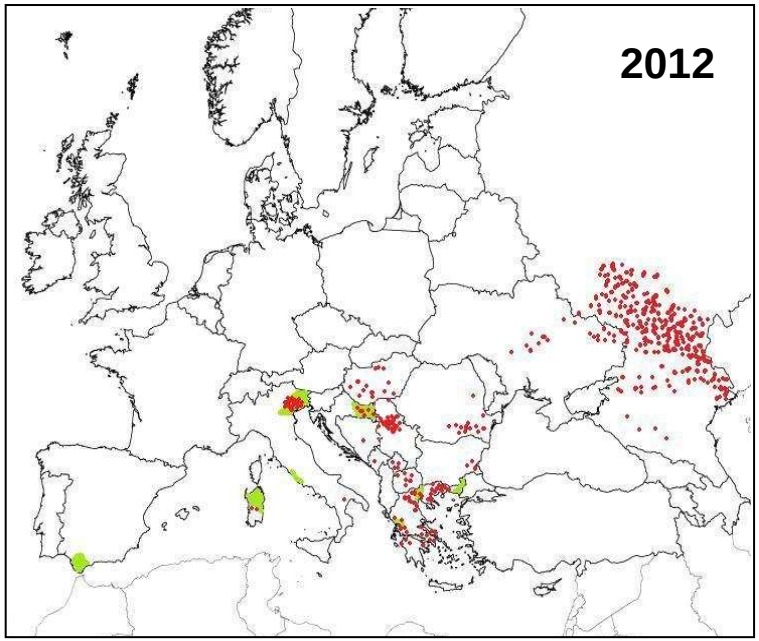
Gobbi F, Napoletano G, Piovesan C et al.

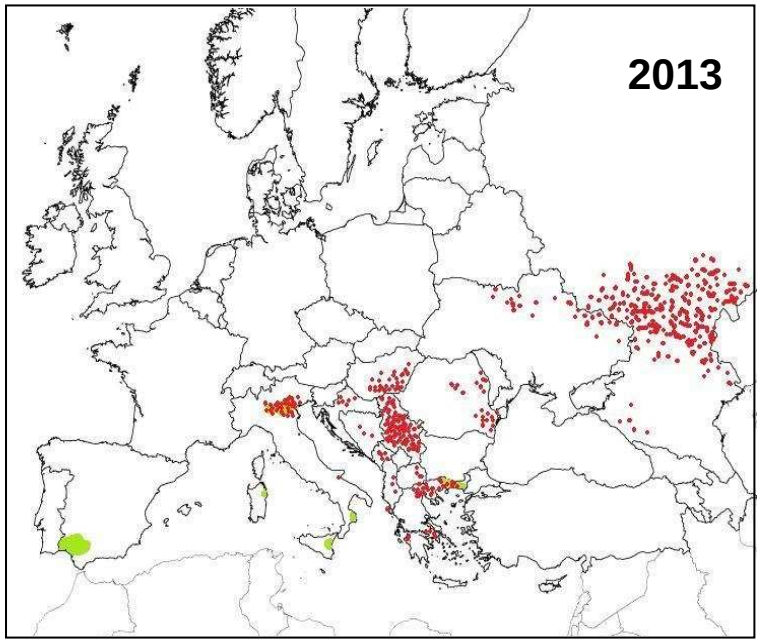
Where is West Nile fever? Lessons learnt from recent human cases in northern Italy.

Euro Surveill. 2009 12;14(10).


A. 2010
B. 2011
C. 2012
Austria
Slovenia
Croatia
BELLUNO
PORDENONE
UDINE
GORIZIA
TRIESTE
TREVISO
VICENZA
VERONA
PADOVA
VENEZIA
ROVIGO
TRENTINO-ALTO ADIGE/SUDTIROL
LOMBARDIA
EMILIA-ROMAGNA
Positive capture sites
Mosquito capture sites
Provinces
Regions
Municipalities with human WNV cases
Culex pipiens - relative density
Not available
Low
Medium-Low
Medium
Medium-High
High
N
0
25
50
100
km
CZ
SK
D
A
H
CH
SLO
HR
YU
F
BIH
MM





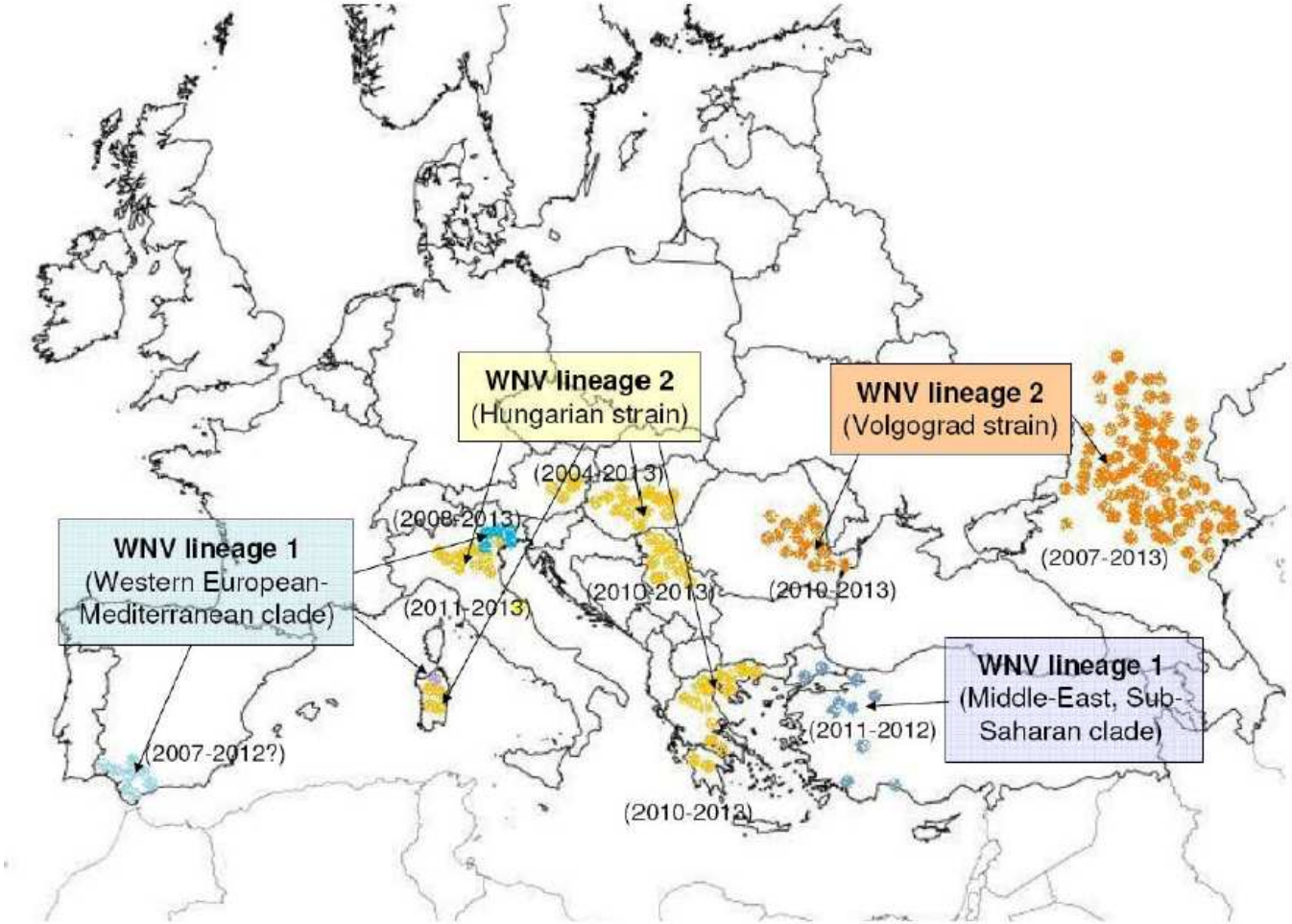


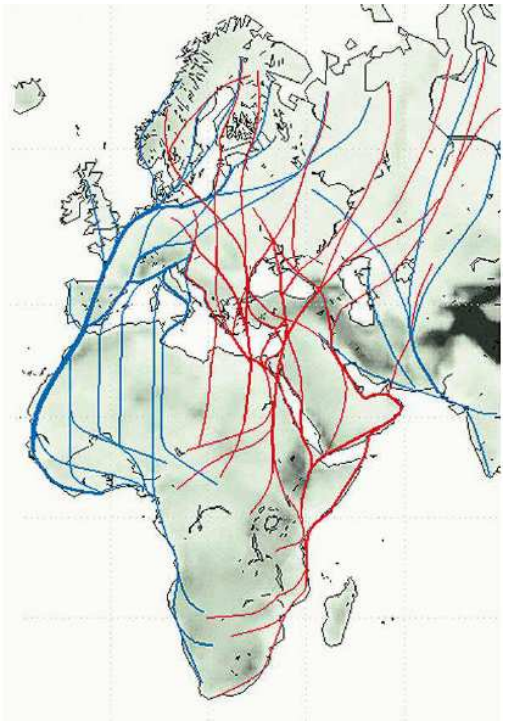
Human cases of WNV infection

Equine cases of WNV infection

Barzon et al., *unpublished*

WNV lineage 1 and WNV lineage 2 strains circulating in European and neighboring countries belong to four phylogenetic clusters geographically related to bird migratory routes





Barzon et al., *unpublished*

Clinical presentation of West Nile virus infection

- **West Nile neuro-invasive disease (<1%)**
  - Encephalitis
  - Aseptic meningitis
  - Acute flaccid paralysis

  (Elderly and immunocompromized individuals are the most affected).

- **West Nile fever (~20%)**
  - “benign” influenza-like illness

- **Asymptomatic (~80%)**

Clinical presentation of WNV infection

Symptoms and signs in patients with WNV infection, Veneto Region, 2012-2013

Symptoms and signs	WNND (n = 35)	WNF (n = 32)	Blood donor (n = 21)
Fever	90 %	100 %	14 %
Headache	68 %	71 %	21 %
Fatigue	60 %	59 %	64 %
Rash	0 %	18 %	14 %
Artralgia	8 %	47 %	21 %
Myalgia	20 %	4 %	29 %
Lymphoadenopathy	0 %	6 %	0 %
Vomiting/diarrhoea	0 %	12 %	21 %
Neurological manifestations	68 %	0 %	7 %
Respiratory failure	24 %	0 %	0 %
Encephalitis	48 %	0 %	0 %
Meningitis	32 %	0 %	0 %
Acute flaccid paresis/paralysis	20 %	0 %	0 %
Asymptomatic	0 %	0 %	29 %

Barzon et al., *unpublished*

Results of Virological Tests Performed in Confirmed Cases of WNV Infection, 2012-2013

Test	No. positive/No. tested (% positive)		
	WNND (no. = 26)	WNF (no. = 30)	Blood donors (no. = 21)*
WNV RNA in plasma	9/26 (**34.6**)	4/30 (**13.3**)	12/21 (**57.1**)
WNV RNA in urine	14/26 (**53.8**)	13/30 (**42.3**)	5/21 (**23.8**)
WNV RNA in CSF	1/19 (**5.3**)	0/3 (0)	0/0
WNV IgM-/ IgG- in serum	0/26 (0)	0/30 (0)	4/21 (**19.0**)
WNV IgM+/ IgG- in serum	8/26 (**30.8**)	5/30 (**16.7**)	8/21 (**38.1**)
WNV IgM+/ IgG+ in serum	18/26 (**69.2**)	25/30 (**83.3**)	9/21 (**42.9**)
WNV IgM+ in CSF	19/19 (**100**)	0/3 (0)	0/0

*First follow-up visit at 3-5 days post donation.

Updated from Barzon *et al. J Infect Dis 2013*

West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011

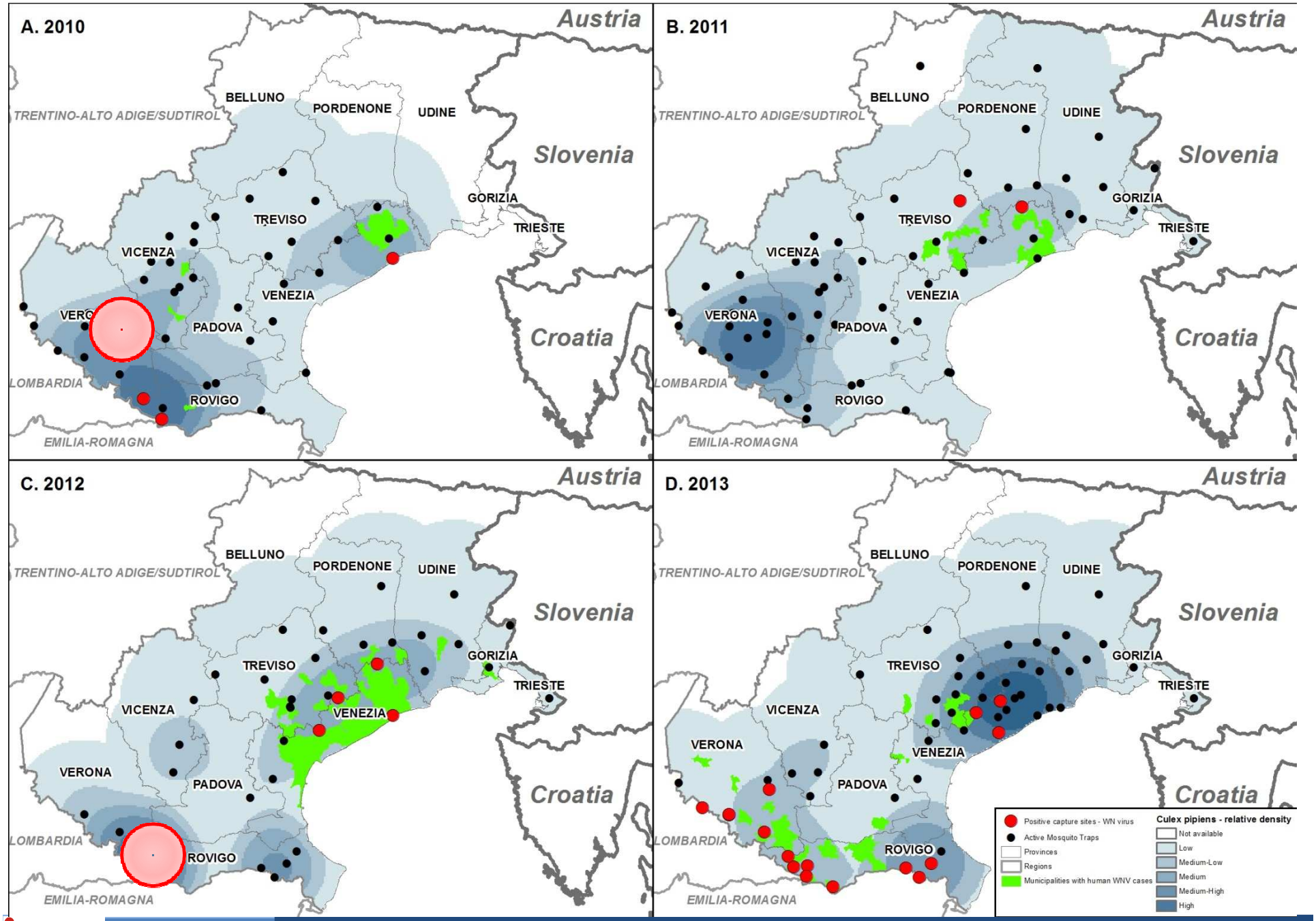
A Nanni Costa (centronazionale.trapianti@iss.it)[1], M R Capobianchi[2], G Ippolito[2], G Palù[3,4], L Barzon[3,4], G Piccolo[5], B Andreetta[6], M Filippetti[1], D Fehily[1], L Lombardini[1], P Grossi[7]

Eurosurveillance, 2011

TABLE

Molecular and serological test results for West Nile virus infection on samples from organ donor and recipients, Italy 2011 (n=6)

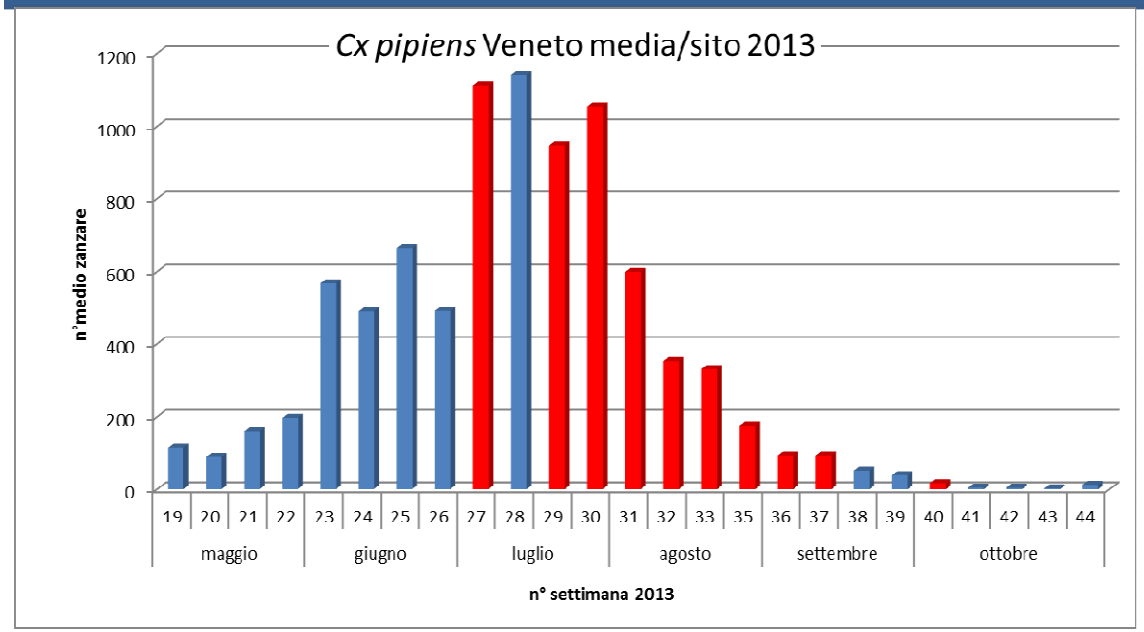
	NAT test result	Antibodies determination
Donor	Negative on blood	Positive (IgG and IgM) on blood
First kidney recipient	Positive on blood and spinal fluid	Positive (IgG and IgM) on blood and spinal fluid
Second kidney recipient	Positive on blood and spinal fluid	Positive (IgG and IgM) on blood and spinal fluid
Heart recipient	Negative on blood	Negative on blood
Liver recipient	Negative on blood	Positive (IgG and IgM) on blood
Lung recipient	Positive on blood	Positive (IgG and IgM) on blood

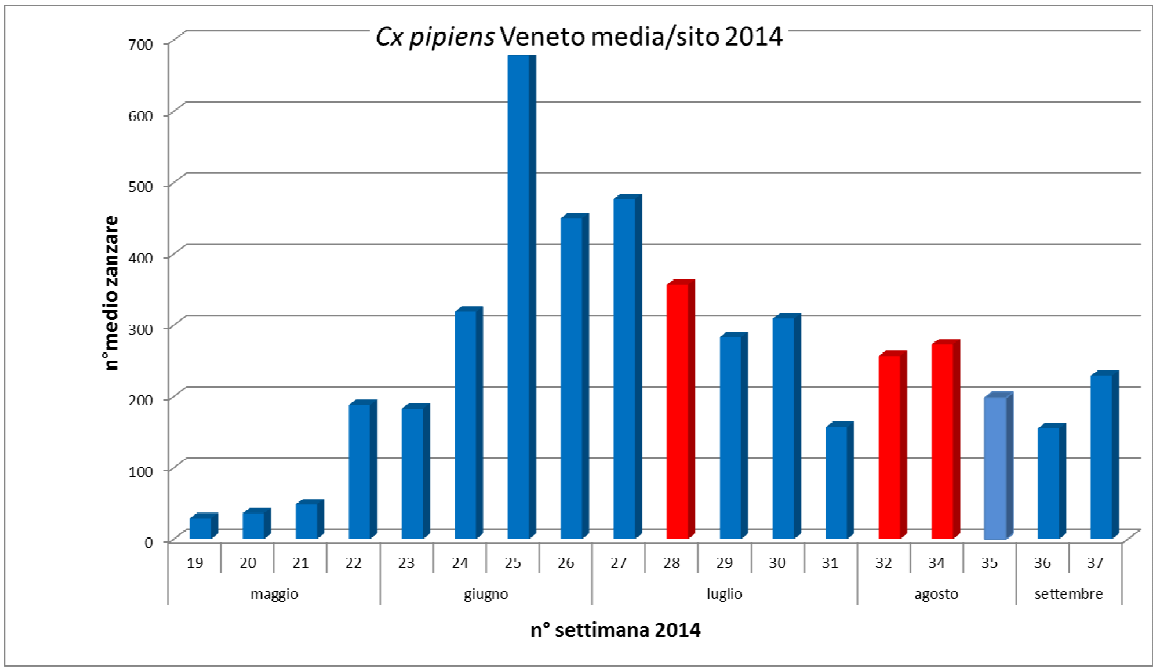


Istituto Zooprofilattico Sperimentale delle Venezie

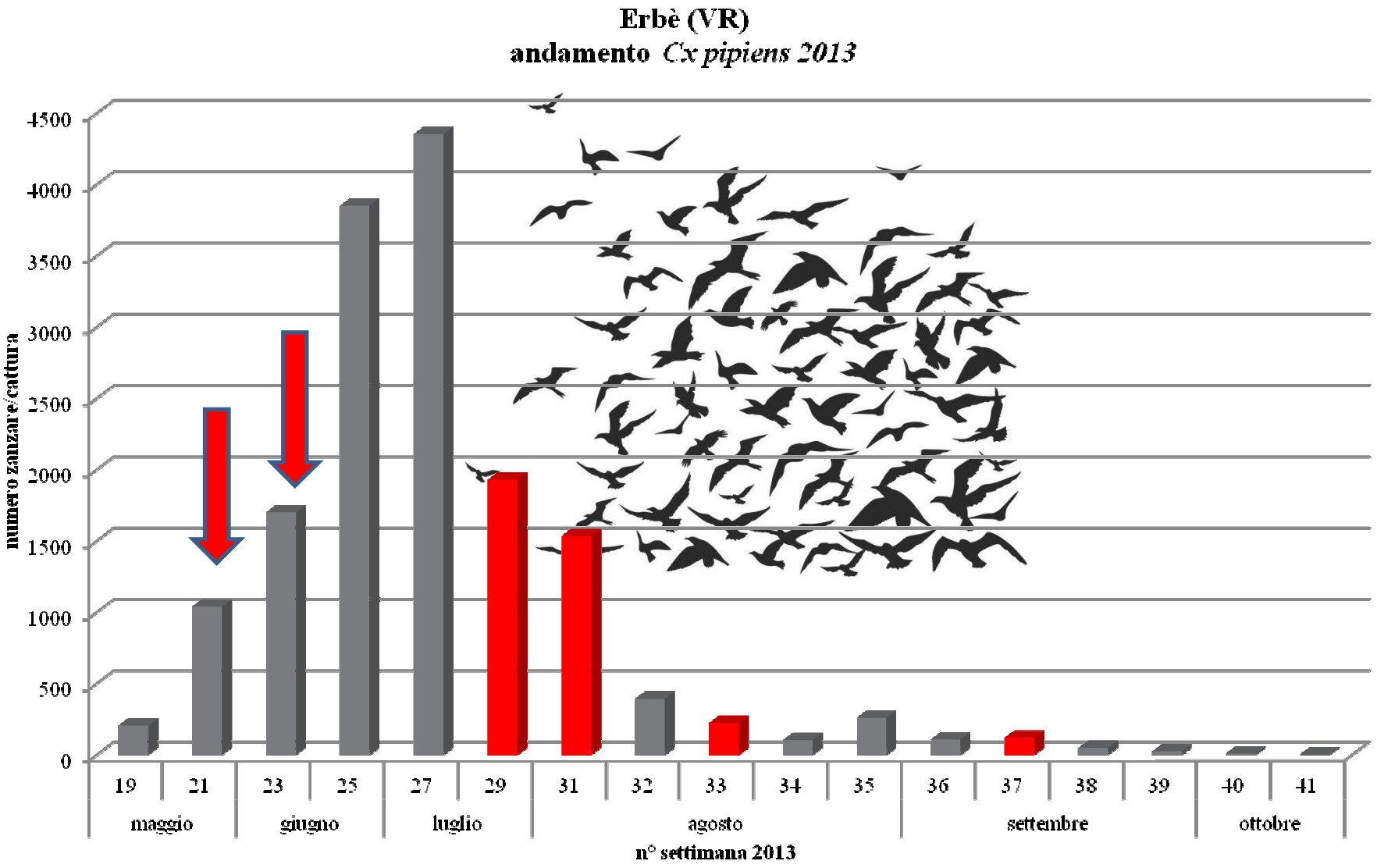
Cx pipiens density and WNV in mosquitoes and humans 2010-2013

l'importanza della densità: quando





l'importanza della densità:



ZIKV-caratteristiche

- Zika virus è un arbovirus del genere *Flavivirus* appartenente alla famiglia *Flaviviridae* come i virus di Dengue, Febbre Gialla, Encefalite Giapponese, West Nile.

ZIKV-trasmissione

ZIKV-trasmissione

- La malattia è trasmessa attraverso la puntura di zanzara del genere *Aedes*

- Descritta anche trasmissione tramite:
  - emotrasfusioni
  - rapporti sessuali (1 case report)
  - trasmissione perinatale

ZIKV-trasmissione

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Zika Virus in Gabon (Central Africa) – 2007: A New Threat from *Aedes albopictus*?

