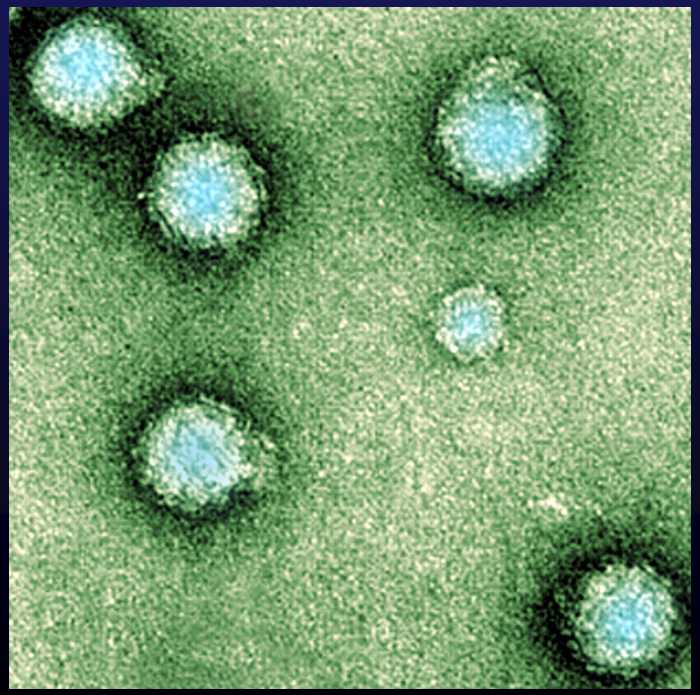


# Infezioni da Chikungunja e Dengue

**Giacomo Magnani**
UO Malattie Infettive
ASM di Reggio Emilia

Reggio Emilia, 15 Aprile 2011

JAMES GATHANY/CDC

The virus has been spread by the *Aedes albopictus* mosquito

## Europe witnesses

**Rory Watson** BRUSSELS

The first known instance of transmission of chikungunya fever by mosquitoes in Europe is currently taking place in northeastern Italy. Previously some travellers from areas where the infection is endemic—parts of Africa, South East Asia, and the Indian subcontinent—had returned home to Europe with the virus. But never before had local transmission taken place.

BMJ | 15 SEPTEMBER 2007 | VOLUME 335

# CHIKUNGUNYA

# Che cos’è il virus chikungunya

- E’ un Alphavirus (genere Togavirus), a RNA singola elica, capsulato.
- Isolato la prima volta nel 1953 in Tanzania. In quell’occasione, isolati due ceppi, Ross e S 27. Un terzo ceppo è stato isolato in Senegal nel 1983.
- Correlato a 5 altri alphavirus in patologia umana: o’nyong,nyong virus (Africa), Ross river e Barma Forest (Australia), Sindbis e Mayaro (Sud America)

# Chikungunya in area tropicale: Vettore e Reservoir

- **In Africa** si trasmette attraverso le punture di zanzare come *Aedes luteocephalus*, *Ae furcifer* o *Ae taylori*, che si infettano pungendo primati selvatici (ma anche roditori e uccelli) che fungono da reservoir.
- **In Asia/Oceano Indiano** il virus si trasmette da uomo a uomo attraverso la puntura della zanzara *Aedes aegypti* e meno frequentemente *Aedes albopticus*.

# Epidemie di CHIKV dal 1950

TABLE I. Chikungunya epidemics by country.

| Country | Year |
|---|---|
| *Africa* | |
| Tanzania | 1952 |
| South Africa | 1956 |
| Congo | 1958 |
| Zimbabwe | 1959 |
| Uganda | 1958 |
| Zambia | 1962 |
| Senegal | 1966 |
| Nigeria | 1964 |
| Angola | 1970 |
| *Asia and Indian Ocean islands* | |
| Thailand | 1958 |
| India | 1963 |
| Cambodia | 1963 |
| Vietnam | 1963 |
| Philippines | 1968 |
| Sri Lanka | 1965 |
| Indonesia | 1985 |
| Malaysia | 1998 |
| Comoros islands | 2005 |
| Mauritius, Reunion islands | 2005 |