Gilda Grard[1]*, Mélanie Caron[1,2], Illich Manfred Mombo[1,2], Dieudonné Nkoghe[1,3], Statiana Mboui Ondo[1], Davy Jiolle[2,4], Didier Fontenille[2], Christophe Paupy[2,4], Eric Maurice Leroy[1,2]

1 UMVE, Centre International de Recherches Médicales de Franceville, Franceville, Gabon, **2** MIVEGEC, Institut de Recherche pour le Développement (IRD-224, CNRS-5290 Universités de Montpellier 1 & 2), Montpellier, France, **3** Ministère de la Santé Publique, Libreville, Gabon, **4** URES, CIRMF, Franceville, Gabon

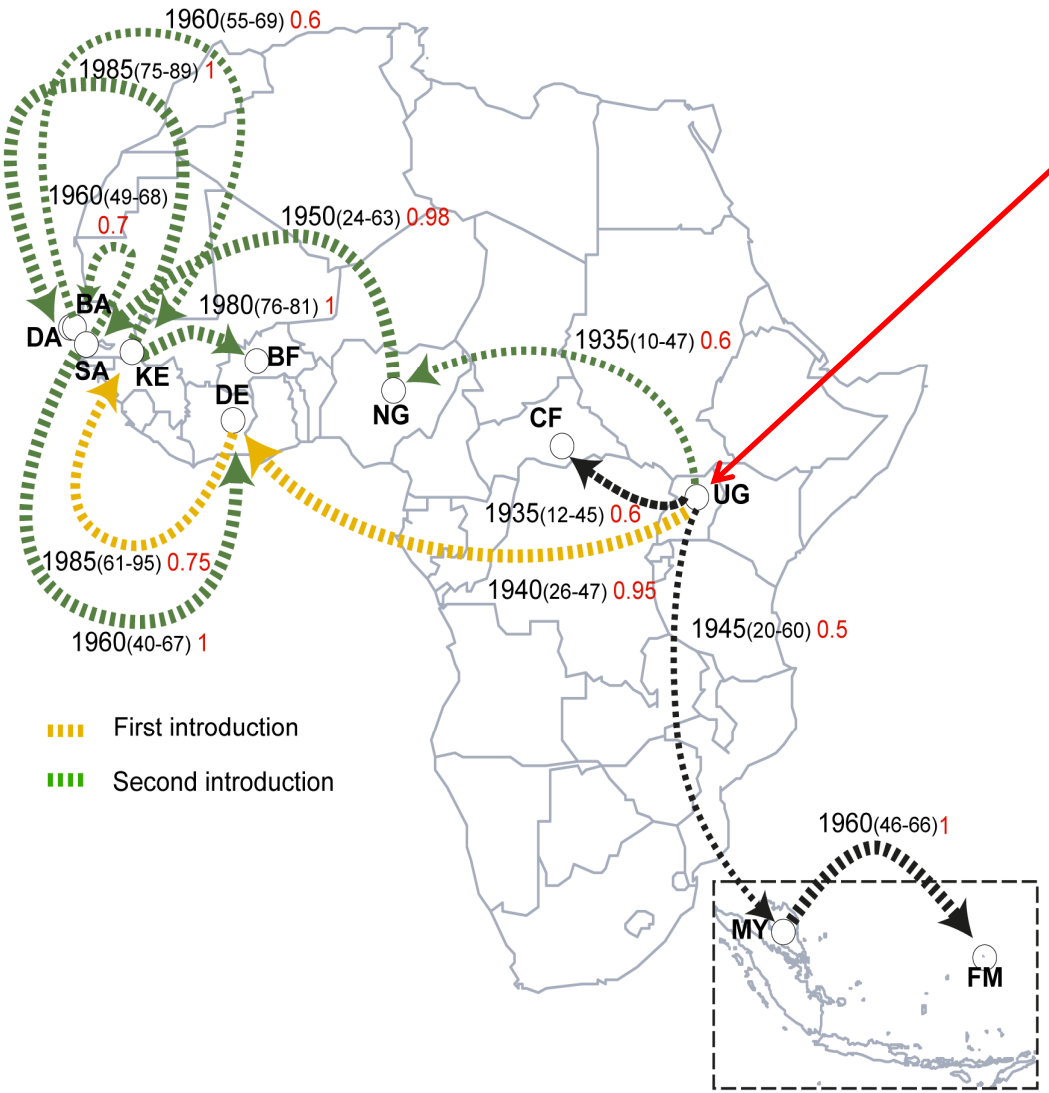
Abstract

Background: Chikungunya and dengue viruses emerged in Gabon in 2007, with large outbreaks primarily affecting the capital Libreville and several northern towns. Both viruses subsequently spread to the south-east of the country, with new outbreaks occurring in 2010. The mosquito species *Aedes albopictus*, that was known as a secondary vector for both viruses, recently invaded the country and was the primary vector involved in the Gabonese outbreaks. We conducted a retrospective study of human sera and mosquitoes collected in Gabon from 2007 to 2010, in order to identify other circulating arboviruses.

Methodology/Principal Findings: Sample collections, including 4312 sera from patients presenting with painful febrile disease, and 4665 mosquitoes belonging to 9 species, split into 247 pools (including 137 pools of *Aedes albopictus*), were screened with molecular biology methods. Five human sera and two *Aedes albopictus* pools, all sampled in an urban setting during the 2007 outbreak, were positive for the flavivirus Zika (ZIKV). The ratio of *Aedes albopictus* pools positive for ZIKV was similar to that positive for dengue virus during the concomitant dengue outbreak suggesting similar mosquito infection rates and, presumably, underlying a human ZIKV outbreak. ZIKV sequences from the envelope and NS3 genes were amplified from a human serum sample. Phylogenetic analysis placed the Gabonese ZIKV at a basal position in the African lineage, pointing to ancestral genetic diversification and spread.

Conclusions/Significance: We provide the first direct evidence of human ZIKV infections in Gabon, and its first occurrence in the Asian tiger mosquito, *Aedes albopictus*. These data reveal an unusual natural life cycle for this virus, occurring in an urban environment, and potentially representing a new emerging threat due to this novel association with a highly invasive vector whose geographic range is still expanding across the globe.

ZIKV-storia



1947 1° isolamento
sangue di scimmia Rhesus
nella foresta Zika
(Uganda)

Evidenza di diffusione anche in:

- **Asia:** Malesia (1969), Indonesia (1981), Pakistan (1983), Cambogia (2010), Thailandia(2013).
- **Pacifico:** Yap (Micronesia-2007), Polinesia Francese e in Nuova Caledonia(2013)

ZIKV-clinica

Incubazione 4-7 gg.

Definizione di caso sospetto (French Polynesia):

- Rash eritematoso maculo-papulare± fever<38.5°
- E almeno due tra:
  i) Iperemia congiuntivale
  ii) Artralgia o mialgia
  iii) Edemi alle mani o ai piedi

ZIKV-
Possibili complicanze?

- 70 casi con complicanze (su 396 casi di ZIKV confermati in laboratorio, Novembre 2013 - 7 Febbraio 2014)
  - 38 Sindrome di Guillain-Barré
  - 25 altre complicanze neurologiche (encefalite, meningo-encefalite, parestesia, paralisi facciale e mielite)
  - 4 porpora trombocitopenica
  - 2 complicanze oftalmologiche
  - 1 complicanza cardiaca
- Zero decessi

[Fonte: Polynesia Epibulletin]

ZIKV-clinica

Eurosurveillance, Volume 19, Issue 9, 06 March 2014

Rapid communications

ZIKA VIRUS INFECTION COMPLICATED BY GUILLAIN-BARRÉ SYNDROME – CASE REPORT, FRENCH POLYNESIA, DECEMBER 2013

E Oehler (erwan.oehler@cht.pf)[1], L Watrin[2], P Larre[2], I Leparc-Goffart[3], S Lastère[4], F Valour[1], L Baudouin[5], H P Mallet[6], D Musso[7], F Ghawche[2]

Ipotesi per spiegare GBS in corso di ZIKV:

1. genetic evolution of the virus to a more pathogenic genotype
2. particular susceptibility in the Polynesian population
3. the simultaneous epidemics of ZIKV and type 1 and 3 dengue fever (sequence of DENV and ZIKA infections)

*Carod-Artal FJ, Wichmann O, Farrar J, Gascón J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12(9):906-19. http://dx.doi.org/10.1016/S1474-4422(13)70150-9

(il paziente aveva segni sierologici di pregressa infezione da dengue e segni sierologici di infezione da ZIKV acuta)

ZIKV-diagnosi

- Storia di viaggio + clinica
- Possibile leucopenia o piastrinopenia, incremento dell'LDH
- Diagnosi eziologica (solo centri di riferimento):
  - Ricerca RNA virale (primi 3-5 gg)
  - Anticorpi IgM-IgG specifici per ZIKV (ELISA e immunofluorescenza) a partire dal 5-6° giorno di malattia [cross-reattività con altri Flavivirus]

Dengue

Lyle R. Petersen, MD, MPH

Presentation Outline

I. What is dengue ?

II. How is it transmitted?

III. Where is dengue found and what is the burden?

IV. Who is affected?

V. Clinical spectrum: what does a case look like?

VI. How can we diagnose dengue?

VII. How can we prevent dengue?

Part I:

What is dengue?

Dengue

- **Most important vector-borne viral disease worldwide**
  - ~50-100 million infections/year
  - ~500,000 hospitalizations/year
  - ~25,000 deaths/year
- **Caused by four viruses , Dengue virus -1, -2, -3 and -4**
- **Emerged only 200-400 years ago**
- **No important non-human reservoir**

Photos credits: "Train-the-Trainer" course material, CDC 2010

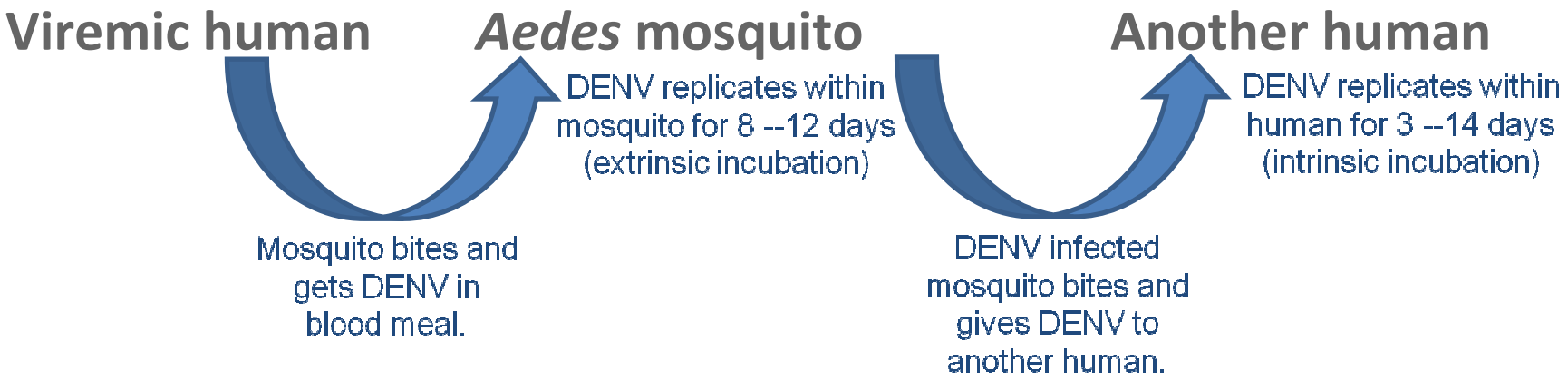
Part II:

How is Dengue virus transmitted?

Transmission: How do we get dengue?

- **Dengue is primarily a mosquito-borne disease**
  - *Aedes aegypti* most common; *Aedes albopictus* can also sustain transmission

- **Transmission Cycle:**



A dengue virus infected mosquito bites human and can transmit virus with as little as 10^2 viral particle per secretion*

Dengue is also blood-borne infection

- **Evidence of transmission through receipt of donor organs or tissue[1]**
  - Bone marrow, renal transplant
- **Transmission documented via receipt of blood products[2,3,4]**
  - 1 donor and 3 recipients, Singapore
  - 1 donor and 1 recipient, Hong Kong
  - 1 donor and 1 recipient, Puerto Rico
- **Seven reports of transmission after occupational exposure in a healthcare setting[1]**
- **Vertical Transmission[5]**

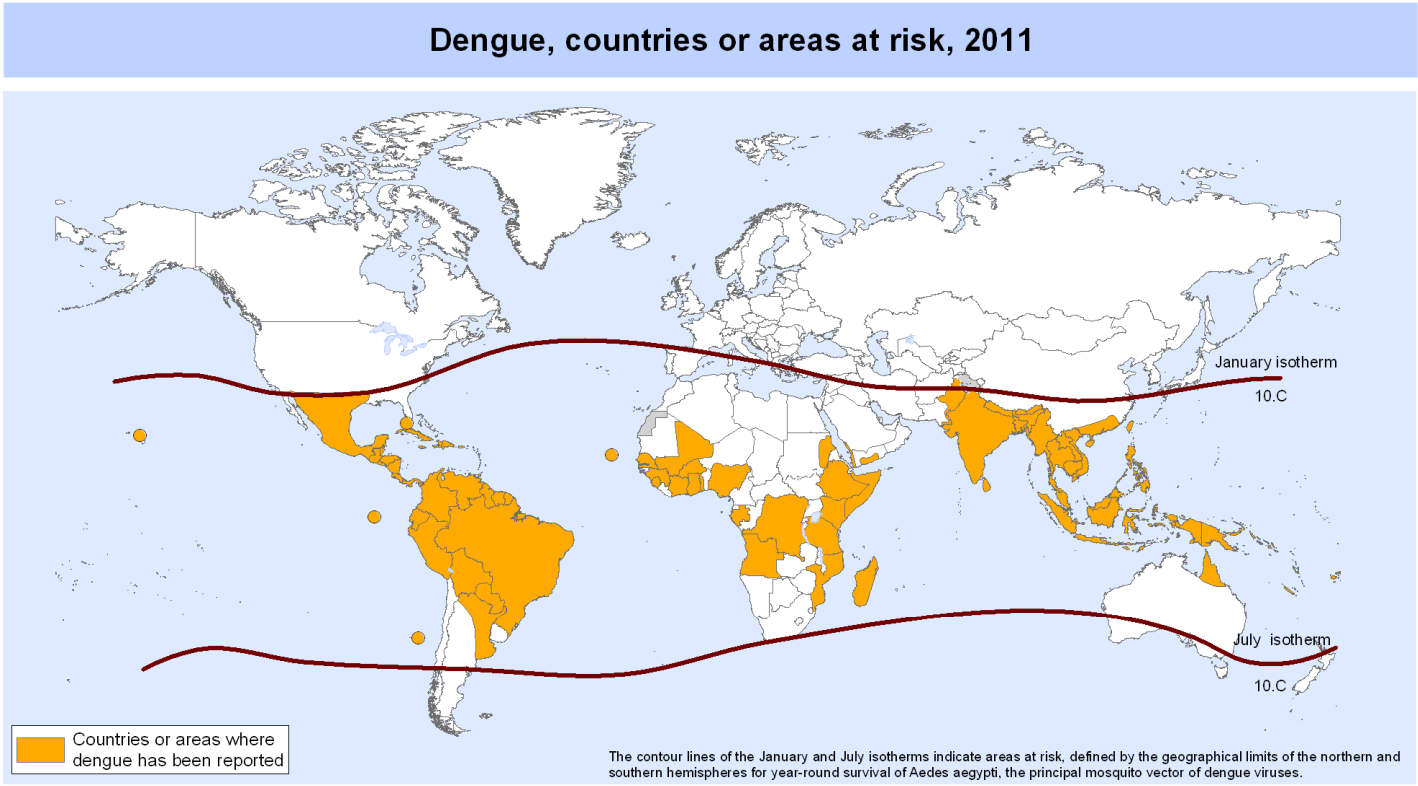
[1] Wilder-Smith A, *et al*. ,Threat of Dengue to Blood Safety in Dengue-Endemic Countries. *EID* 2009; 15(1):8-11.
[2] Chuang *et al*., Review of dengue fever cases in Hong Kong during 1998 to 2005. *Hong Kong Med J* 2008;14:170-177.
[3] Tambyah *et al*., Dengue hemorrhagic fever transmitted by blood transfusion. *N Engl J Med* 2008;359:1526-1527.
[4] Stramer et al, Dengue viremia in blood donors identified by RNA and detection of dengue transfusion transmission during the 2007 dengue outbreak in Puerto Rico. Transfusion 2012 on line
[5] Pouliot S.H., *et al.,* Maternal dengue and pregnancy outcomes: a systematic review. *Obstetr Gynecol Survey* 2010.

Part III:

Where is dengue found and what is the burden?

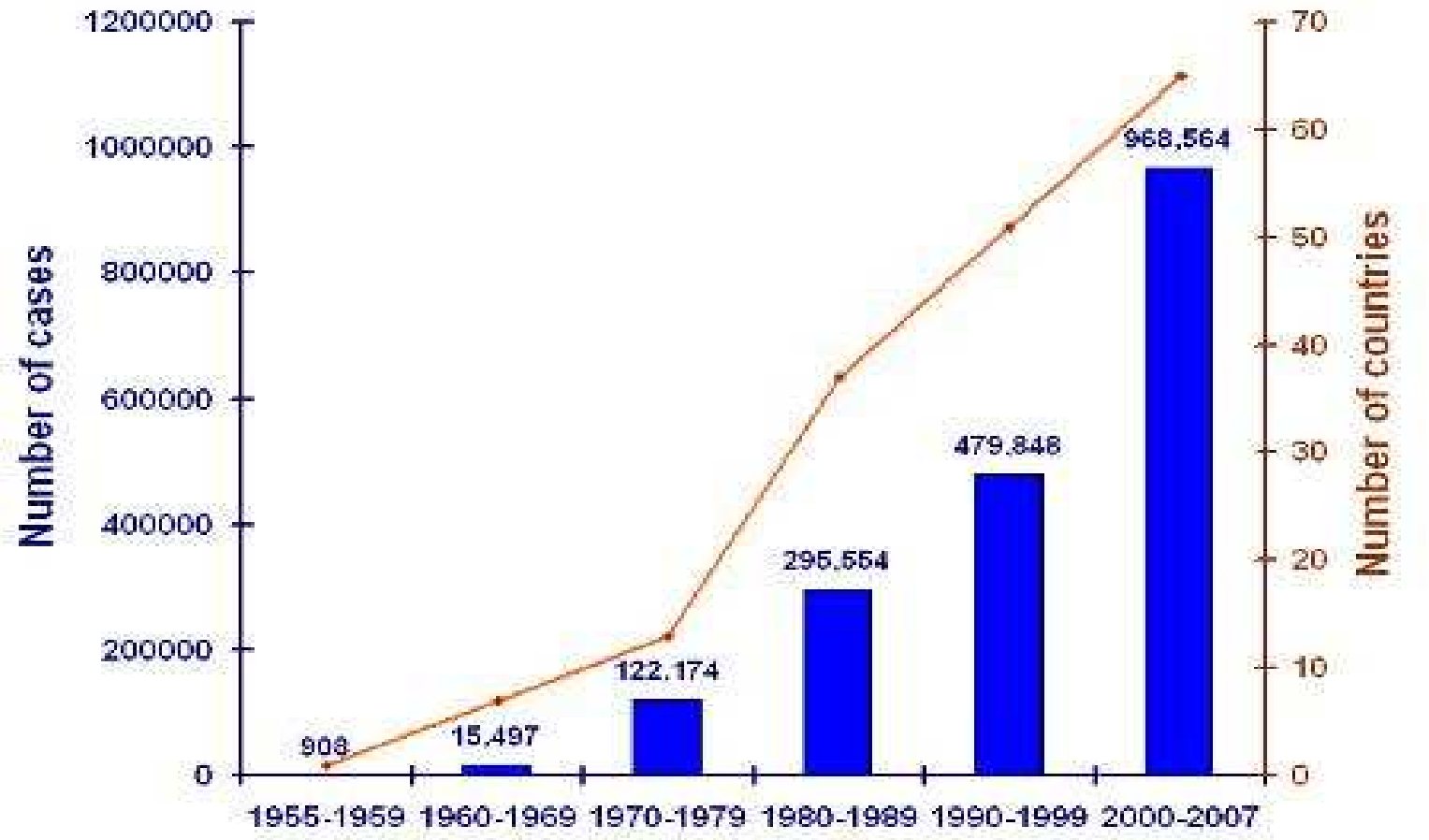
Where do dengue cases occur worldwide?

Countries where dengue reported as of 2011



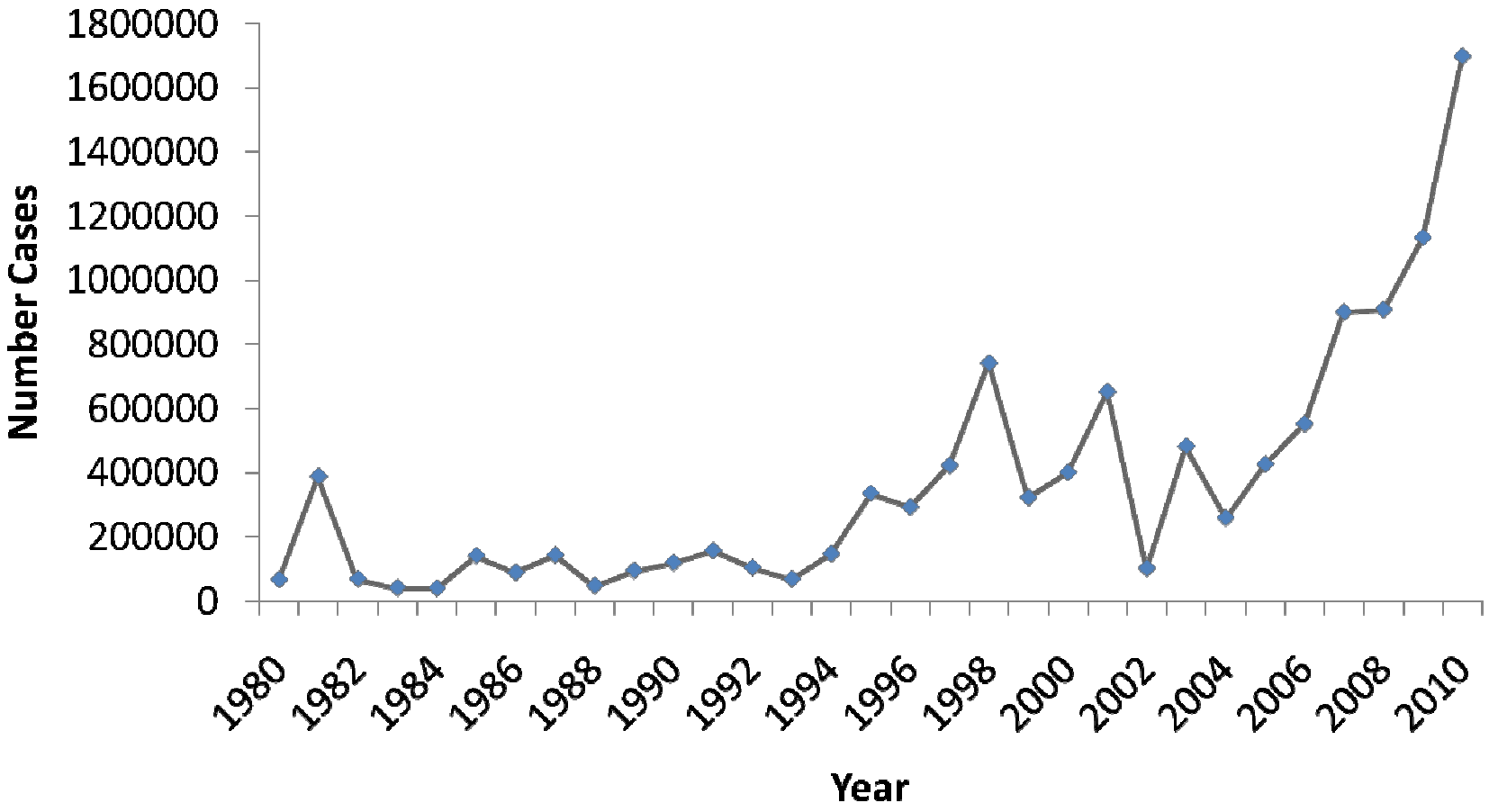
Source: WHO, International Travel and Health http://www.who.int/ith/en

Global Increase in Dengue Cases and Countries Reporting Dengue



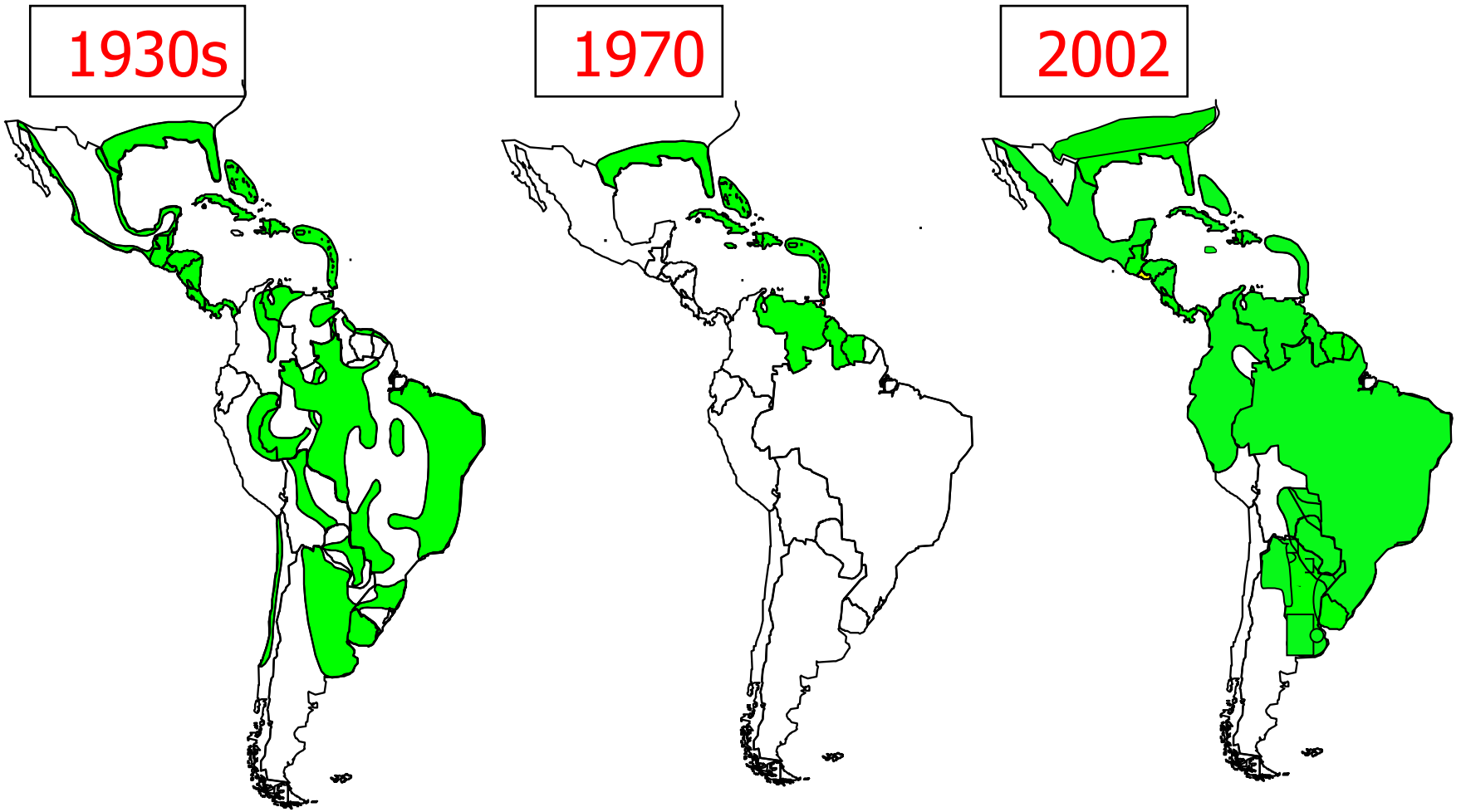
Source: WHO www.who.int/csr/disease/dengue/impact/en/

Number of Reported Dengue Cases, Western Hemisphere, 1980-2010



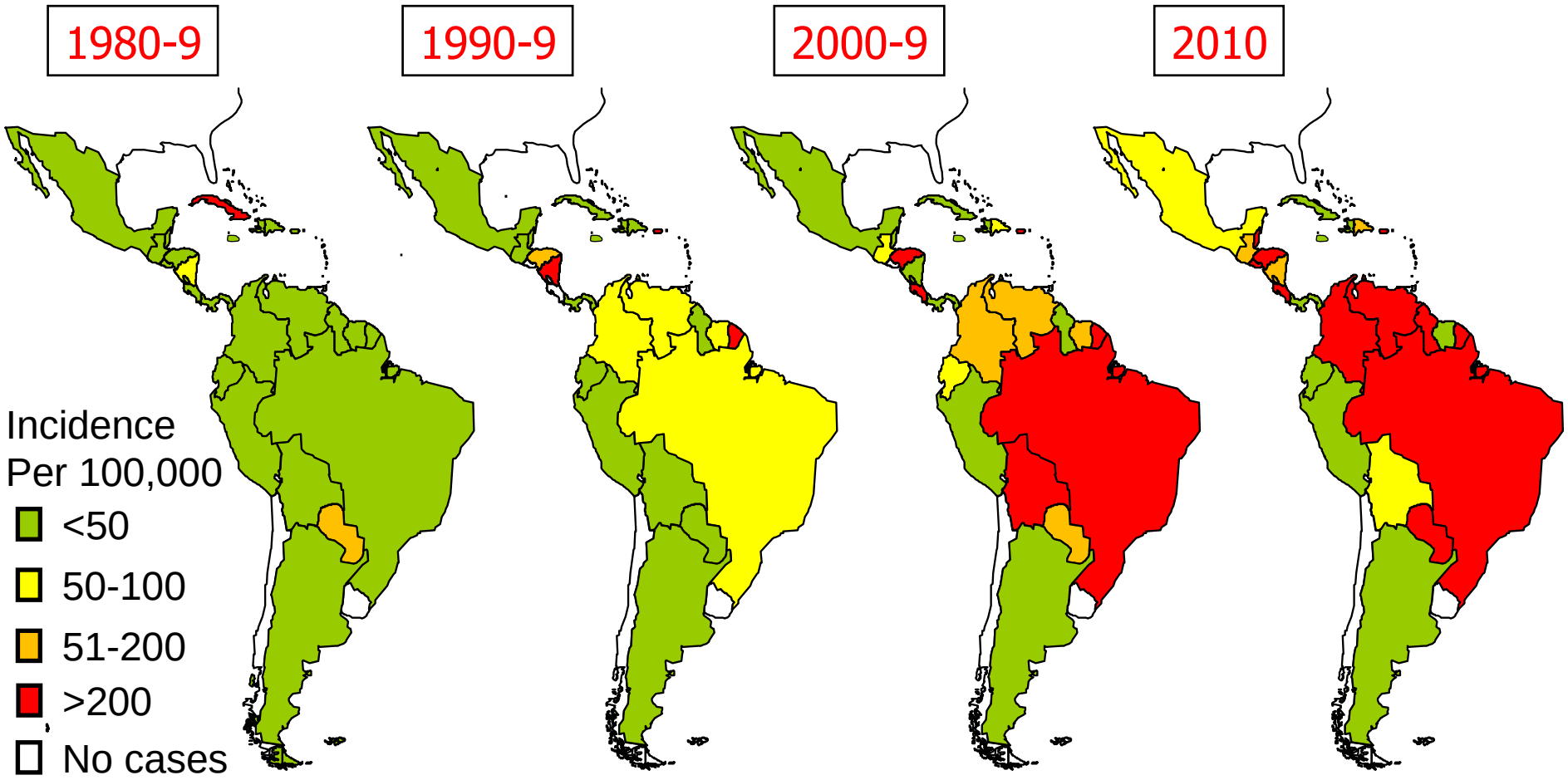
Source: PAHO

Reinfestation of *Aedes aegypti* after Cessation of Control Efforts from 1947-1970*



* Continental plan for eradication of the *Aedes aegypti.* PAHO Resolution–CD1.R1

Dengue Incidence in Latin America and the Caribbean, 1980-2010



Source: PAHO

How Good Are the Numbers?

- Poor global and national disease burden estimates
- National disease surveillance data generally poor
  - Case definitions not comparable
  - No assessments of reporting and data quality
  - Inconsistent laboratory methods to confirm cases
  - Poor ascertainment of disease severity / clinical outcomes

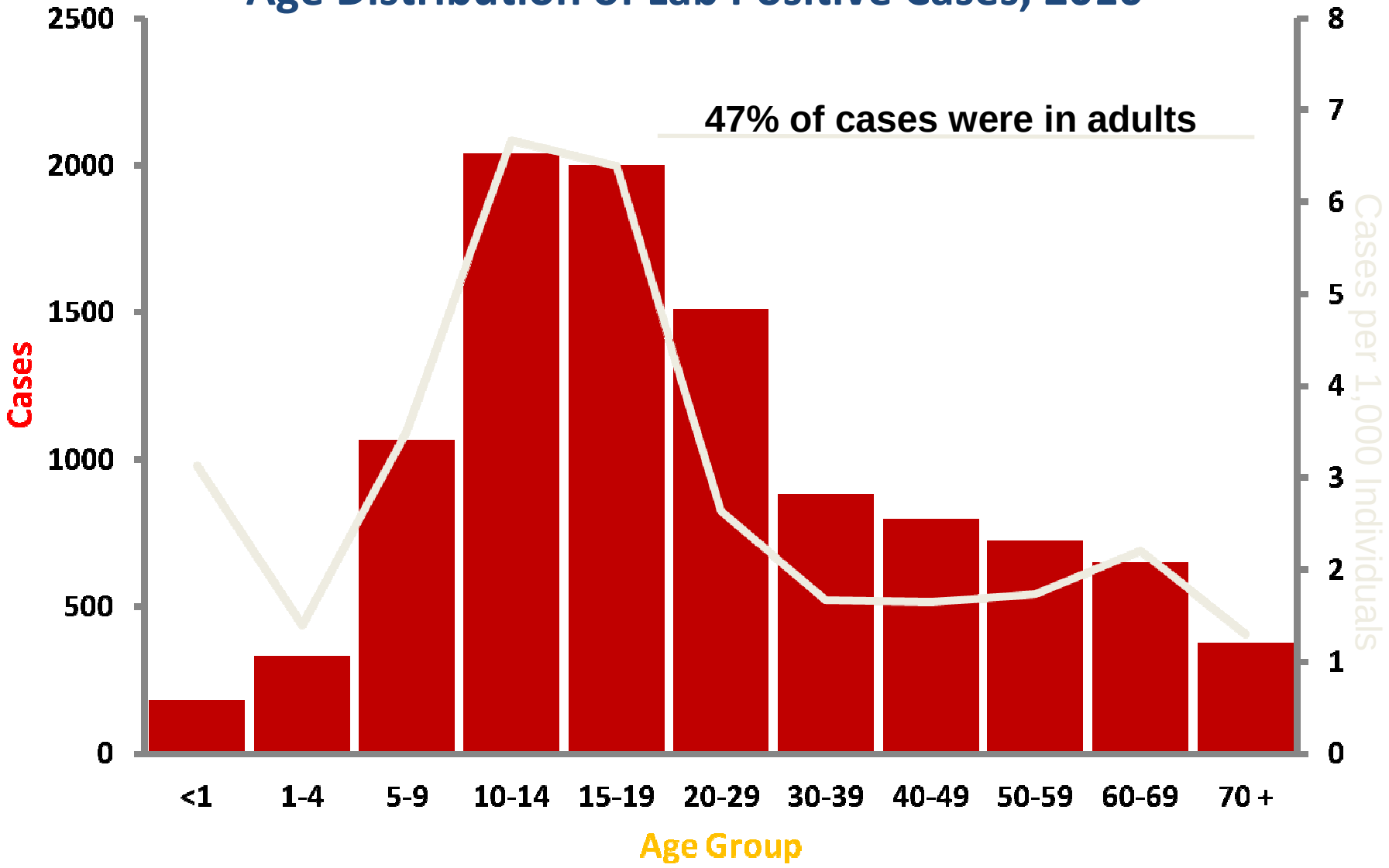
Adapted from Beatty et al: Plos Negl Trop Dis 2010 4: e890

Part IV:

Who is affected?

Epidemiology: Who gets dengue?

Age Distribution of Lab Positive Cases, 2010



Antibodies Protect

- **Homotypic Antibodies**
  - Protect against homologous DENV disease / infection
    (Sabin 1952; Halstead 1974)
- **Heterotypic Antibodies**
  - Cross protection against disease ~ 6 months (Sabin, 1952)
  - Cross protection against infection may last longer

Antibody Dependent Enhancement of Infection (ADE)

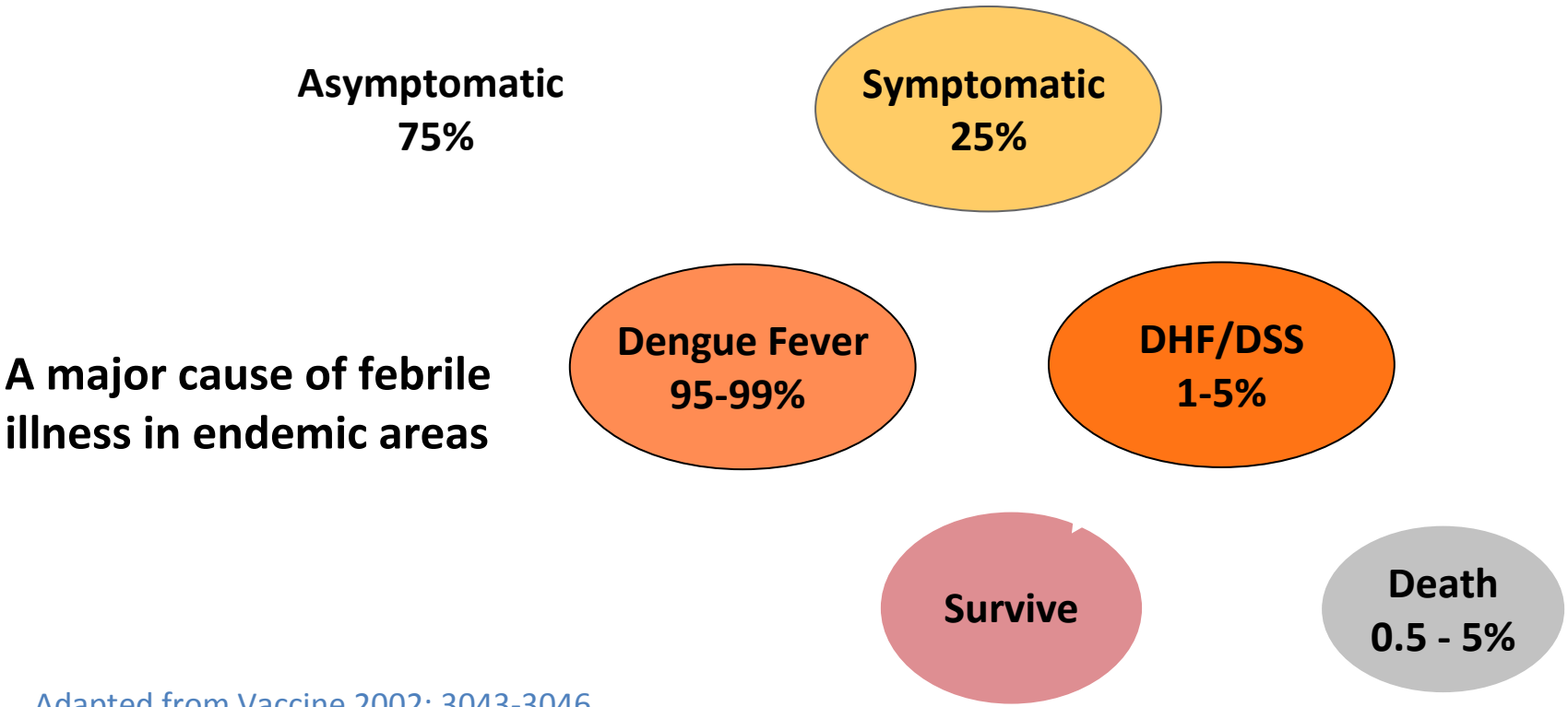
- **Enhanced infection in presence of heterotypic (non-neutralizing) antibodies**
  - *In vitro* observations
  - Chimpanzee studies with passively transferred antibodies
  - AG129 interferon deficient mouse model
- **Severe dengue (DHF) – epidemiologic observations**
  - DHF among infants with 1st DENV infection (passively acquired maternal antibody)
  - Increased risk for DHF with 2° infections

Part V:

Clinical Spectrum of Dengue

Dengue Virus Infections

Infection Incidence
~ 5% / year



A major cause of febrile illness in endemic areas

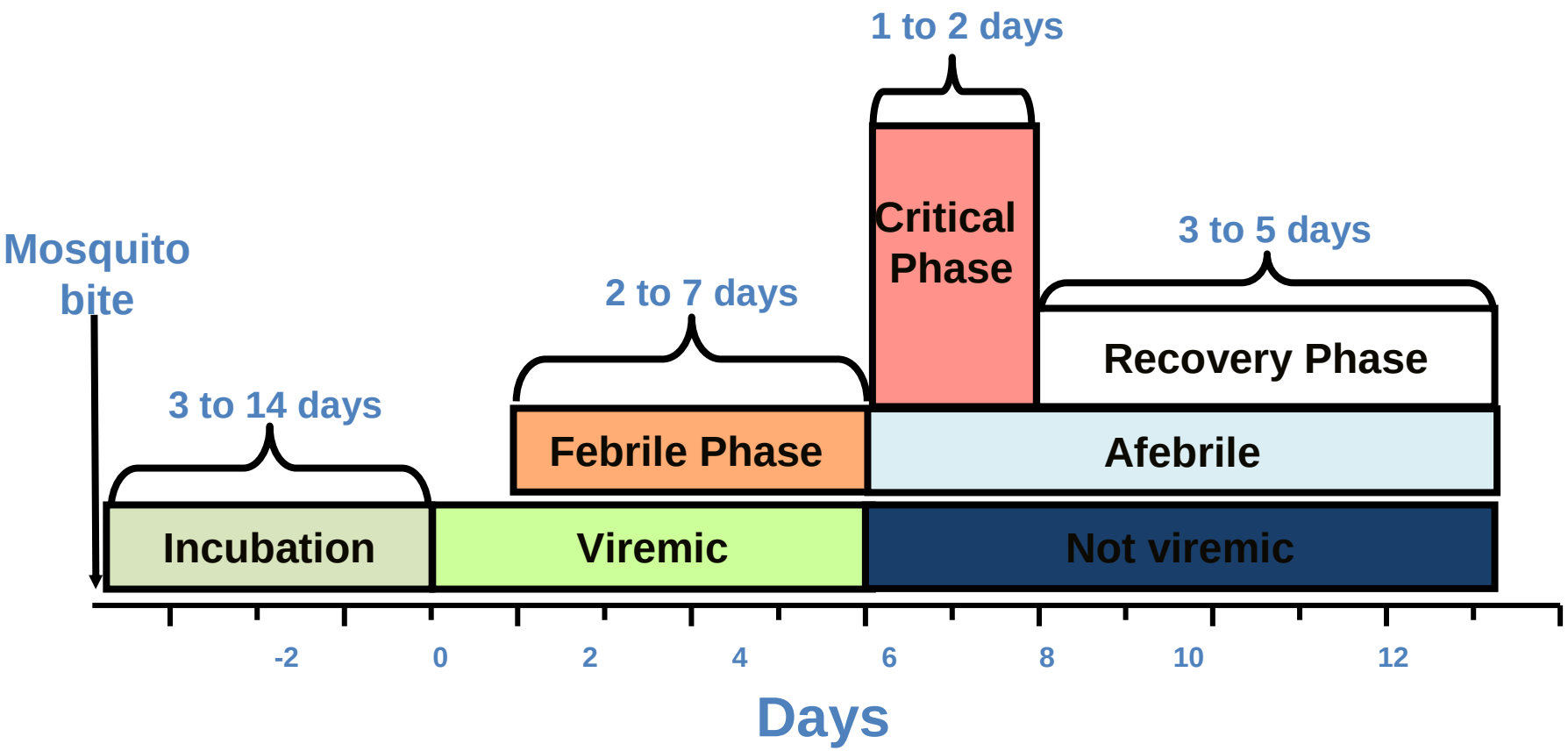
Adapted from Vaccine 2002; 3043-3046

Course of Dengue Virus Infection

- **Incubation period 3 to 14 days after being bitten**
- **Viremia in humans:**
  - Begins slightly before onset of symptoms (~24 to 48 hours)[1]
  - Lasts about 1 week (period of infectivity)[1]
  - Viremia even in asymptomatic blood donors can be as high as in symptomatic patients (10^5 – 10^9 viral copies per mL)[2]
- **Many people have asymptomatic infections[3,4]**
  - Especially children and those with primary infections

1. Nishiura & Halstead, 2007.
2. Mohammed, H. et al. , Dengue Virus in Blood Donations, Puerto Rico, 2005. Transfusion 2008; 48:1348-1354.
3. Vaughn DW. Am J Epi 2000;152(9):800-803;
3. AL Rothman (ed.), Dengue Virus, Current Topics in Microbiology and Immunology 338, Springer-Verlag Berlin Heidelberg 2010. pgs 1-13.

Clinical Course of Dengue



* Typically uncomplicated DHF/DSS lasts for 10 to 12 days

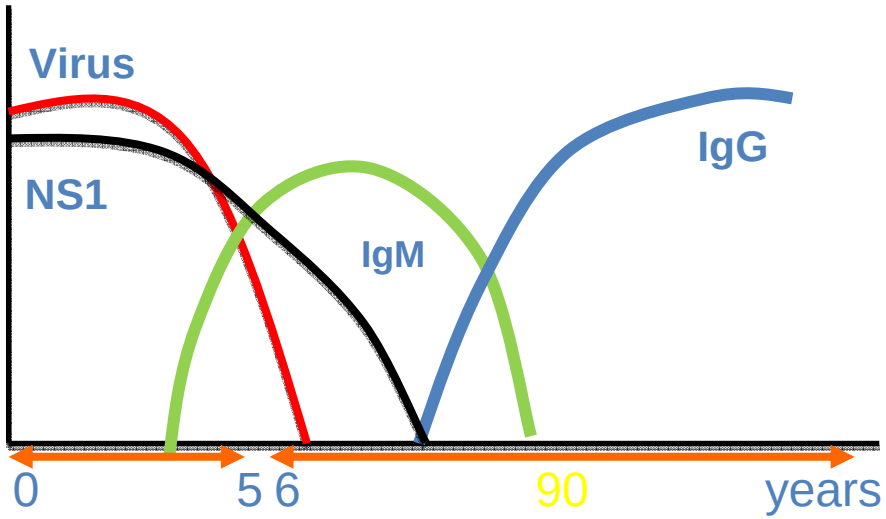
Part VI:

How can we diagnose dengue?

Dengue Diagnostics

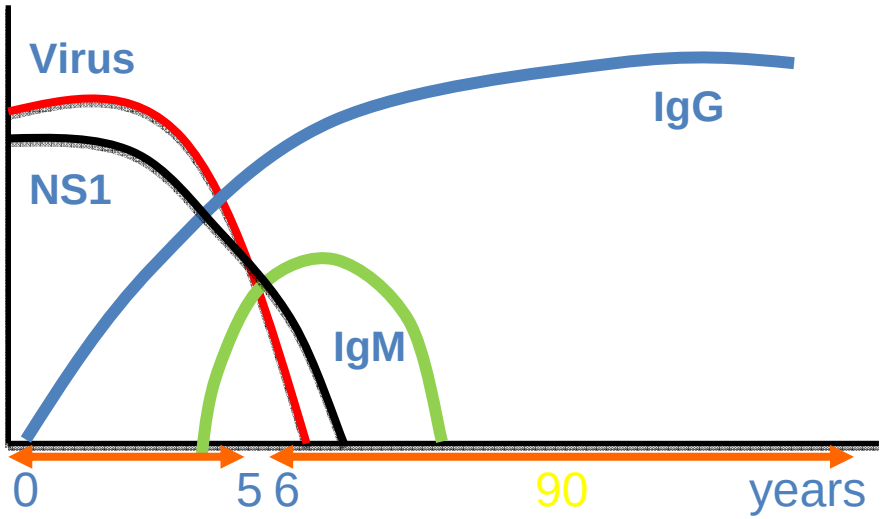
- Detect virus
  - Nucleic acid detection
  - NS1 antigen
- Detect antibodies
  - IgM, IgG

Primary Dengue Infection

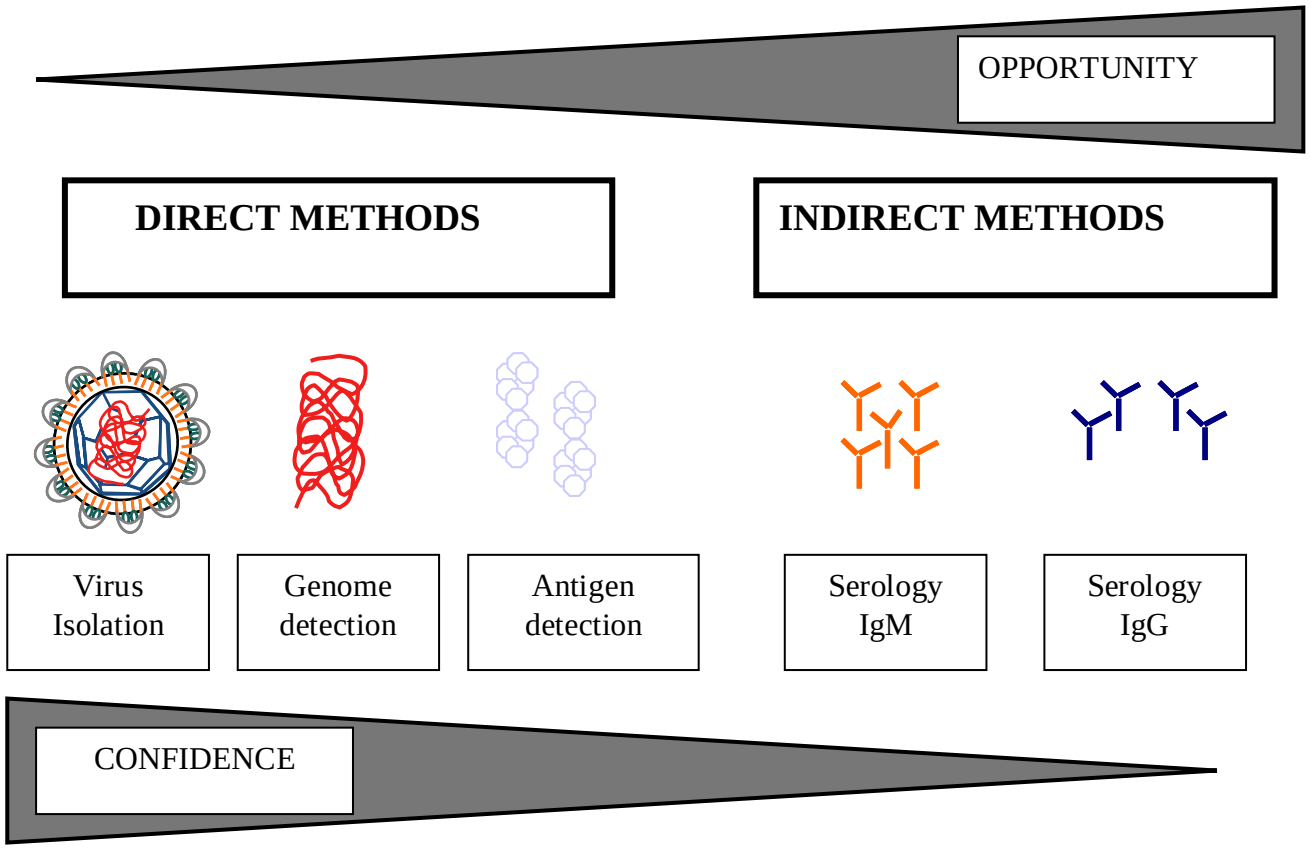


Days Post-Onset of Symptoms

Secondary Dengue Infection



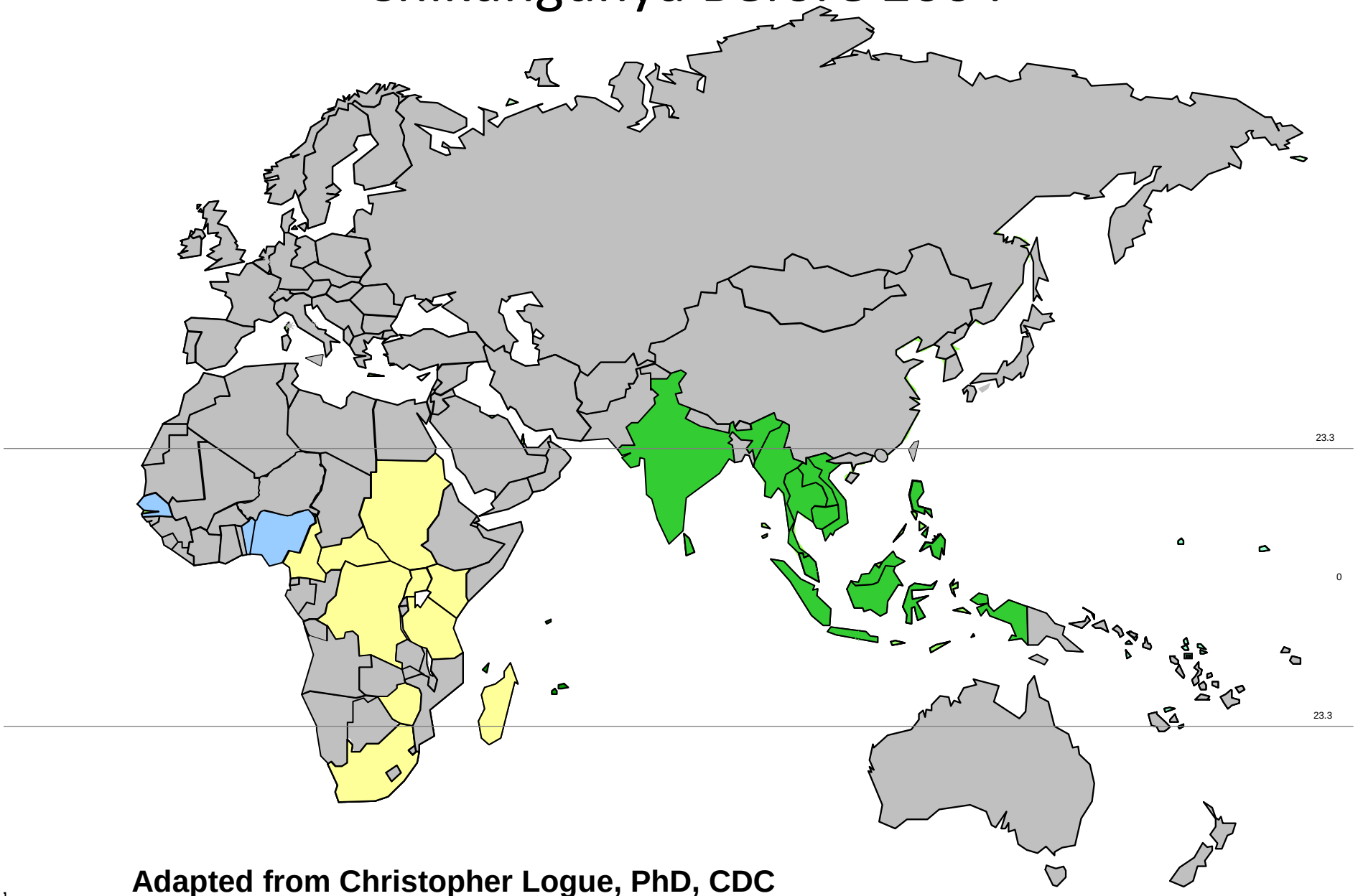
Days Post-Onset of Symptoms


OPPORTUNITY
DIRECT METHODS
INDIRECT METHODS
Virus Isolation
Genome detection
Antigen detection
Serology IgM
Serology IgG
CONFIDENCE

Chikungunya

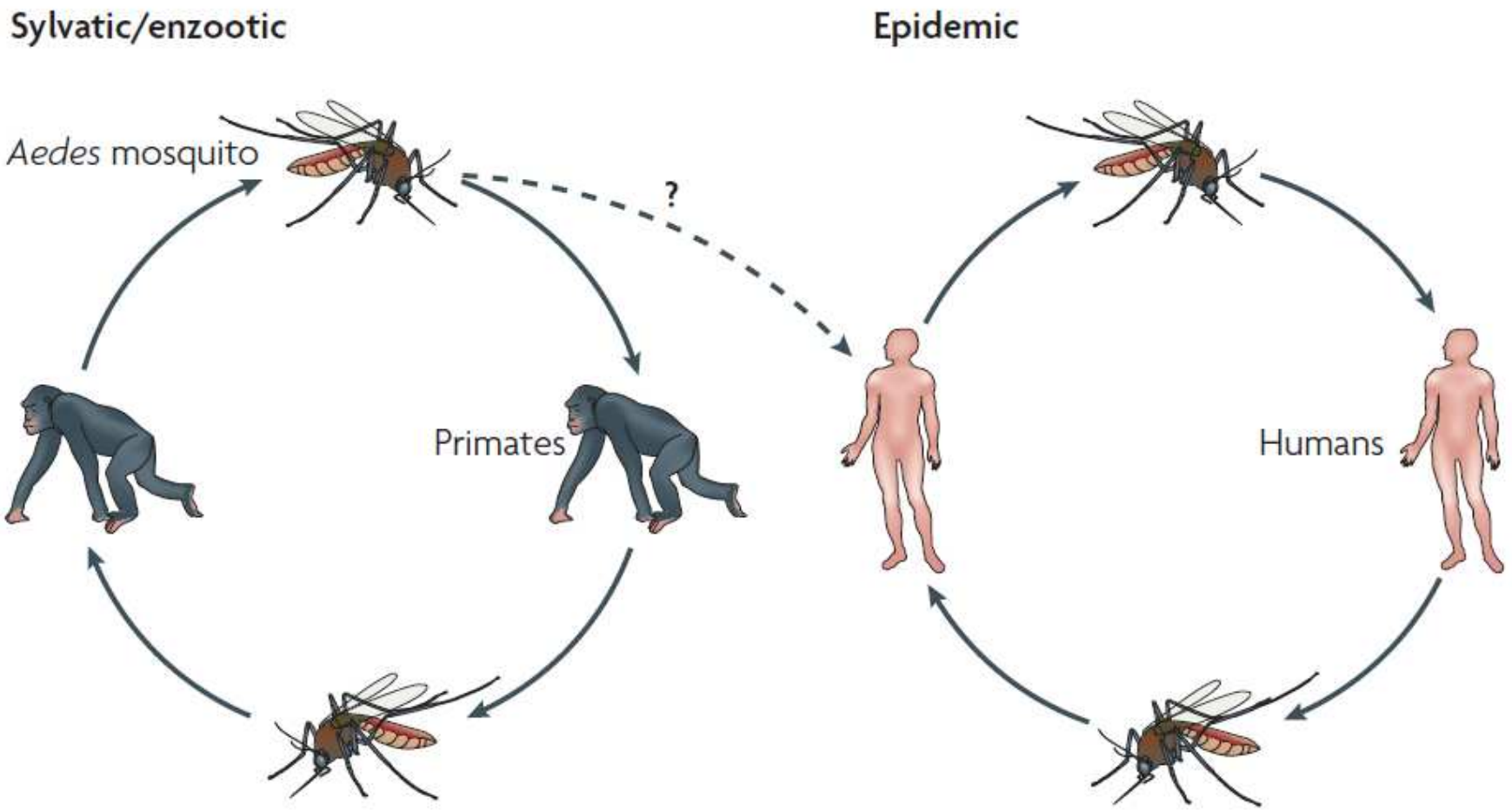
- Derived from Swahili or Makonde: “that which bends up”
- Isolated from febrile patient during outbreak on Makonde Plateau, Tanzania in 1953
- Fever, headache, arthralgia, rash
- Arthritis may persist months to years

Approximate Known Distribution of Chikungunya Before 2004



Adapted from Christopher Logue, PhD, CDC

Transmission Cycle



Whitehead, et al. Nature Reviews 2007

Non Vector-Borne Transmission

- Mother to infant transmission
  - Rare if mother infected well before delivery
  - 50% transmission with intrapartum infection
  - Breastfeeding transmission not reported
- Direct transmission through blood
  - One case of nosocomial transmission*
  - Potential for blood transfusion

* Cordel et al. Eurosurveillance 2006

Chikungunya and Dengue: A Case of Mistaken Identity?

DONALD E. CAREY

FROM 1961 through 1966 the writer was involved in studies of endemic dengue at Vellore, South India.[1] In 1964 the recurrent, yearly cycle of dengue in the area was broken by a massive wave of chikungunya virus infection that swept through Madras State.[2] Although chikungunya illness has generally been described as

Carey DE. J Hist Med Allied Sci. 1971 Jul;26(3):243-62.

David Bylon, Batavia 1779

- “I noticed a gnawing pain in my right hand and in the joints of the hand and arm which gradually increased, extending to the shoulder and then over my whole body so that at 9 o’clock that evening I was in bed with a high fever. I had a restless night…severe pains…especially in the legs and arms and in the joints.”

Hirsch, Cairo 1779

- “Its first attack lasted for three days, after which the illness increased or diminished…accompanied by pain in the joints, knees, and extremities…often with swelling of the fingers.”

CHIKV-associated rheumatism

polyarthritis and multiple tenosynovitis of wrists and fingers

hypertrophic tenosynovitis of one ankle
(Dr. F Simon, Laveran Military Hospital, Marseille, France)

swelling observed in the right knee of a CHIKV infected patient
(Dr Adil Fakim, Mauritius)

Clinical Presentation
Reunion Outbreak, 2007

157 patients with lab confirmed CHIKV infection

- Arthralgia: 96%
- Fever: 89%
- Headache: 47%
- GI symptoms: 47%
- Rash: 40%
- Swollen joints: 32%
- CNS signs: 12%
- Hemorrhage: 6%

- Lymphopenia: 79%
- Hypocalcemia: 55%
- Elevated AST: 38%
- Platelets < 150K: 44%
- Platelets < 100K: 10%

Borgherini et al. Clin Inf Dis 2007

Symptoms of Cases, Ravenna, 2007

	Number of cases (%)
Fever*	205 (100%)
Joint pain†	199 (97%)
Fatigue	190 (93%)
Skin rash	106 (52%)
Headache	105 (51%)
Muscle pain	94 (46%)
Diarrhoea	48 (23%)
Itching	42 (20%)
Vomiting	40 (19%)
Photophobia	31 (15%)
Conjunctivitis	7 (3%)

Rezza, et al. *Lancet* 2007; 370: 1840–46

Pathogenesis

- Incubation period 2-12 days, typically 3 to 7 days
- 3-25% of infections are asymptomatic
- Viremia up to day 6 after onset
- Acute signs usually resolve in 1-2 weeks, arthralgia can persist for months
- Case fatality rate 1:1000 or less
- Although joint effusions are rare, soft tissue swelling around joints is common
- Some studies suggest viral replication in muscle and joints with recruitment of host inflammatory response

Diagnosis

- Fever, polyarthritis…in patient with potential exposure and no other cause
- Acute phase: viral culture, PCR, antigen detection, IgM antibody
  - PCR days 1 to 7 after onset
  - IgM day 2 ? to 120 ? after onset
- Convalescent or chronic phase: IgM, IgG, neutralizing antibody, seroconversion
- Antibody to CHIKV can cross-react with ONNV

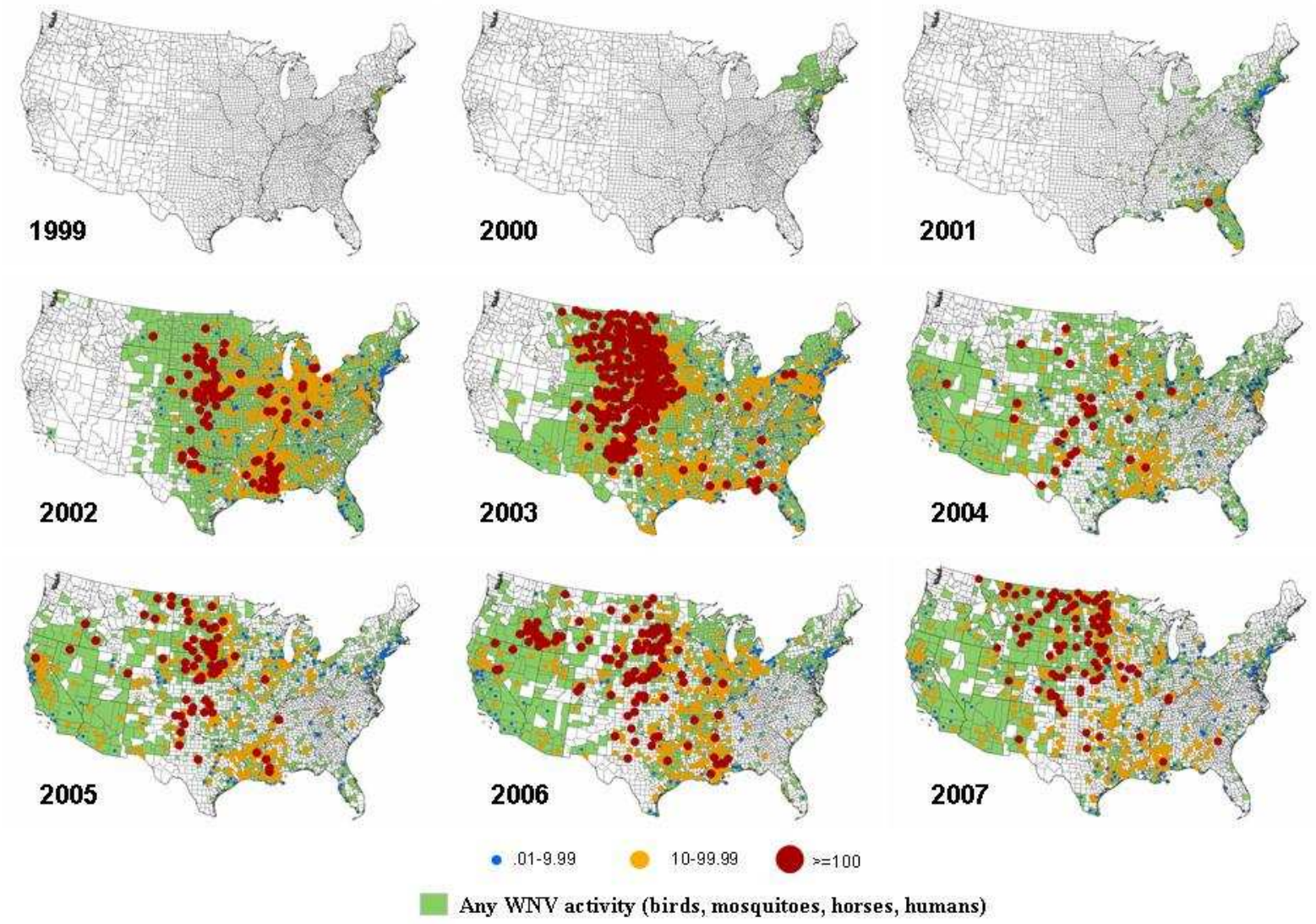
Treatment

- Non-steroidal anti-inflammatory drugs
- Interferon, ribavirin?
- Chloroquine in chronic disease?

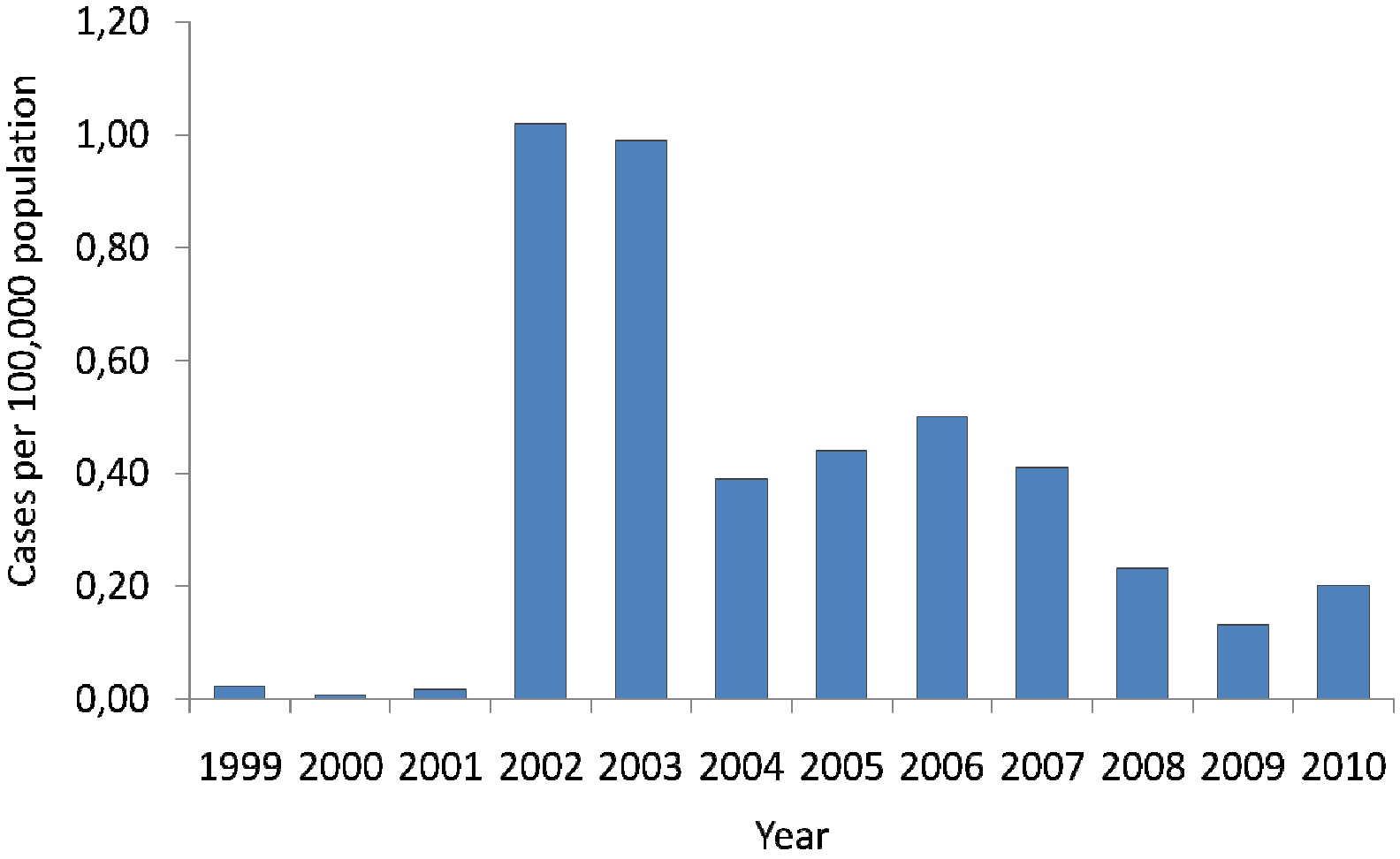
West Nile Virus in North America: Background

- Discovered in 1999 in New York City during an outbreak of meningitis and encephalitis in humans and an accompanying epizootic in birds
- Emergence during heat wave
- Means of importation unknown

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



Incidence WNV Neuroinvasive Disease, United States, by Year, 1999-2010



West Nile Virus Clinical Syndromes

- West Nile fever
- West Nile neuroinvasive disease
  - Meningitis
  - Encephalitis
  - Acute flaccid paralysis

Development of WN Fever

- Follow-up of blood donors*
  - 576 NAT-positive, IgM-negative donors negative at the index donation and 615 unconfirmed (control) donors

- 26% became symptomatic (≥3 indicator symptoms)
  - Females>males (OR=1.6; 95% CI 1.1, 2.3)
  - Age not a risk factor
  - Viral load a risk factor
  - 38% sought medical care due to WNV symptoms
    - 5% diagnosed WNV infection
    - 2% hospitalized

* J Infect Dis 2010;202:1354-61

Symptom Frequency within 14 Days After Donation (N=167)*

Symptom	Frequency (percent)
Headache	75
Generalized weakness	75
New rash	58
Fever	56
Severe muscle pain	54
Joint pain	49
Chills	47
Painful eyes	40

* Persons meeting symptomatic case definition (≥3 indicator symptoms)

WNV Rash

*Ferguson et al., Clin Infect Dis 2005;41:1204-07; Huhn et al. AJTMH. 2005;72:768-76.

Number of Infections to Produce One Case of WNV Neuroinvasive Disease

Age (years)	Males	Females
16-24	719	1231
25-44	356	330
45-64	248	387
≥65	50	61
All ages	220	244

Emerg Infect Dis 2012; 18:684-6

Surveillance Systems for Arboviral Disease Detection, Monitoring, and Research

Lyle Petersen, MD, MPH

Topics

- Surveillance definition
- Why conduct arbovirus surveillance
- Surveillance systems that work and those that don’t
- Human surveillance
- Ecologic surveillance

Surveillance Definition: IHR 2005

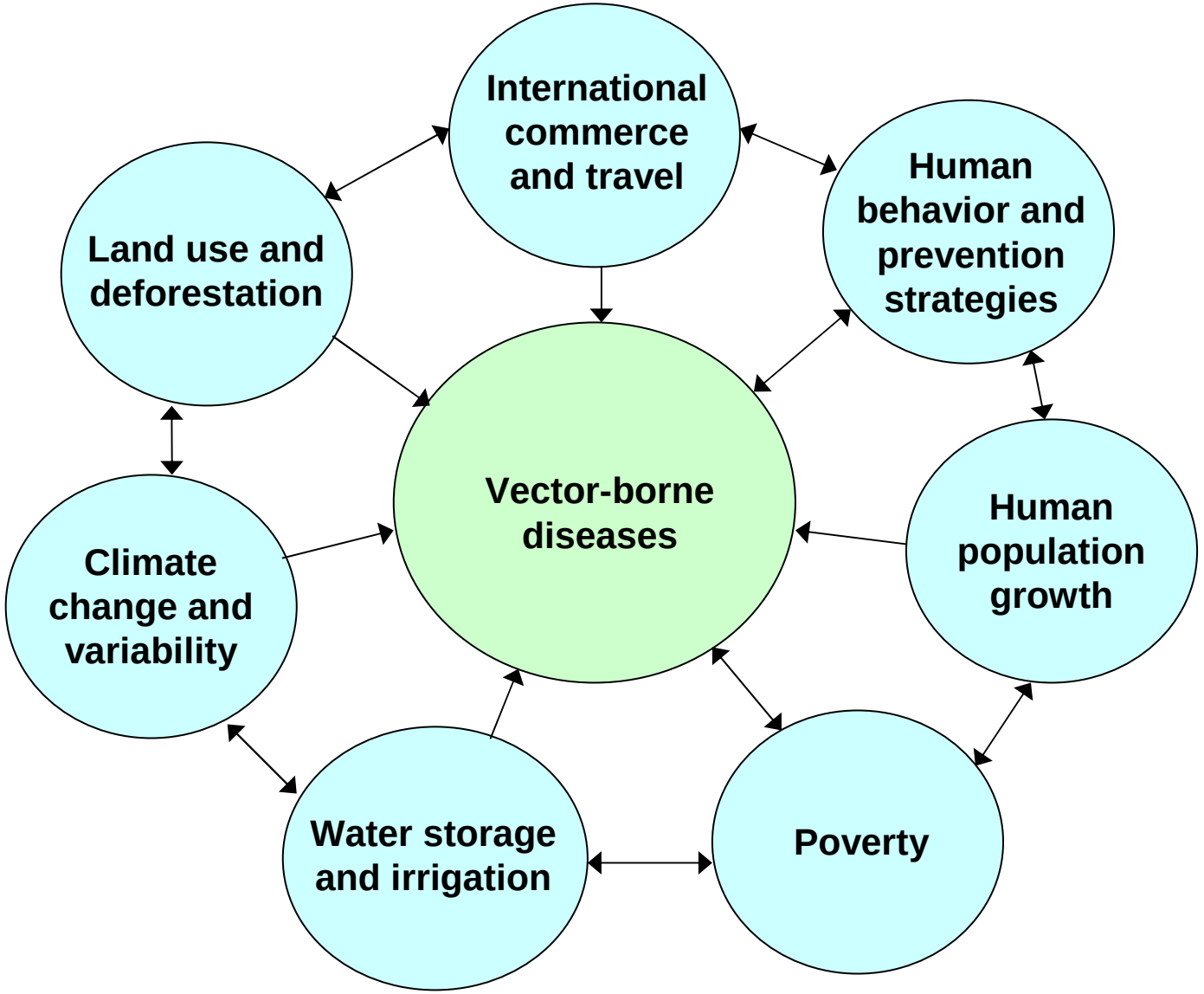
"systematic ongoing collection, collation and analysis of data for public health information for assessment and public health response as necessary"

Three Surveillance Components

- Systematic collection of pertinent data
- Analyses of these data
- Timely dissemination of results to guide interventions

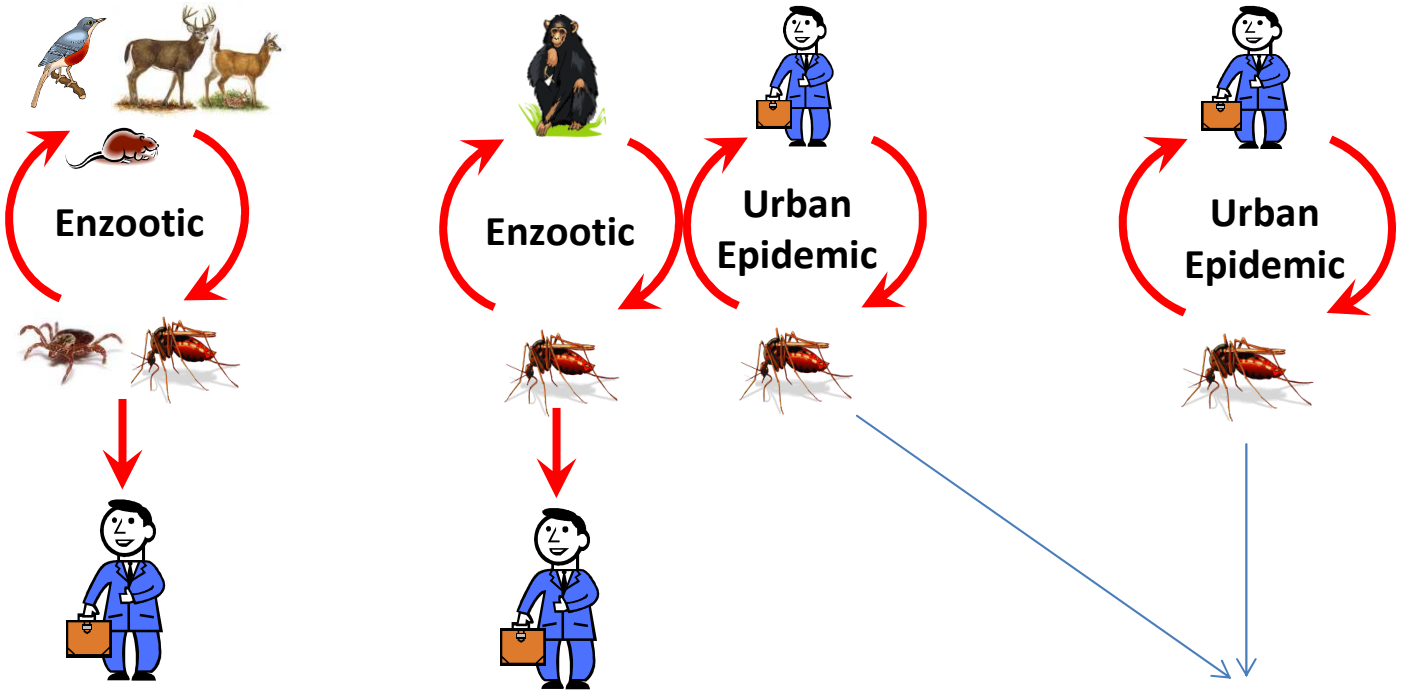
Arboviruses

- Arthropod-borne viruses
- Transmitted by mosquitoes, ticks, sand flies
- Public health focus on 3 virus families:
  - Flaviviridae (genus flavivirus)
  - Togaviridae (genus alphavirus)
  - Bunyaviridae (genera orthobunyavirus and phlebovirus)



Modified from Sutherst R.W. Clin Micribiol Rev 2004;17:136-73

General Patterns of Viral and Bacterial Vector-Borne Disease Transmission

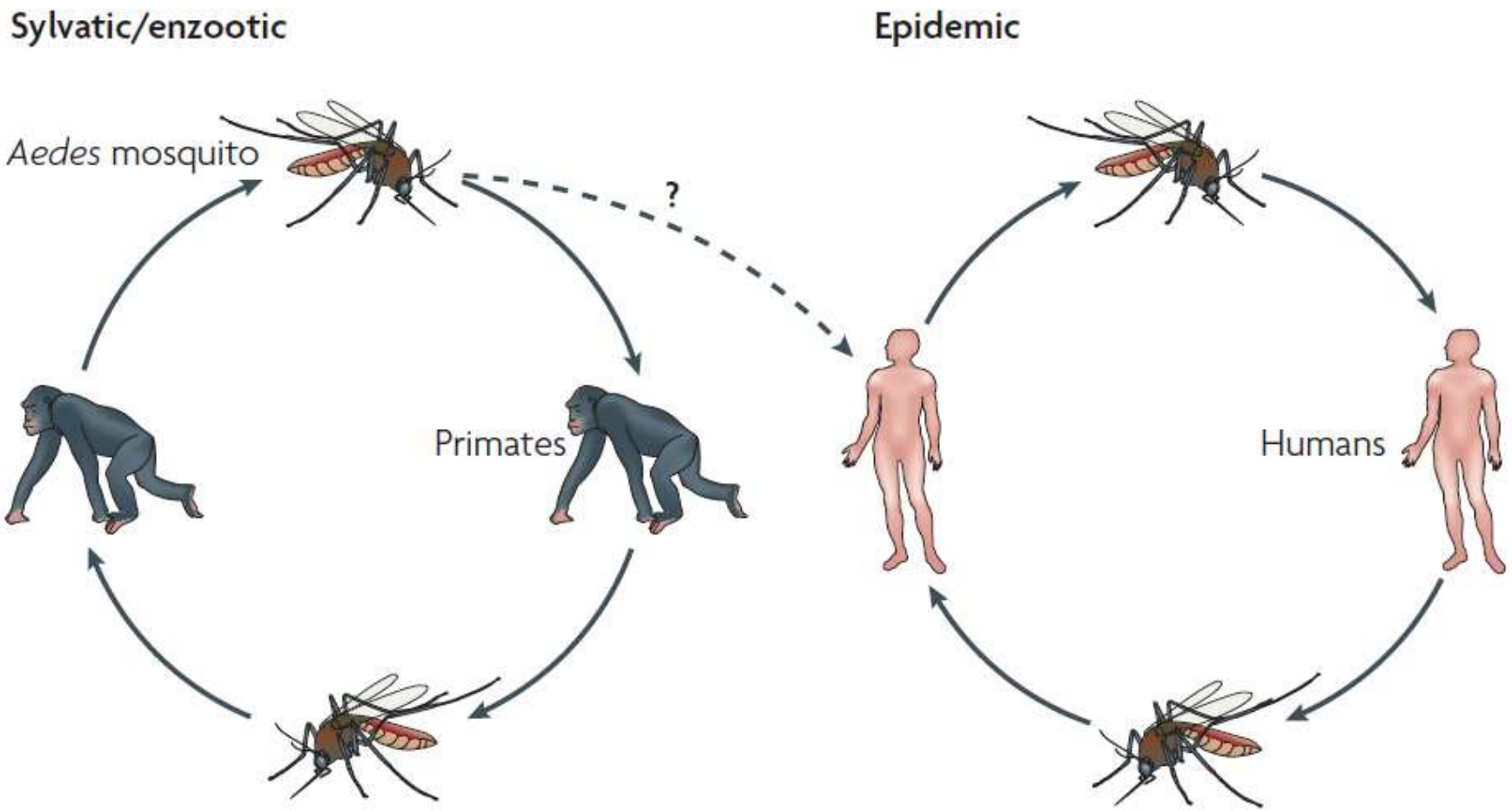


Culex spp mosquitoes
West Nile virus
Japanese encephalitis
Ixodes spp ticks
Tick-borne encephalitis

Aedes spp mosquitoes
Haemogogus spp mosquitoes
Yellow fever
Chikungunya

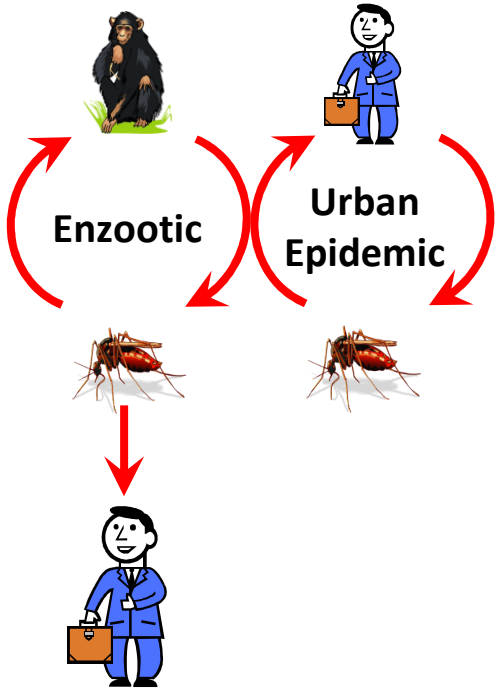
Aedes aegypti
Aedes albopictus
Dengue
Urban yellow fever
Urban Chikungunya

Transmission Relationships



Whitehead, et al. Nature Reviews 2007

What Happens When Surveillance Doesn't Function: Yellow Fever in Africa

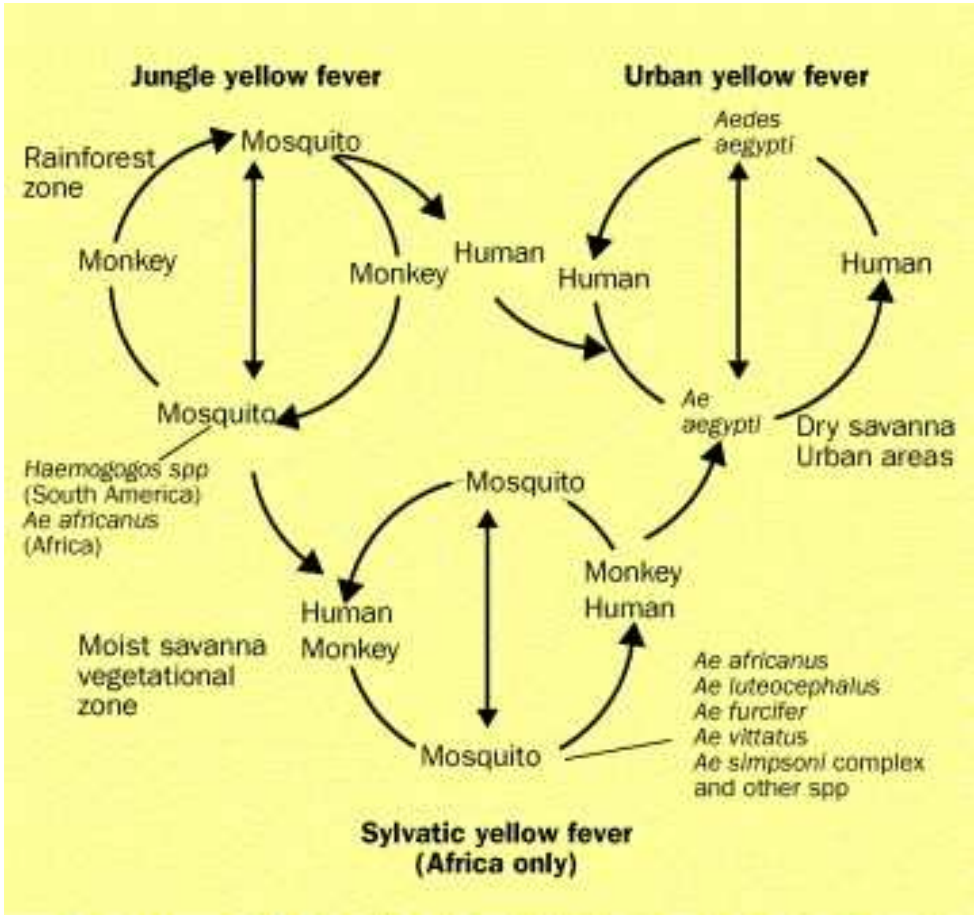


- No surveillance
- Little or no laboratory capacity
- Little epidemiologic follow-up

Leads to…

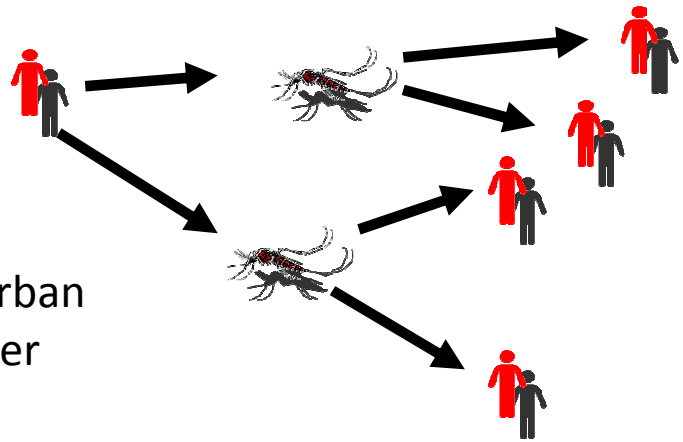
- Delayed identification
- Unclear epidemiology
- Confusion with other co-circulating arboviruses
- Inappropriate, delayed, or misguided vaccination campaigns

Yellow Fever – Hybrid Cycle



Reproductive Rate

- R_0 is the number of expected secondary cases by one infectious individual in a naïve population.
- If R_0 >1, an outbreak can happen.
- Amplification will occur among vertebrate hosts if R_0 >1.



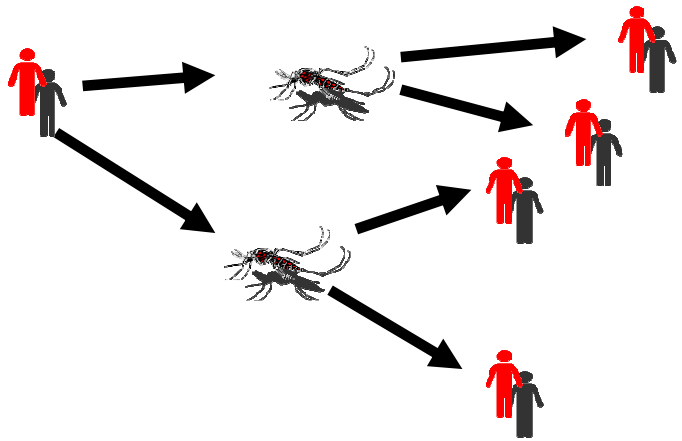
R_0=4 for urban yellow fever

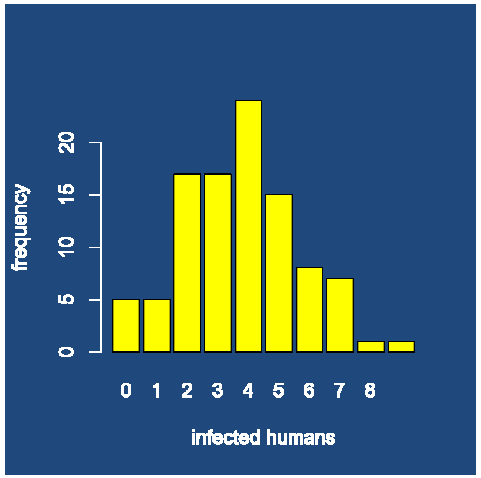
Outbreak Timing

- In temperate climates, usually peaks in late summer when amplification has occurred through late spring and summer.
- In tropical climates, outbreaks usually occur in rainy season.

Outbreaks are Difficult to Predict

- Any enviromental change will affect many variables in R_0 equation, so effect on R_0 unclear
- Transmission is a stochastic process (sequence of random events), so expect a range of outcomes



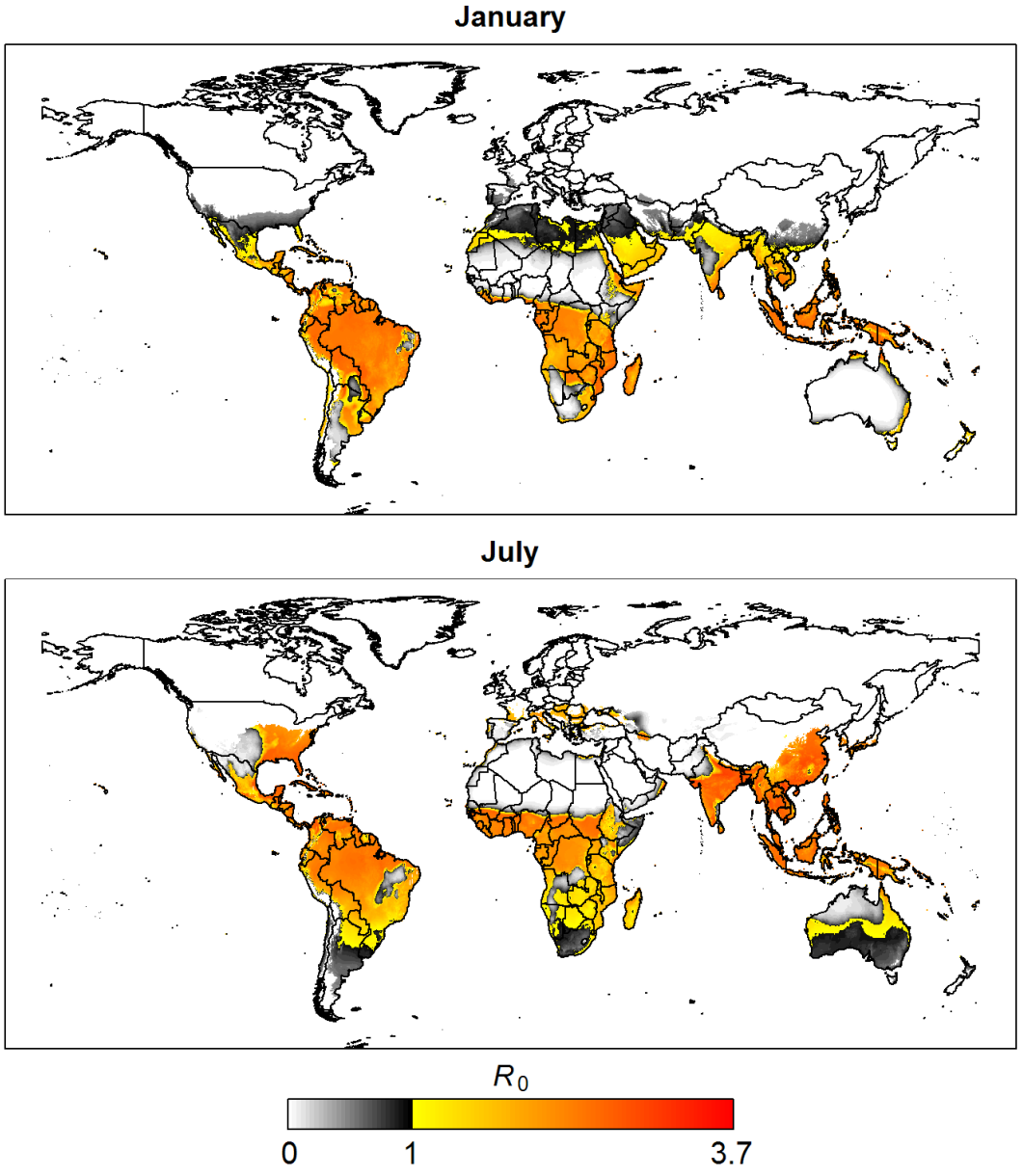


Stochastic Metapopulation Model for Yellow Fever Spread from a Single Urban Outbreak via Airplane Travel

- Question
  - Given a single introduction to Asunción, Paraguay, what is liklihood of
    - a local outbreak in Asunción,
    - infected travelers from Asunción,
    - distant outbreaks via air travel to 141 cities?
- Model accounted for time of year, air travel routes, and parameters in Asunción and other cities that would influence reproductive rate (R_o)
- 1000 simulations

Am J Trop Med Hyg 2012; 86:349-58

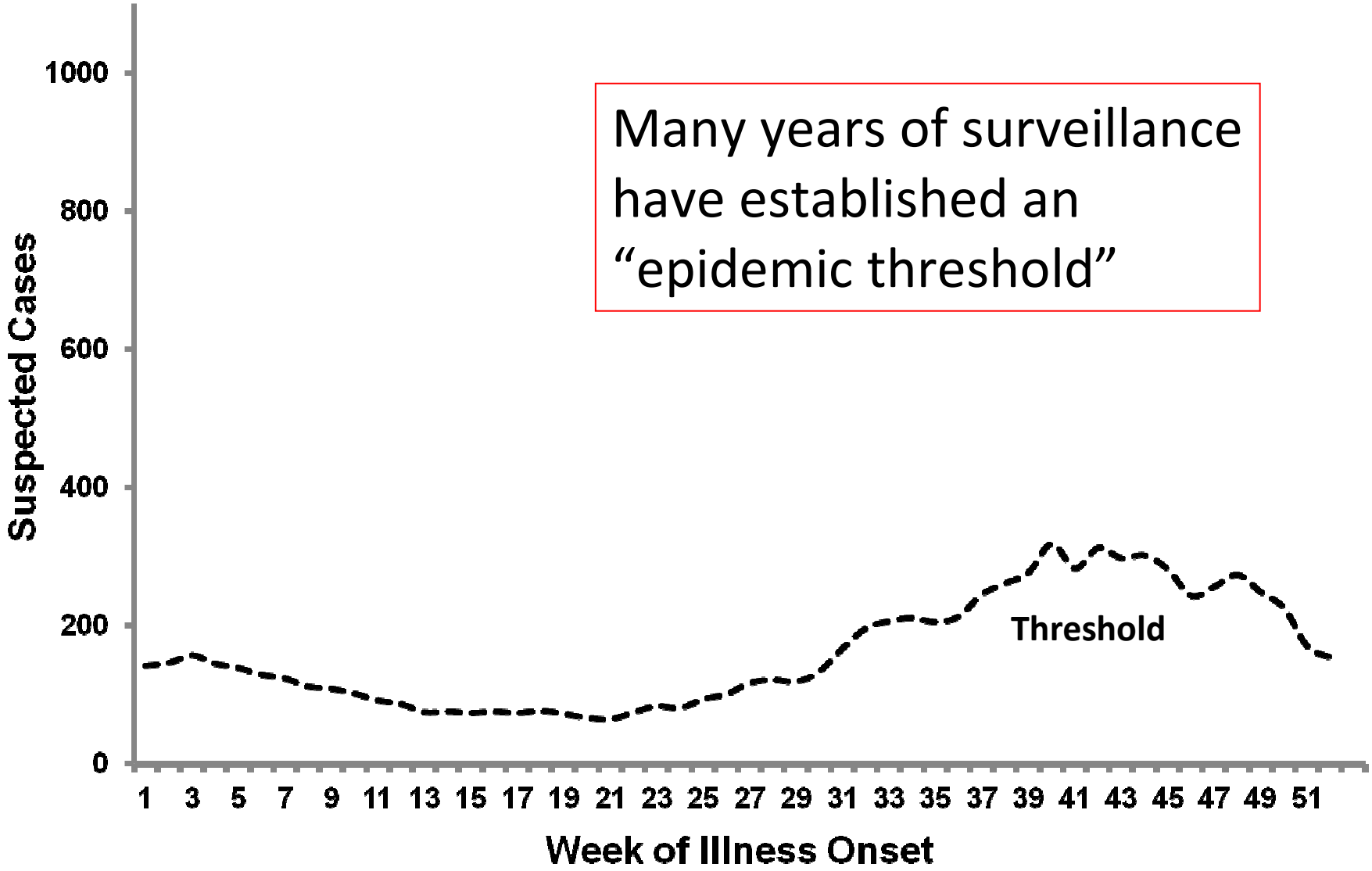
Estimated Yellow Fever Transmission Ro



Yellow Fever Transmission Model: Results from 1000 Simulations

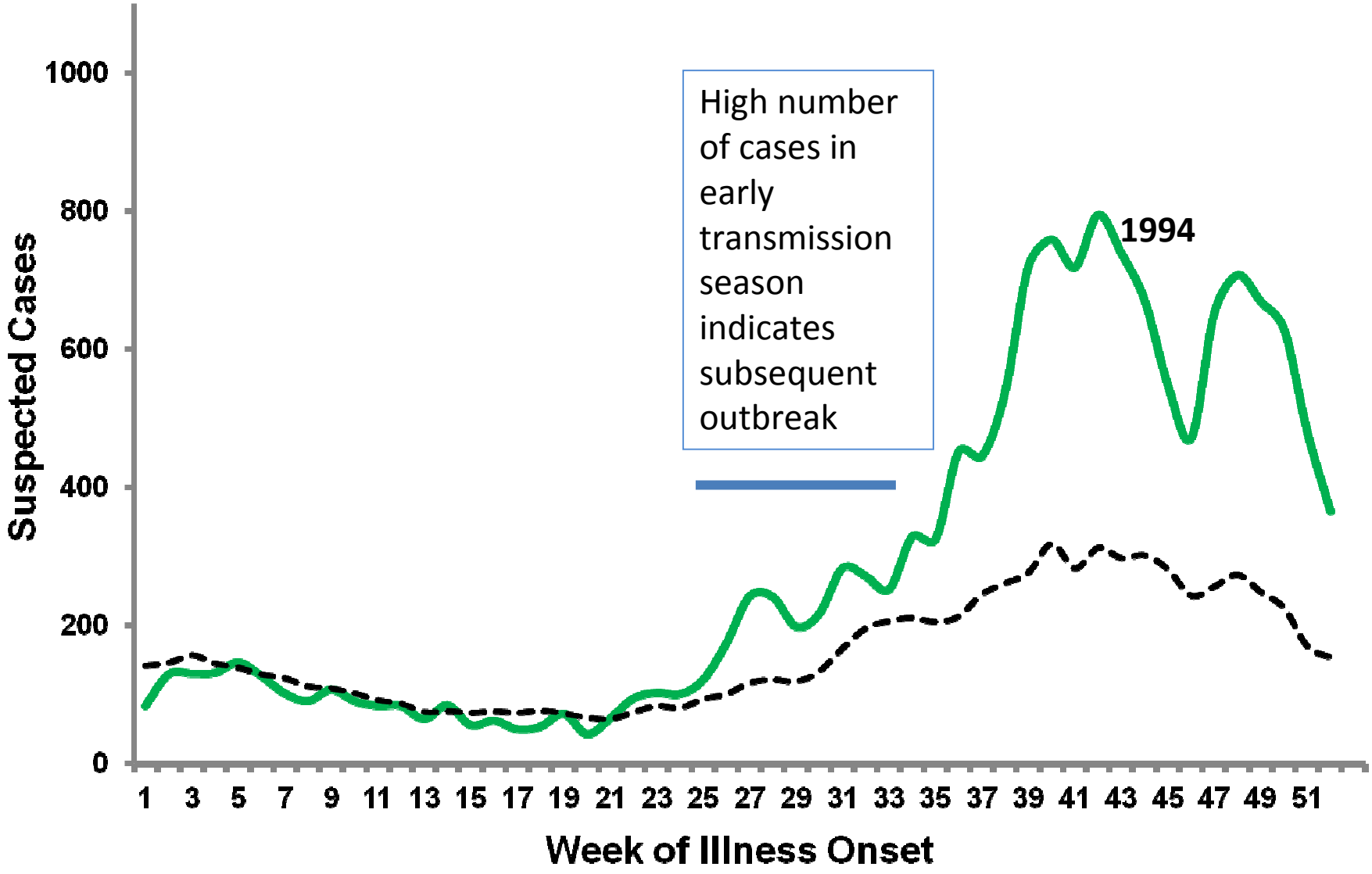
- Addition human transmission in Asunción occurred in 128 (13%) of 1000 simulations
  - In 108 (84%), limited outbreaks: median 2 persons, range 1-981
  - In 20 (16%), large outbreaks: 450,000-550,000 persons
- Infected travelers from Asuncion in 2.2% of 1000 simulations
- Outbreaks in other cities in 2.0% of 1000 simulations

What Happens When Surveillance Functions: Dengue in Puerto Rico

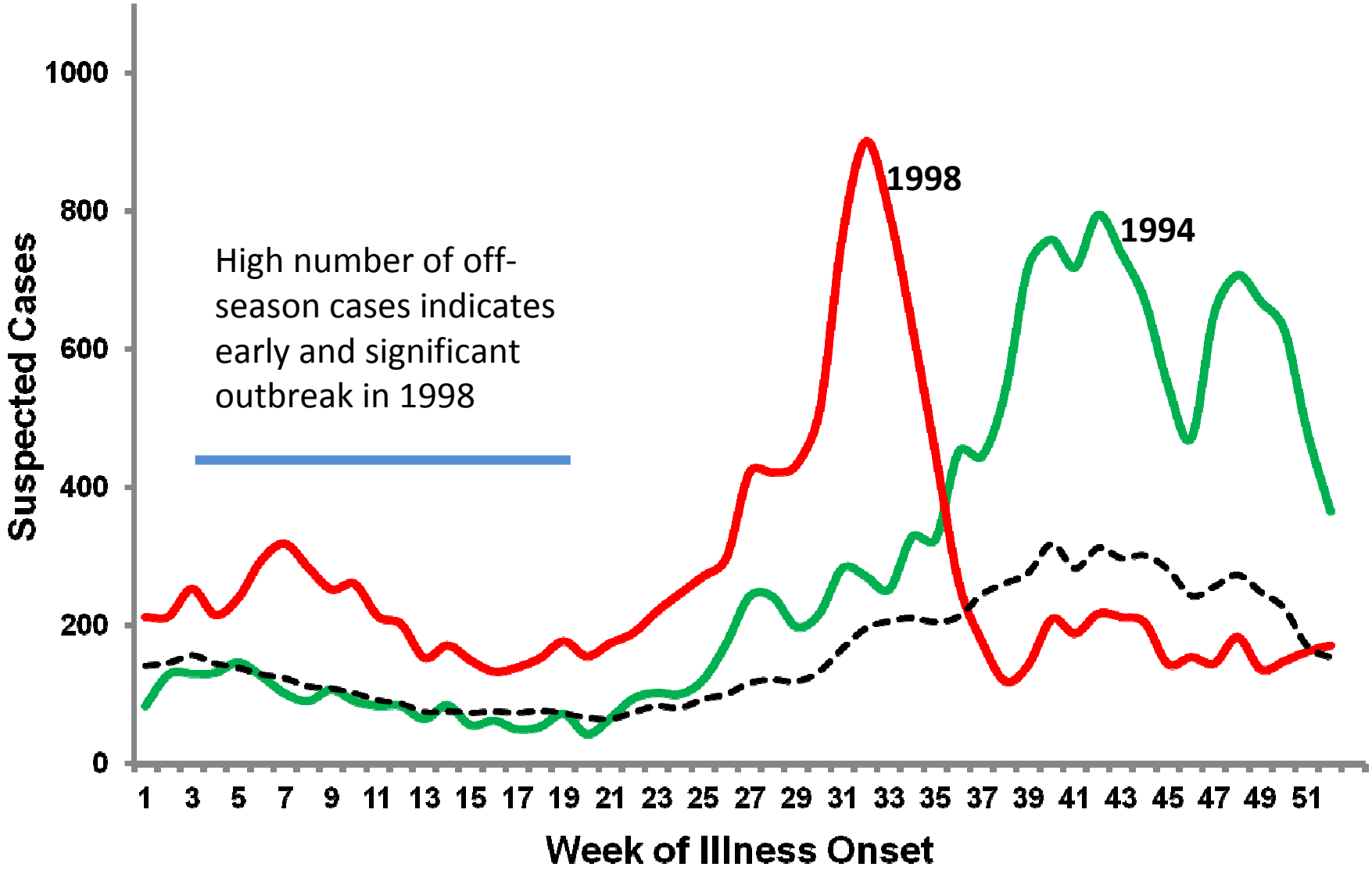


* Threshold is defined by the 75% percentile of the mean. Epidemics are defined by 2 consecutive weeks of above threshold activity.

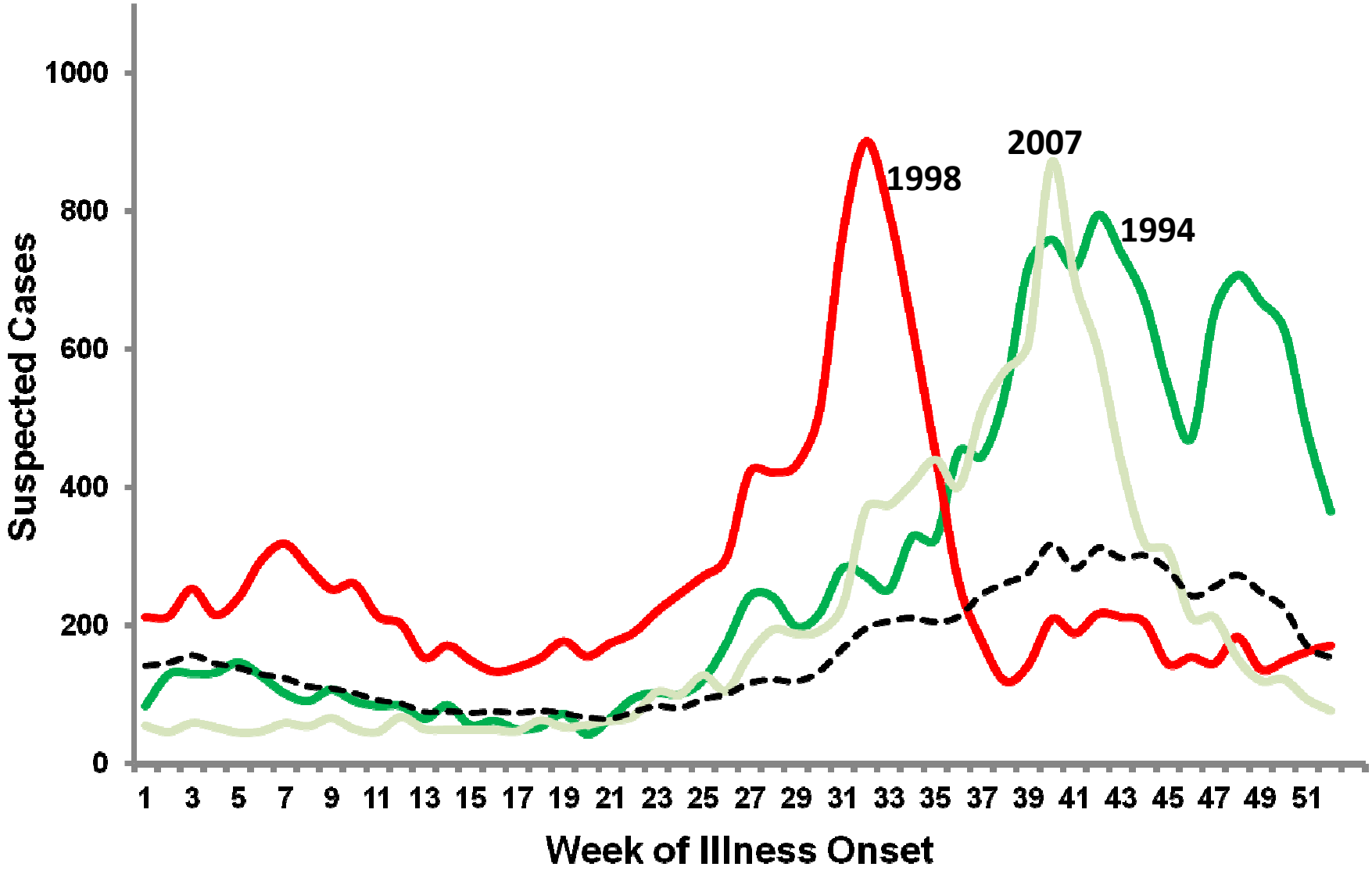
Recent Dengue Epidemics in Puerto Rico



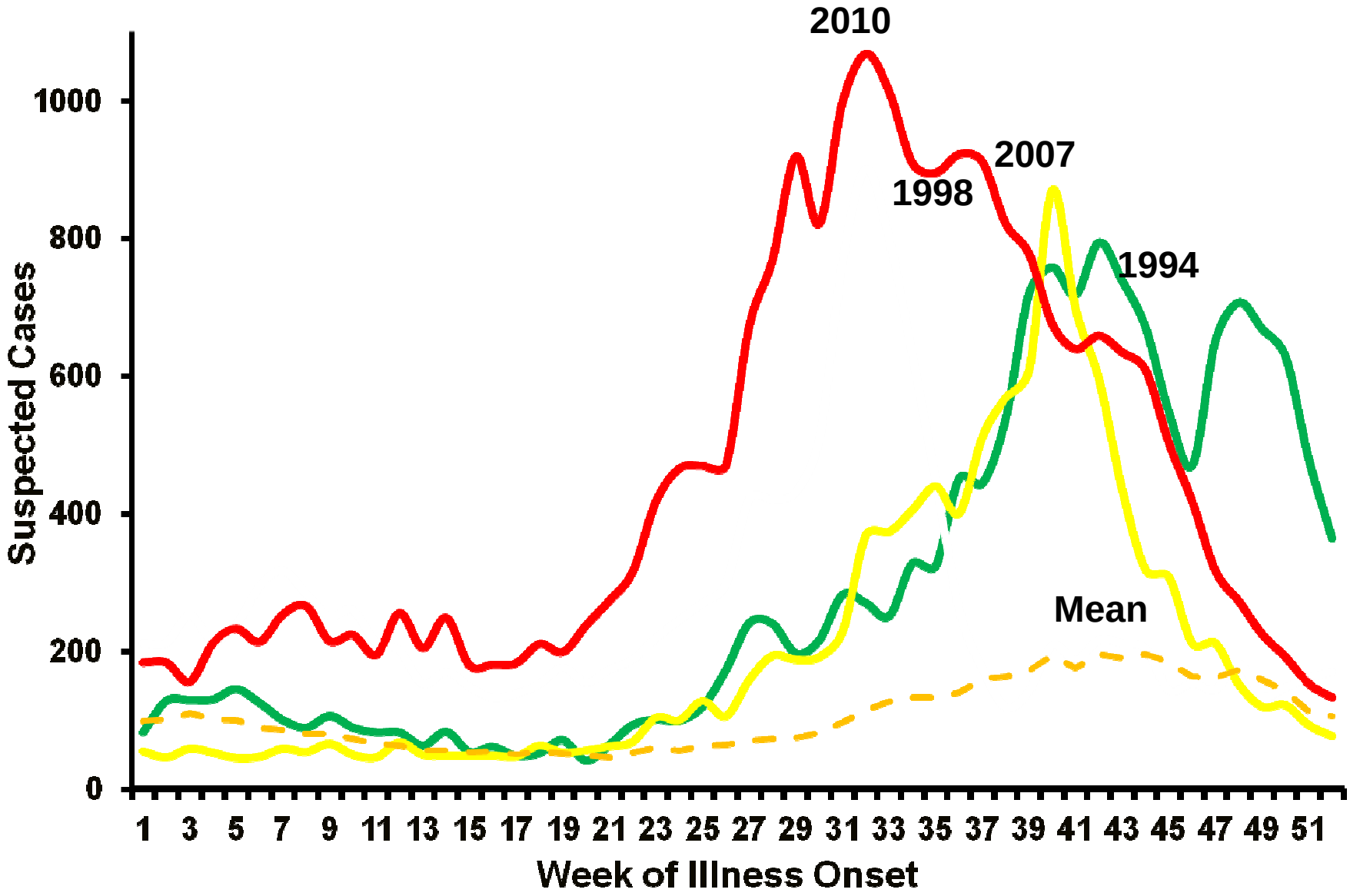
Recent Dengue Epidemics in Puerto Rico



Recent Dengue Epidemics in Puerto Rico



Recent Dengue Epidemics in Puerto Rico



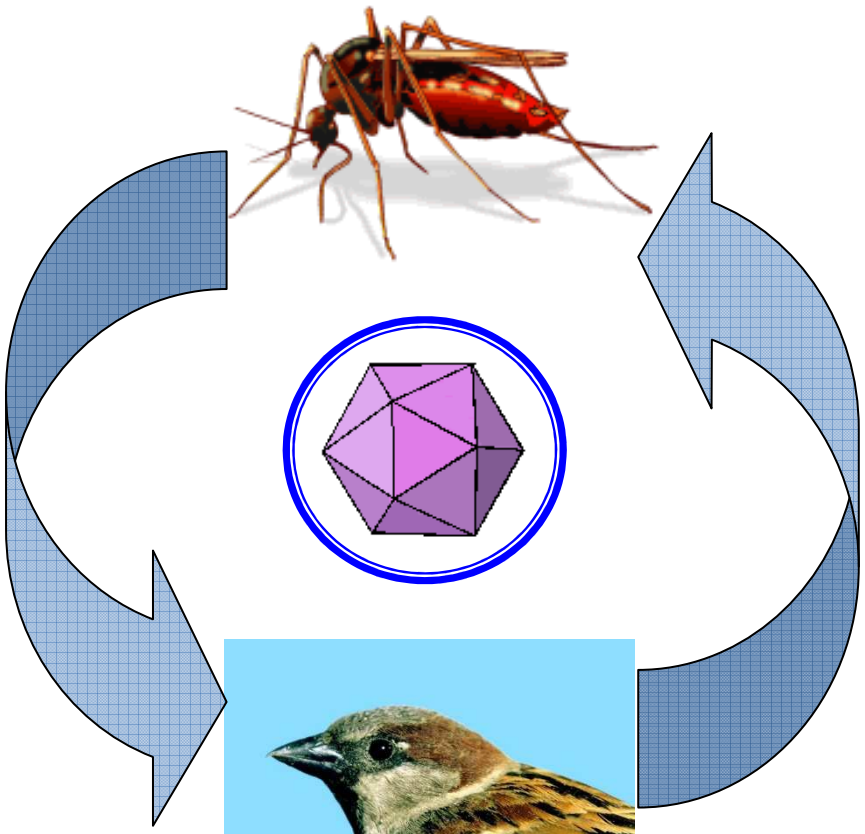
Some Challenges with Arboviral Disease Surveillance

- Outbreaks widely dispersed by time and space – hard to maintain interest and resources
- Difficult to link ecological surveillance with subsequent human disease
- Time from detection to development of a huge outbreak is often very short
- Serological cross-reactivity
- Lack of laboratory resources
- Interaction of human and animal health professionals often lacking
- Asymptomatic disease
- Resource intensive

Arbovirus Surveillance

- Human surveillance
  - Disease incidence, morbidity, mortality
  - Infection incidence, cumulative incidence
  - Behaviors
- Ecological surveillance
  - Primary vertebrate hosts
  - Other affected species
  - Sentinel animals
  - Vectors
  - Pathogens

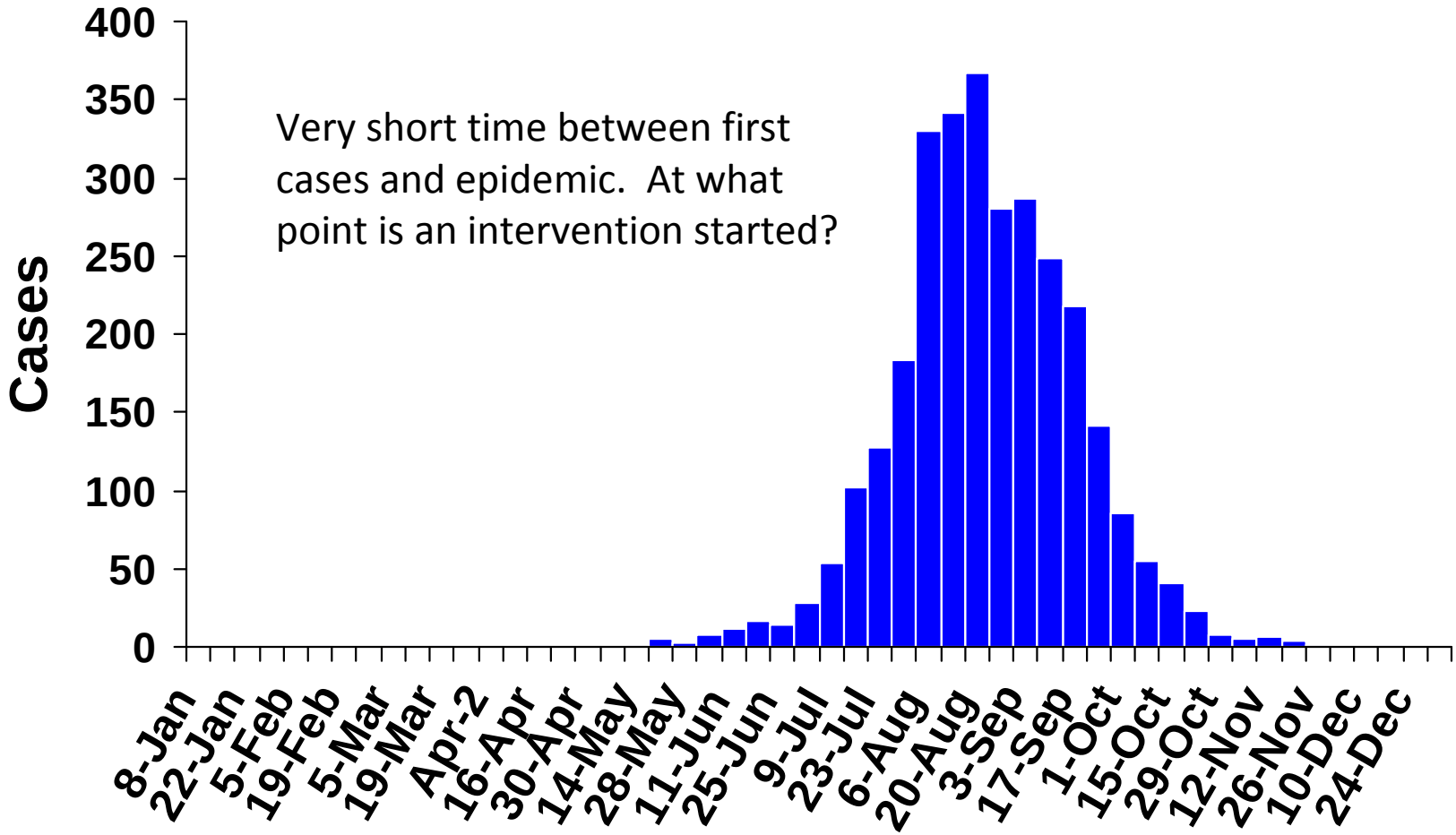
Enzootic (Maintenance/Amplification)



Epidemic

Epizootic

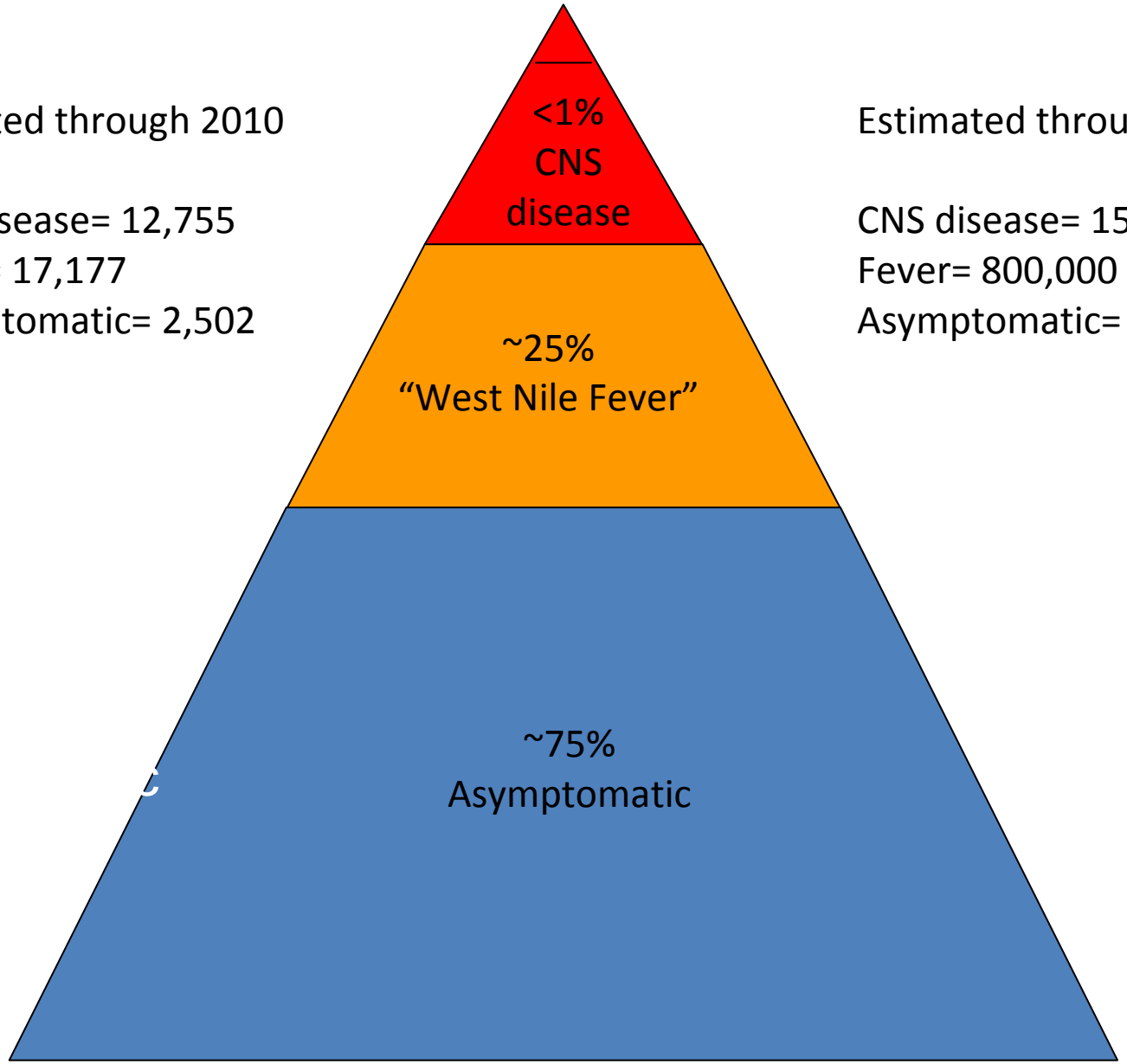
Human WNV Disease Cases, by Week of Onset, United States, 2005



WNV Human Disease and Infection “Iceberg”, 1999-2010

Reported through 2010

CNS disease= 12,755
Fever= 17,177
Asymptomatic= 2,502



Estimated through 2010

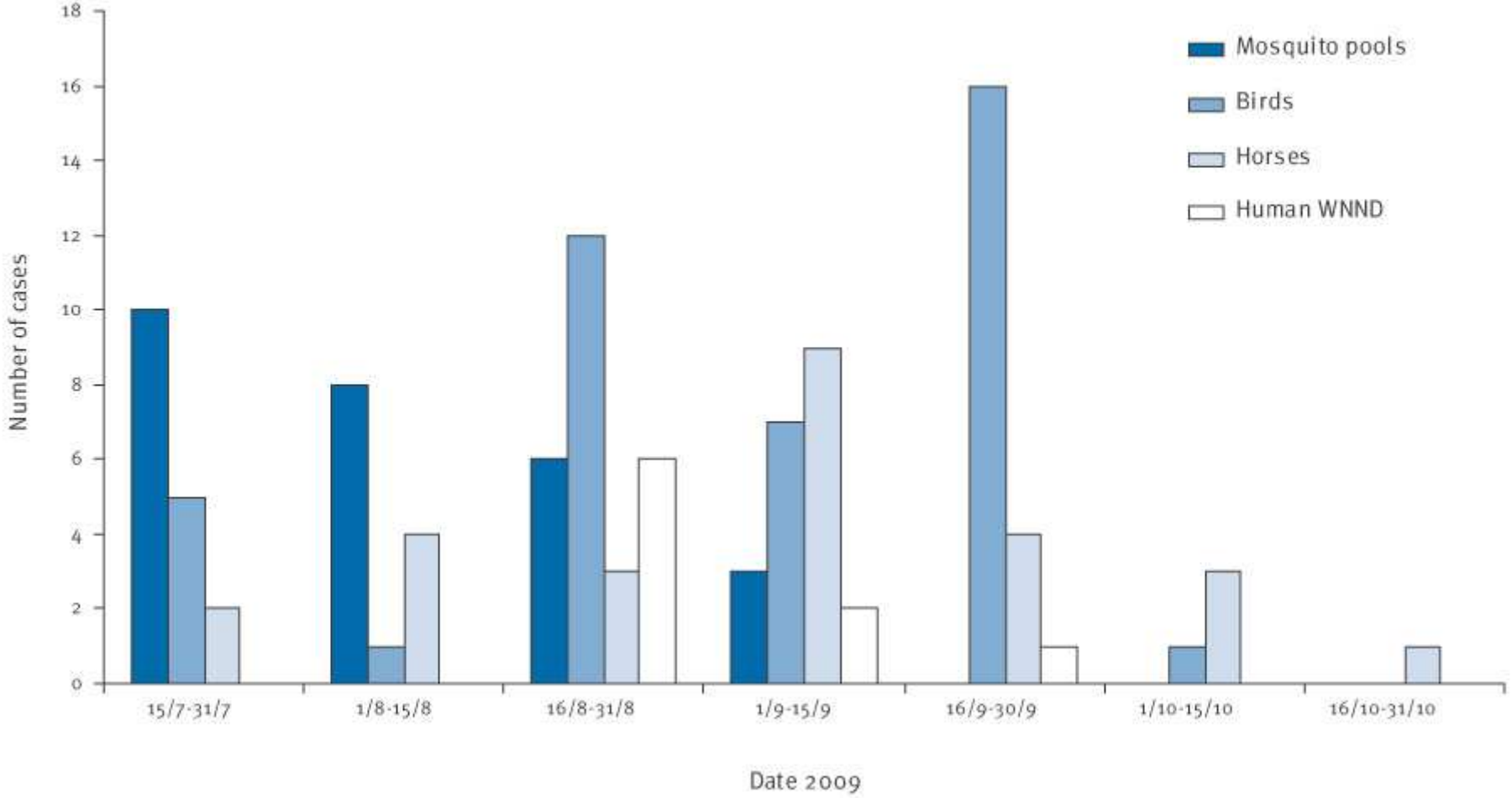
CNS disease= 15,000
Fever= 800,000
Asymptomatic= 2,400,000

Surveillance Artifact and WNV

Year	WNND	Fever	% WNND	
1999	59	3	95	Very limited testing
2000	19	2	90	
2001	64	2	97	
2002	2946	1160	71	
2003	2866	6830	30	Commercial tests
2004	1142	1269	47	
2005	1294	1607	45	
2006	1459	2616	39	
2007	1217	2350	34	
2008	687	624	52	Decreased funding for surveillance
2009	373	322	54	
2010	629	392	62	

FIGURE 2

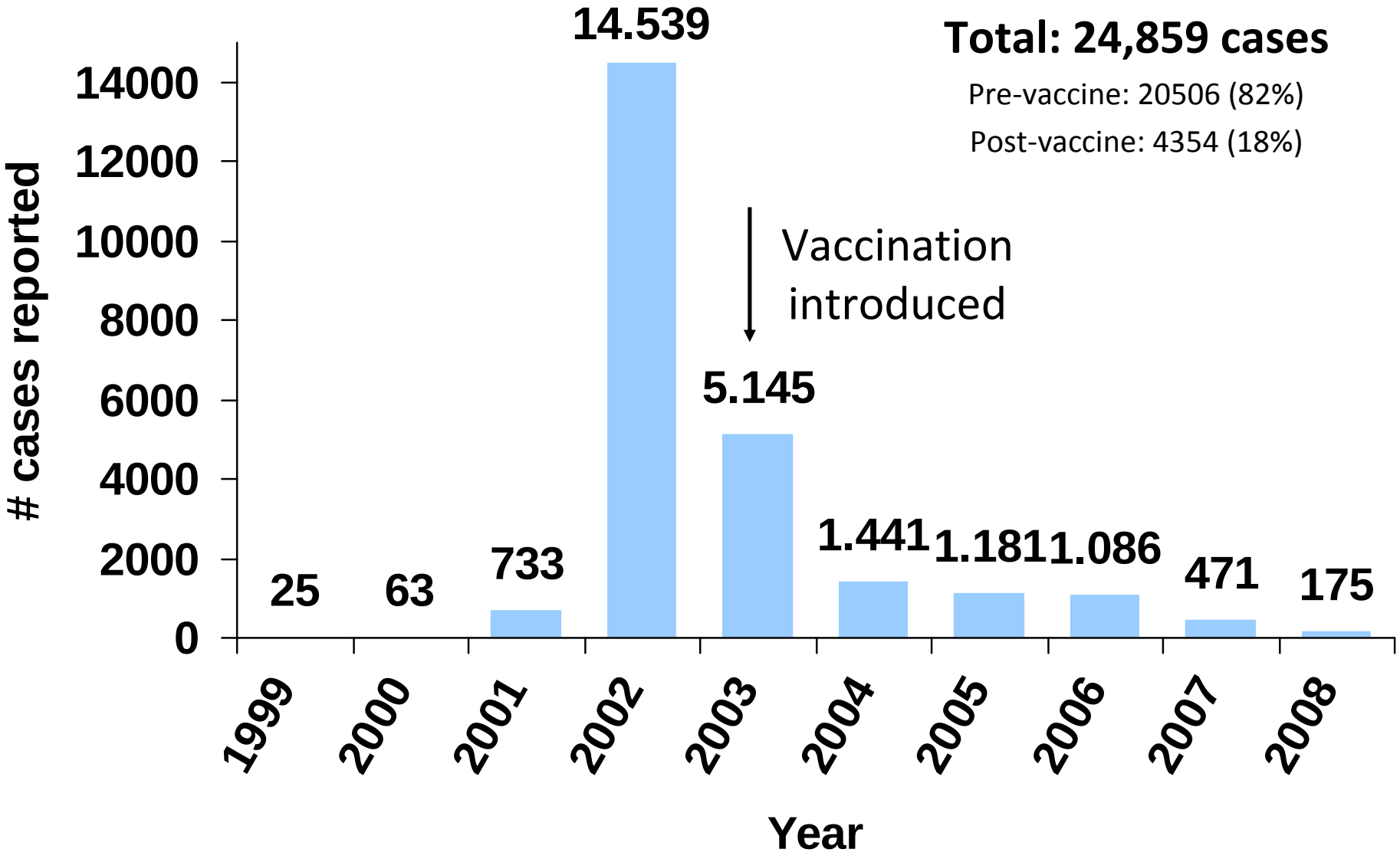
Distribution of West Nile virus confirmed cases (mosquito pools, birds, horses, and human West Nile neuroinvasive disease) by date, Emilia-Romagna, Italy, July-October 2009



WNND: West Nile neuroinvasive disease

Note: The figure does not include a magpie (found in early May) or a jay (found in early November).

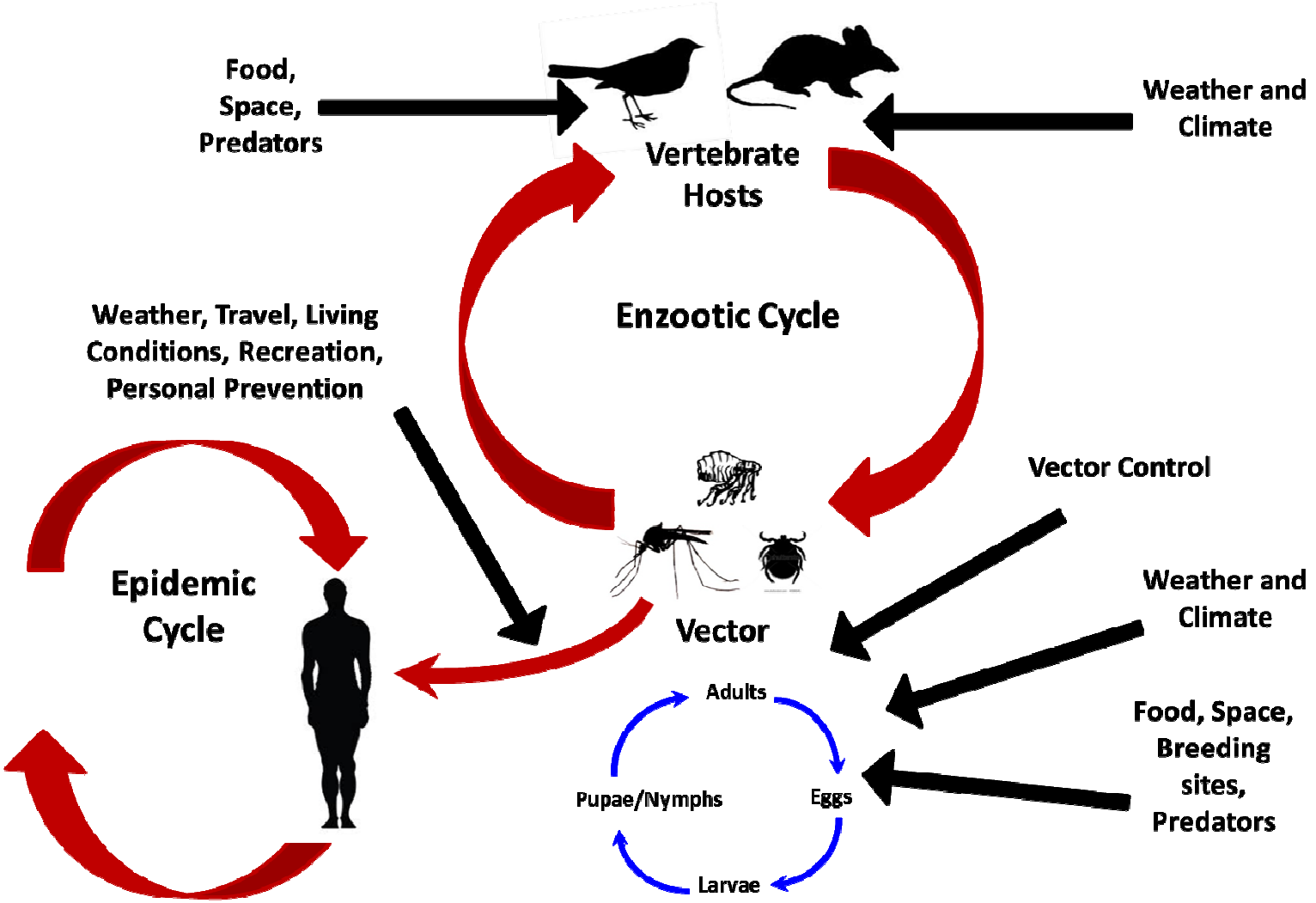
Equine WNV Disease Cases Reported, U.S., 1999-2008



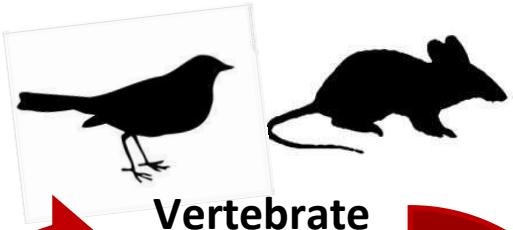
Ecological Surveillance – Sentinel Animals

- Most commonly sentinel chickens to monitor arbovirus infection in bird-biting mosquitoes
- Chickens bled periodically and seroconversion monitored
- Advantages
  - Monitor enzootic activity
  - Place of infection is known
- Disadvantages
  - Expensive
  - Theft and vandalism
  - Timeliness (must wait for seroconversion)
  - Translation of results to assess human risk requires considerable experience

Transmission Cycle Influenced by Many Interacting Factors



Opportunities for Prevention



Vertebrate Hosts

Enzootic Cycle

Repellents
Barriers

Adult Vector Control

Vector

Urban Epidemic Cycle

Adults

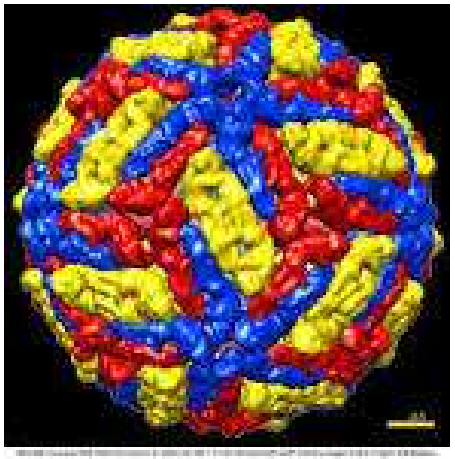
Eggs

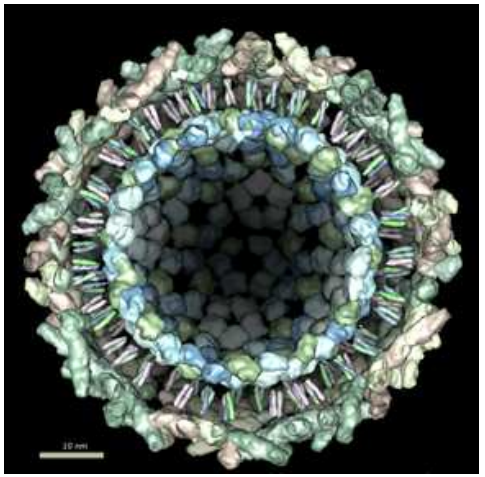
Larvae

Pupae/Nymphs

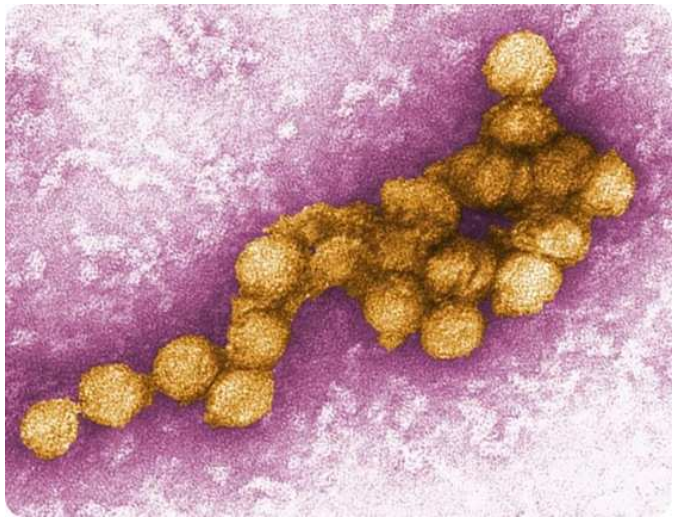
Source reduction
Chemical control
Biological control

Vaccines





La fase pilota 2010



REGIONE DEL VENETO

AZIENDA ULSS 20

SOCIÉTÉ DE PATHOLOGIE EXOTIQUE

MALATTIE TRASMESSE DA VETTORI E SALUTE GLOBALE

VECTOR BORNE DISEASES AND GLOBAL HEALTH

Is surveillance of summer fevers possible?

VENEZIA
14 - 15 giugno 2010

Centro Malattie Tropicali
NEGRAR - VERONA - ITALY
Centre for Tropical Diseases

Ospedale
Sacro Cuore Don Calabria

FONDAZIONE DON GIOVANNI CALABRIA
PER LE MALATTIE TROPICALI

Quando?

- Dal 15 giugno al 30 novembre

Perché una sorveglianza delle febbri autoctone?

- Non c'è terapia specifica…?!?

- Individuare precocemente casi autoctoni di West Nile Fever per avere un'idea più realistica della circolazione del virus

Perché una sorveglianza delle febbri di importazione?

- Individuare precocemente casi importati di dengue e chikungunya

- Misure tempestive di lotta al vettore attorno ai casi individuati, se alta densità vettoriale

- Riferimento immediato ai centri specialistici…. in primis **escludere la malaria**

Protocollo DEN/CHIK

- Febbre >38° negli ultimi 7 gg
- Soggiorno in paesi endemici negli ultimi 15 gg
- Assenza di leucocitosi (WBC < 10,000 microl)
- Assenza di altre cause evidenti di febbre

Medico di base
Pronto soccorso

- RAPID TEST (anti-CHIK IgM and NS1 DENV) positivo

Unità di Malattie infettive e tropicali

- PCR DENV and CHIK positiva
- Sieroconversione o aumento del titolo anticorpale IgM IgG

Laboratorio regionale di riferimento

Protocollo West Nile fever

- Febbre >38° negli ultimi 7 gg
- Assenza di altre cause evidenti di febbre

Medico di base
Pronto soccorso

- Assenza di leucocitosi (WBC < 10,000 microl)

Unità di Malattie infettive e tropicali

- PCR WNV
- Sieroconversione o aumento del titolo anticorpale IgM IgG

Laboratorio I livello
Laboratorio II livello

Risultati preliminari (fase pilota) 2010

N. caso	Malattia	Sesso	Età	Residenza	Permanenza ultime settimane	Esito test	Data
1	Dengue	M	48	Vedelago (TV)	Guyana	IgM + IgG +.	27/7/2010
1	WN Fever	M	67	Fratta Polesine (RO)		IgM + IgG +. Conferma test neutralizzazione	27/7/2010
1	Chikungunya	F	58	Padova	Bali	IgM + IgG +.	4/8/2010
2	Dengue	F	24	Arcugnano (VI)	Bali	PCR. Dengue virus tipo 3	11/8/2010
3	Dengue	M	32	Campodarsego (PD)	India	IgM + IgG +. RNA +	11/8/2010
4	Dengue	M	42	Costa d'Avorio	Costa d'Avorio	PCR. Dengue virus tipo 3	17/8/2010
2	WNND	M	41	S. Stino di Livenza (VE)	Ricoverato Friuli	IgM + IgG +. Confermato dal Laboratorio di riferimento Nazionale	3/9/2010
5	Dengue	M	44	Bassano Grappa (VI)	Thailandia	Igm + IgG +.	15/9/2010
6	Dengue	F	43	Verona	Cambogia	PCR	10/9/2010
7	Dengue	F	31	Minerbe (VR)	Caraibi	PCR . Dengue virus tipo 1	10/9/2010
8	Dengue	M	35	Verona	Thailandia	PCR	10/9/2010
9	Dengue	F	51	Montebelluna (TV)	India	IgM + IgG +.	15/9/2010
10	Dengue	M	40	Melo (VE)	Bangladesh	IgG +	10/09/2010
11	Dengue	M	43	Verona	Thai, Vietnam	PCR. Dengue virus tipo 2	14/09/2010
12	Dengue	F	17	Treviso	Martinica	IgM + IgG +.	23/9/2010
13	Dengue	M	36	Tarzo (TV)	Thailandia	IgM + IgG +.	1/10/2010
14	Dengue	M	25	Trevignano	India	RNA +	10/10/2010
3	WNND	M	67	Barbarano Vic. (VI)	Villaga (VI)	IgM, IgG + nel liquor, conferma test di neutralizzazione	14/10/2010
4	WN Fever	F	48	Portogruaro (VE)		IgM + IgG +. Conferma test neutralizzazione	12/10/2010
5	WNND	M	68	Concordia Sagit. (VE)		IgM, IgG + nel liquor e siero, conferma test di neutralizzazione	25/10/2010
6	WN Fever	M	40	Bassano (VI)		IgM + IgG +.	28/10/2010

Gobbi F, Barzon L, Capelli G, et al; Veneto Summer Fever Study Group.
Surveillance for West Nile, dengue, and chikungunya virus infections, Veneto Region, Italy, 2010.
Emerg Infect Dis. 2012 Apr;18(4):671-3.

Pronto Soccorso

Centro di medicina dei viaggi

Malattie infettive/tropicali

Dengue chikungunya

Laboratorio I livello

Laboratorio II livello

Salute pubblica

Istituto Zooprofilattico

Medico di famiglia/PS

Malattie infettive/tropicali

Medicina interna

West Nile fever

Laboratorio I livello

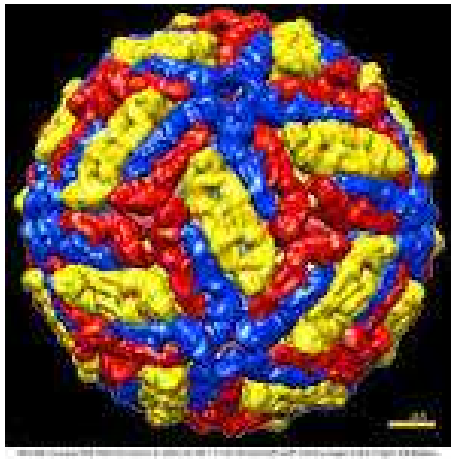
Trapianti

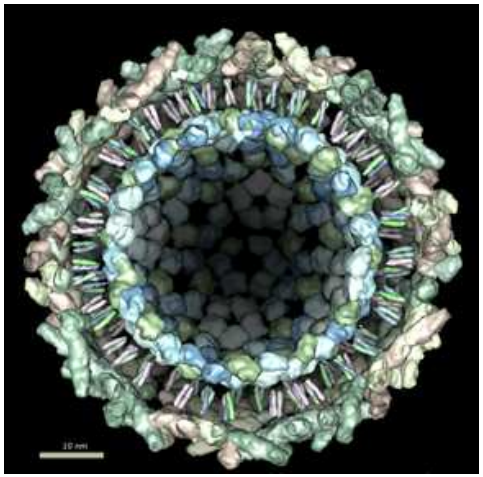
Trasfusioni

Salute pubblica

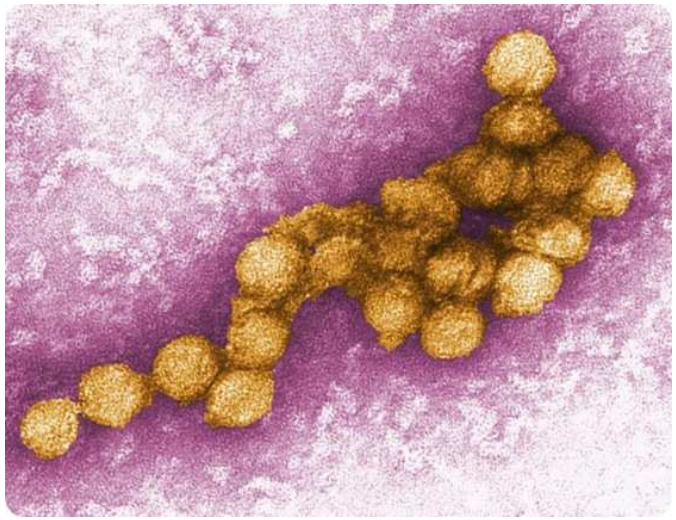
Laboratorio II livello

Istituto Zooprofilattico





Risultati della sorveglianza 2011-2013 (2014)



Sorveglianza DENV/CHIK/WNF, Veneto

Year (15th june-30th November)	Imported dengue cases	Imported chikungunya cases	%	Autochthonous WNF cases	%	Autochthonous WNND cases
2008	2	1		1		5
2009	4	0		0		7
2010*	**14/79**	**1/79**	**(15/79) 18.9**	**4/38**	**10.5**	**3**
2011	**3/29**	**0/29**	**(3/29) 10.3**	**3/51**	**5.8**	**10**
2012	**7/126**	**2/126**	**(9/126) 7.1**	**17/319**	**5.3**	**21**
2013	**14/203**	**0/203**	**(14/203) 6.9**	**16/330**	**4.8**	**15**
2014	**5/79**	**8/93**	**(13/93)14.0**	**1/119**		**1**

Gobbi F, Capelli G, Angheben A, et; Summer Fever Study Group.
Human and entomological surveillance of West Nile fever, dengue and chikungunya in Veneto Region, Italy, 2010-2012.
BMC Infect Dis. 2014 Feb 5;14:60.

Caratteristiche dei casi di DENV/CHIKV/WNF
Veneto, anni 2010-2013

	N° of cases	Sex M/F	Mean age (range), years	Area of exposure	Time from Symptoms to diagnosis, (range) days	Positivity of PCR and/or viral isolation	Serotype
DENV	**38**	24/14	37 (17-80)	America (13) Asia (23) Africa (1) Europe (1)	14 (2-37)	28/38 (73%)	1 (13cases) 2 (7 cases) 3 (8 cases)
CHIKV	**3**	1/2	29 (13-58)	Asia (3)	17 (16-19)	0/3 (0%)	-
WNF	**40**	27/13	56 (25-80)	Italy (40)	23 (6-66)	4/24 (17%)	-

Gobbi F, Capelli G, Angheben A, et; Summer Fever Study Group.
Human and entomological surveillance of West Nile fever, dengue and chikungunya in Veneto Region, Italy, 2010-2012.
BMC Infect Dis. 2014 Feb 5;14:60.

Casi WNND / WNF Italia

Region	2007	2008	2009	2010	2011	2012	2013
Emilia -Romagna	-	**3** (3/0)	**9** (9/0)	-	-	-	**32** (16/16)
Veneto	**-**	**6 (5/1)**	**7 (7/0)**	**7 (3/4)**	**13 (10/3)**	**38 (21/17)**	**31 (15/16)**
Lombardy	-	-	**2** (2/0)	-	-	-	**10** (10/0)
Friuli-Venezia Giulia	-	-	-	-	**2** (2/0)	**4** (4/0)	-
Marche	-	-	-	-	**1** (0/1)	-	-
Sardinia	-	-	-	-	**4** (4/0)	**2** (2/0)	-
Tuscany	**1** (1/0)	-	-	-	**1** (1/0)	-	-
Basilicata	-	-	-	-	-	**1** (1/0)	-
Puglia	-	-	-	-	-	-	**1** (1/0)
TOTAL	**1 (1/0)**	**9 (8/1)**	**18 (18/0)**	**7 (3/4)**	**21 (17/4)**	**45 (28/17)**	**74 (42/32)**

Rizzo C, Salcuni P, Nicoletti L, et al.
Epidemiological surveillance of West Nile neuroinvasive diseases in Italy, 2008 to 2011.
Euro Surveill. 2012 May 17;17(20).

Obiettivi 2014

- Cruciale la collaborazione con i PS

  (problema dei “codici di uscita”)

Cruciale la collaborazione con i MMG (possibile predisporre un programma formativo ad hoc per 2014 sulla sorveglianza delle febbri estive?)

Malattie trasmesse da vettori

Aggiornamento al 12/09/2014*

*sorveglianza epidemiologica relativa al periodo di presenza di attività vettoriale nel territorio

West Nile Neuroinvasiva

N.	Sesso	Data di nascita	Residenza	Inizio sintomi	Data segnal.	Ulss	Classificazione	WNV
1	M	14/12/1938	Bovolone	12/08/2014	29/08/2014	21	probabile	Lineage 2

Febbre da West Nile virus

N.	Sesso	Data di nascita	Residenza	Inizio sintomi	Data segnal.	Ulss	Classificazione	WNV
1	F	17/04/1967	Isola Rizza	16/08/2014	29/08/2014	21	probabile	Lineage 2

Donatori

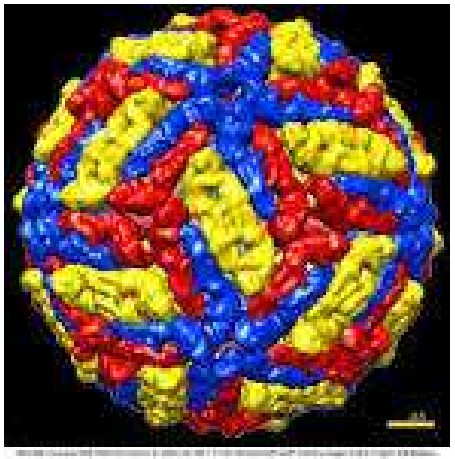
N.	sesso	Data nascita	Prov. Residenza	Ulss	diagnosi	WNV

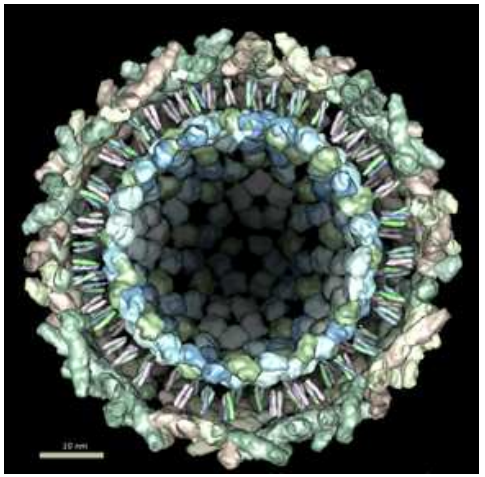
Dengue

N. casi	Sesso	Data nascita	Inizio sintomi	Soggiorno estero	COMUNE RESIDENZA	ULSS	Classificazione	Dengue virus
1	M	18/07/1967	24/06/2014	India	Sona (VR)	22	confermato	Tipo 1
2	F	22/01/1990	25/08/2014	Thailandia	Vicenza	6	confermato	
3	F	27/03/1973	08/08/2014	Brasile	Negrar (VR)	22	probabile	
4	F	11/05/1986	05/09/2014	Indonesia	Pedavena (BL)	2	probabile	
5	M	28/08/1967	02/06/2014	Cerro Veronese	Verona	20	probabile	

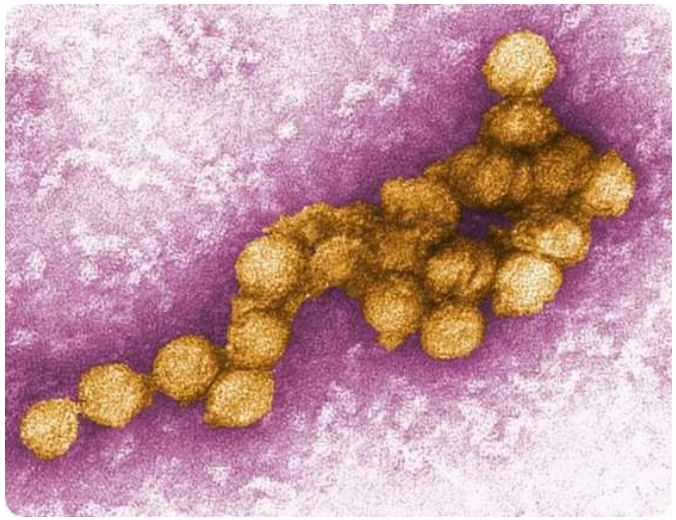
Chikungunya

N. casi	Sesso	Data nascita	Inizio sintomi	Soggiorno estero	COMUNE RESIDENZA	ULSS	Classificazione
1	M	22/08/1983	02/07/2014	Santo Domingo	Pernumia (PD)	17	confermato
2	F	30/09/1969	20/06/2014	Santo Domingo	Preganziol (TV)	9	confermato
3	F	11/07/1965	02/07/2014	Santo Domingo	Alano di Piave (BL)	2	confermato
4	F	12/11/1971	05/06/2014	Santo Domingo	Rovigo	18	confermato
5	F	01/09/1972	01/07/2014	Santo Domingo	Padova	16	confermato
6	F	11/06/1962	11/07/2014	Santo Domingo	Polverara (PD)	16	confermato
7	M	27/08/1946	25/07/2014	Filippine	Riese Pio X	8	confermato
8	M	05/10/1973	07/08/2014	Rep.Dominicana	Sandrigo	6	confermato
9	F	07/08/1972	10/08/2014	Rep.Dominicana	Preganziol	9	confermato





I test rapidi DENV/CHIK



Andries AC, Duong V, Ngan C,

Field evaluation and impact on clinical management of a rapid diagnostic kit that detects dengue NS1, IgM and IgG.

PLoS Negl Trop Dis. 2012;6(12):e1993.

BACKGROUND:
Dengue diagnosis is complex and until recently only specialized laboratories were able to definitively confirm dengue infection. Rapid tests are now available commercially making biological diagnosis possible in the field. The aim of this study was to evaluate a combined dengue rapid test for the detection of NS1 and IgM/IgG antibodies. The evaluation was made prospectively in the field conditions and included the study of the impact of its use as a point-of-care test for case management as well as retrospectively against a panel of well-characterized samples in a reference laboratory.
METHODOLOGY/PRINCIPAL FINDINGS:
During the prospective study, 157 patients hospitalized for a suspicion of dengue were enrolled. In the hospital laboratories, the overall **sensitivity, specificity**, PPV and NPV of the **NS1/IgM/IgG** combination tests were 85.7%, 83.9%, 95.6% and 59.1% respectively, whereas they were **94,4%, 90.0%,** 97.5% and 77.1% respectively in the national reference laboratory at Institut Pasteur in Cambodia. These results demonstrate that optimal performances require adequate training and quality assurance. The retrospective study showed that the sensitivity of the combined kit did not vary significantly between the serotypes and was not affected by the immune status or by the interval of time between onset of fever and sample collection. The analysis of the medical records indicates that the physicians did not take into consideration the results obtained with the rapid test including for care management and use of antibiotic therapy.
CONCLUSIONS:
In the context of our prospective field study, we demonstrated that if the SD Bioline Dengue Duo kit is correctly used, a positive result highly suggests a dengue case but a negative result doesn't rule out a dengue infection. Nevertheless, Cambodian pediatricians in their daily practice relied on their clinical diagnosis and thus the false negative results obtained did not directly impact on the clinical management.

Evaluation TDR chikungunya IgM

- ✓ TDR IgM: SD Bioline, CTK
- ✓ Evaluation initiale sur 25 sérums
- ✓ Caractérisation des sérums par le CNR et confirmation par le CDC

		SD Bioline	
		Positif	Négatif
CNR	Positif (10)	3	7
	Négatif (15)	4	11

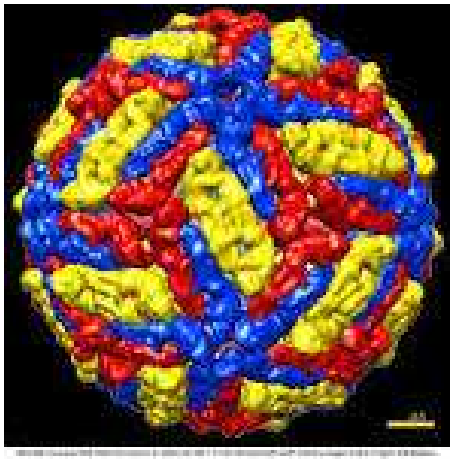
Sensibilité: 30%
Spécificité: 73%

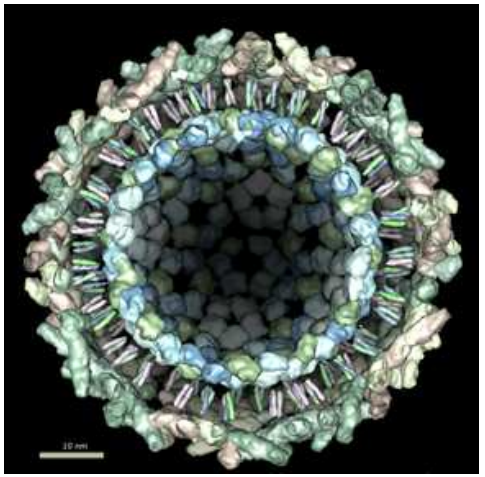
Faux positifs: 57% (4/7)
Faux négatifs: 39% (7/18)

		CTK	
		Positif	Négatif
CNR	Positif (10)	2	8
	Négatif (15)	1	14

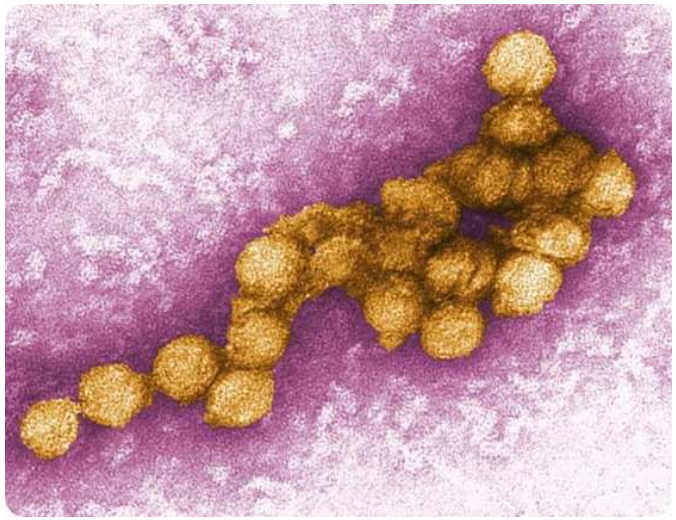
Sensibilité: 20%
Spécificité: 93%

Faux positifs: 33% (1/3)
Faux négatifs: 36% (8/22)





Casi clinici interessanti



Caso Negrar

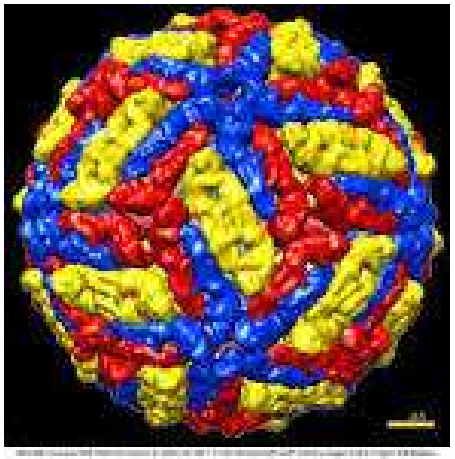
- Veterinaria di 41 aa che soggiorna in Brasile dal 8 al 28 agosto 2014
- Dal 29 agosto insorgenza di mialgie, rash cutaneo, artralgie: ne febbre, ne storia di febbre
- Il 4 settembre si presenta presso il nostro PS
- Il 5 settembre esegue test rapidi dengue: NS1 neg, IgM dubbio
- L'8 settembre : IgM dengue positivo, NS1 neg
- Invio a Padova: IgM positivo, inviare II campione dopo 15 gg

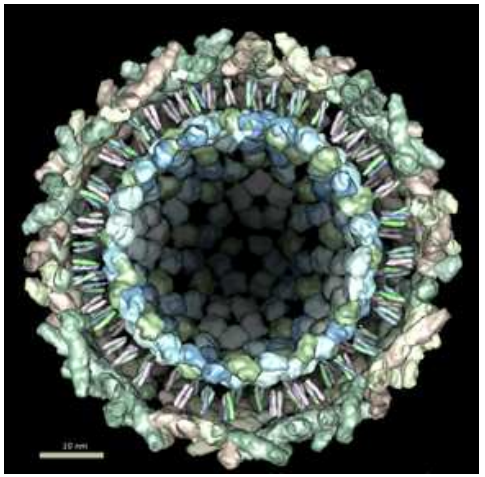
Casi di Treviso 2012

- **Maschio 41 aa, muratore, ricoverato il 15 settembre per febbre, cefalea, dimagrimento 10 kg**
- **Esegue Rx torace, Tac torace, emocolture, ecocardio TE**
- **Il 5 ottobre sierologia per WNV positiva**

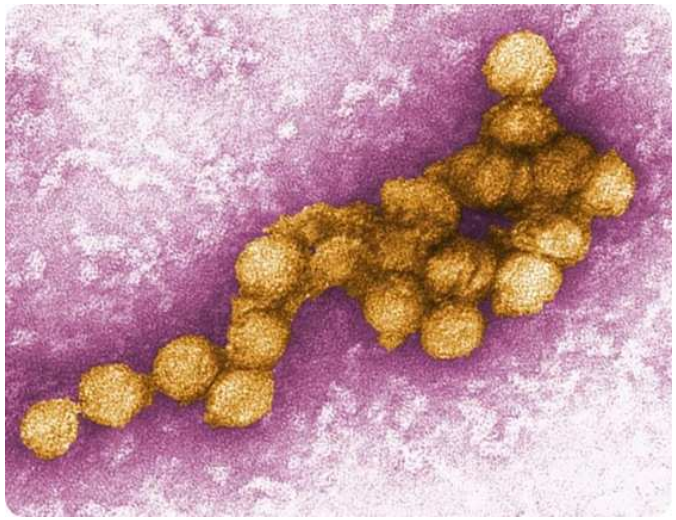
- **Maschio 61 aa, imprenditore, lamenta febbre e cefalea dal 18 luglio**
- **Il 21 luglio MMG prescrive bactrim**
- **Il 24 luglio ricovero per febbre ndd**
- **Il 27 luglio scotomi a ragnatela OD**
- **Esegue emocolture, Tac cranio-torace addome, RMN encefalo, ecocardio TT, EEG**
- **CMV/EBV, malaria, HIV, HBV, HCV, TB, Borrelia, Widal Wright negativi**
- **Il 13 agosto sierologia per WNV positiva**

Tasso di ospedalizzazione WNF 2010-2012 22/25 88%





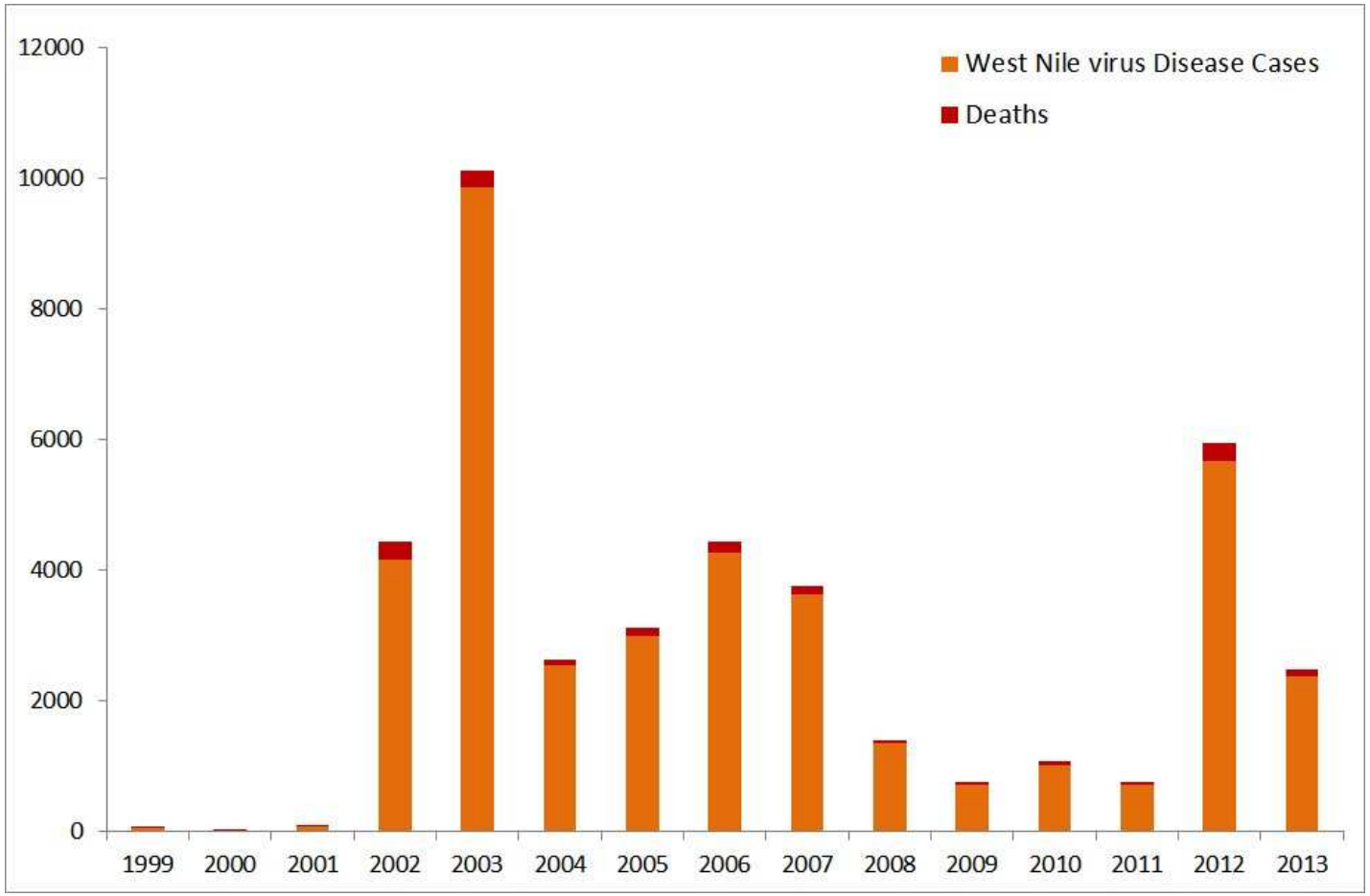
….e nel mondo 2011-2014 ?



Petersen LR, Fischer M.

Unpredictable and difficult to control--the adolescence of West Nile virus.

N Engl J Med. 2012 Oct 4;367(14):1281-4.



Dengue

Outbreak a Madeira,
ottobre – novembre 2012 (***Aedes aegypti***)

Lourenço J, Recker M.

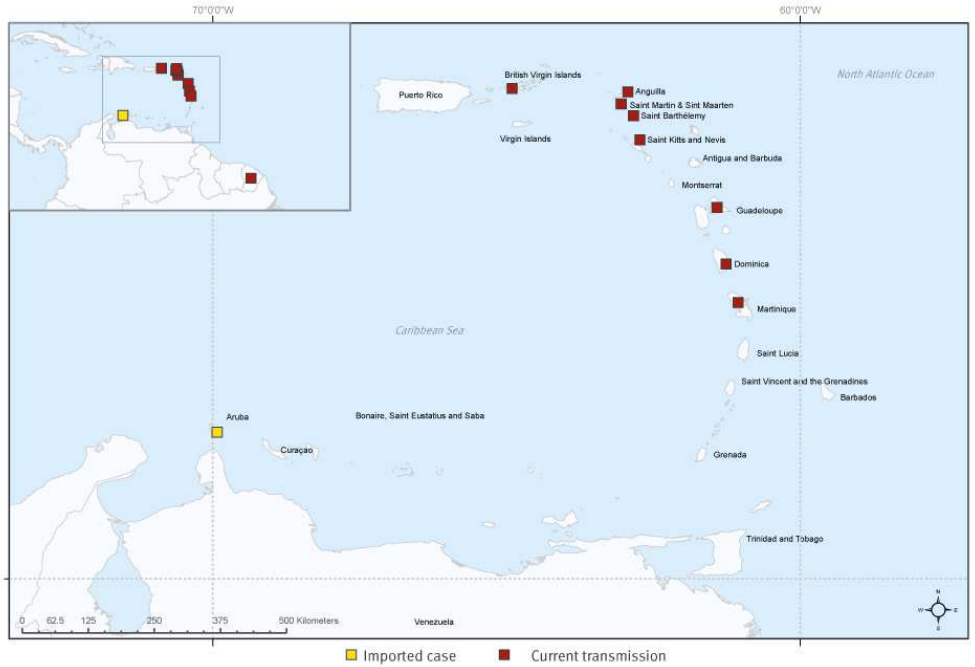
The 2012 Madeira dengue outbreak: epidemiological determinants and future epidemic potential.

PLoS Negl Trop Dis. 2014 Aug 21;8(8):e3083.

Chikungunya nei Caraibi

FIGURE 3

Local chikungunya transmission and imported cases in the islands of the Caribbean region and in French Guiana, 1 December 2013–23 February 2014



The period 1 December 2013–23 February 2014 corresponds to week 48 2013–week 8 2014.

Paty MC, Six C, Charlet F et al.

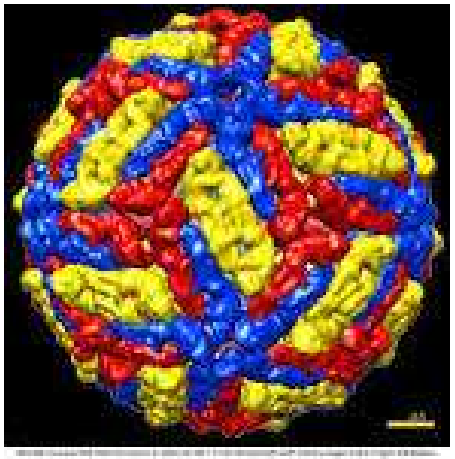
Large number of imported chikungunya cases in mainland France, 2014: a challenge for surveillance and response.

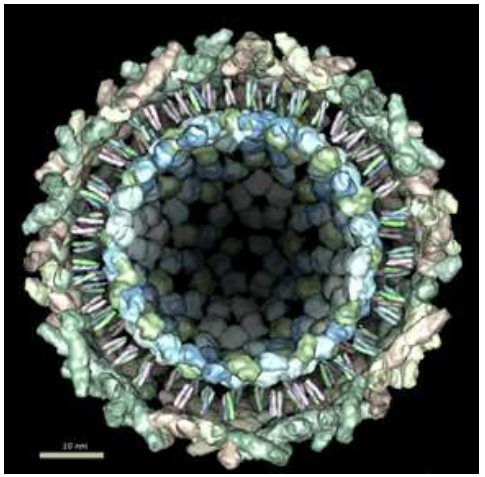
Euro Surveill. 2014 Jul 17;19(28):20856.

Eurosurveillance, Volume 19, Issue 3, 23 January 2014
Rapid communications

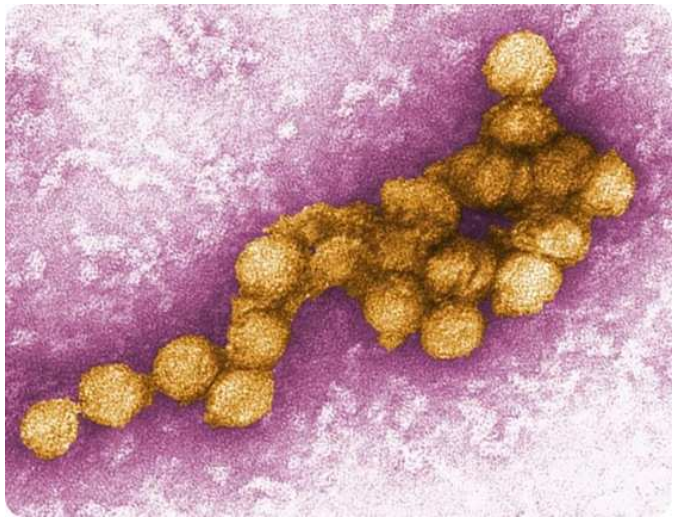
Autochthonous dengue virus infection in Japan imported into Germany, September 2013

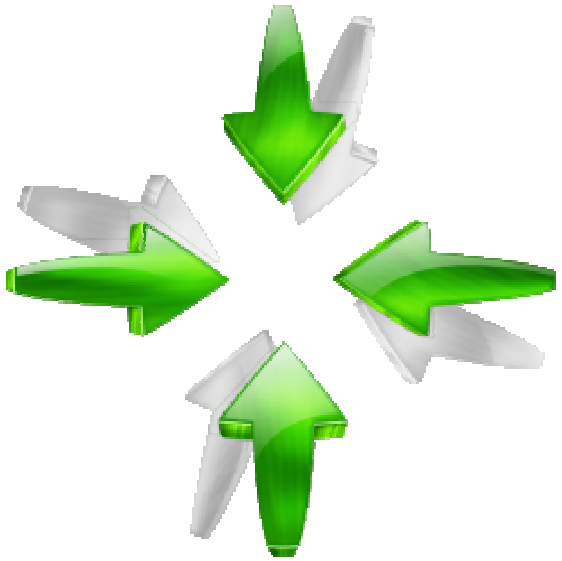
J Schmidt-Chanasit ( )1,2, P Emmerich1, D Tappe1, S Günther1, S Schmidt3, D Wolff3, K Hentschel4, D Sagebiel4, I Schöneberg5, K Stark5, C Frank5



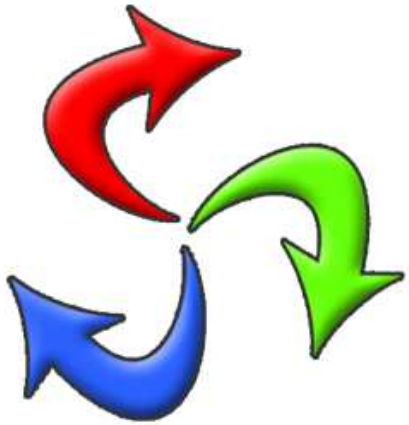


Conclusioni





Dengue/Chikungunya

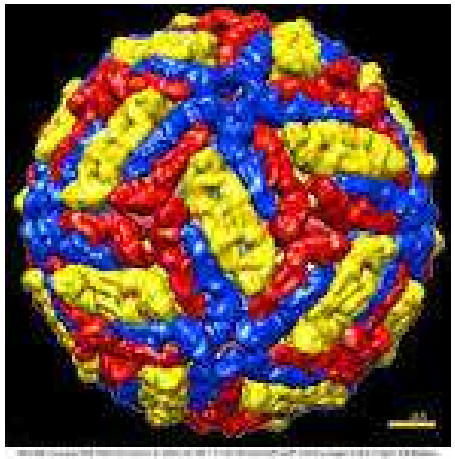


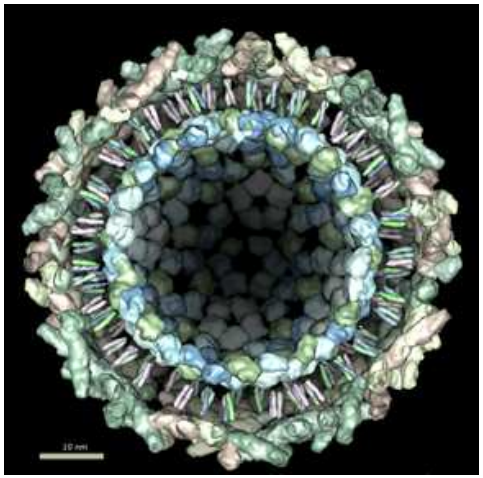
West Nile Fever

- Test rapidi dengue 
- Test rapidi chikungunya 
- Dotare test di I livello laboratori degli ospedali con reparti di malattie infettive 
- Febbri di ritorno dai tropici: codice verde PS 
- Molte WNF rimangono non diagnosticate 
- Collaborazione con i MMG 
- Collaborazione tra Salute pubblica, malattie infettive, Laboratorio di microbiologia, Istituto zooprofilattico 

Continuare a cercare…..

Grazie per l'attenzione…





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PER LE MALATTIE TROPICALI