# CHIKV DAL 1950

## Forte potenziale epidemico anche dopo lungo periodo di silenzio

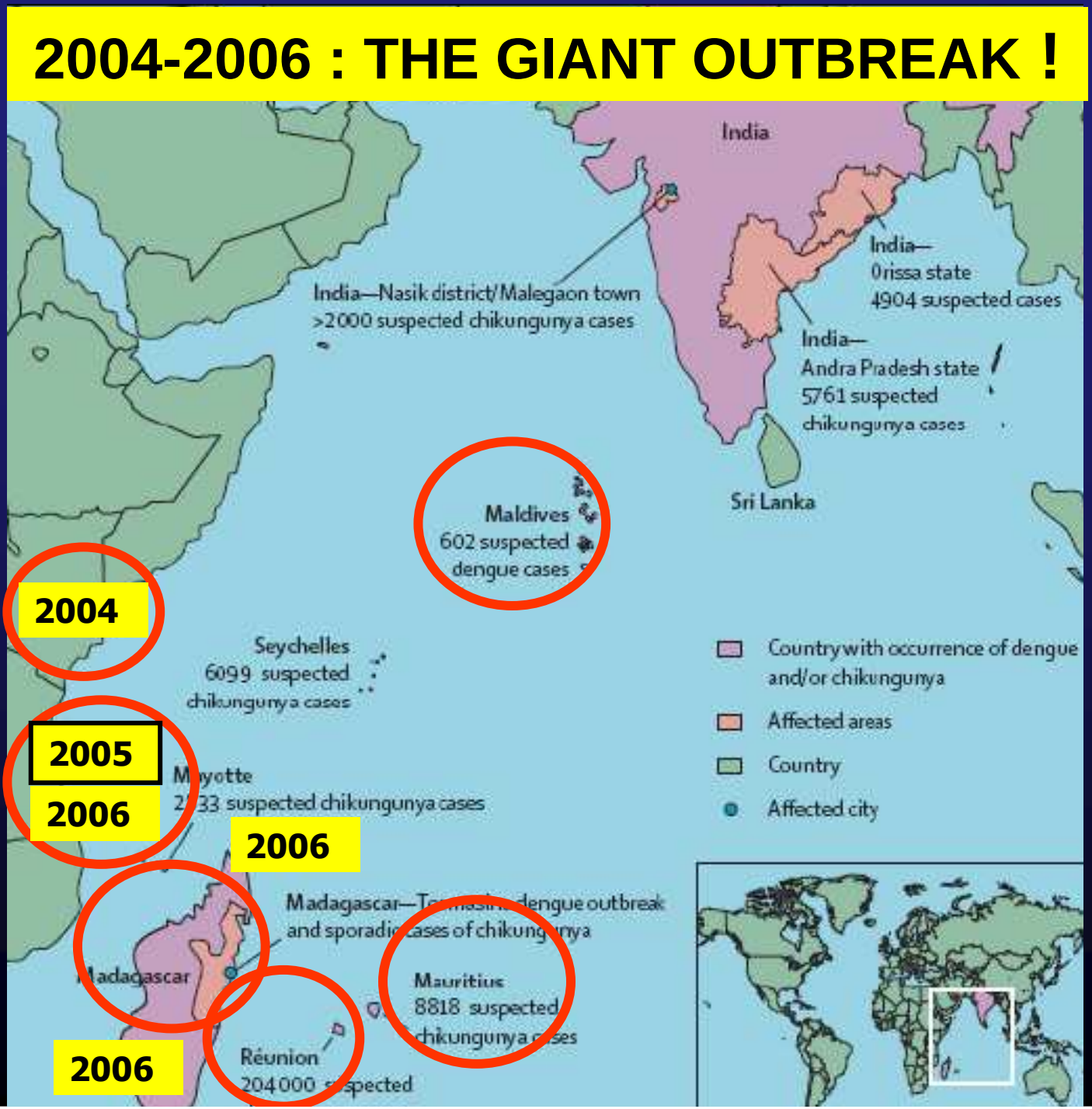
- **1999–2000:** **Rep.Democratica del Congo: circa di 50,000 persone infette**
- **Dopo 39 anni senza isolamento del virus**


Pastorino et al. J Med Virol 2004;74:277-82; Laras K et al. Trans R Soc Trop Med Hyg 2005;99:128-141

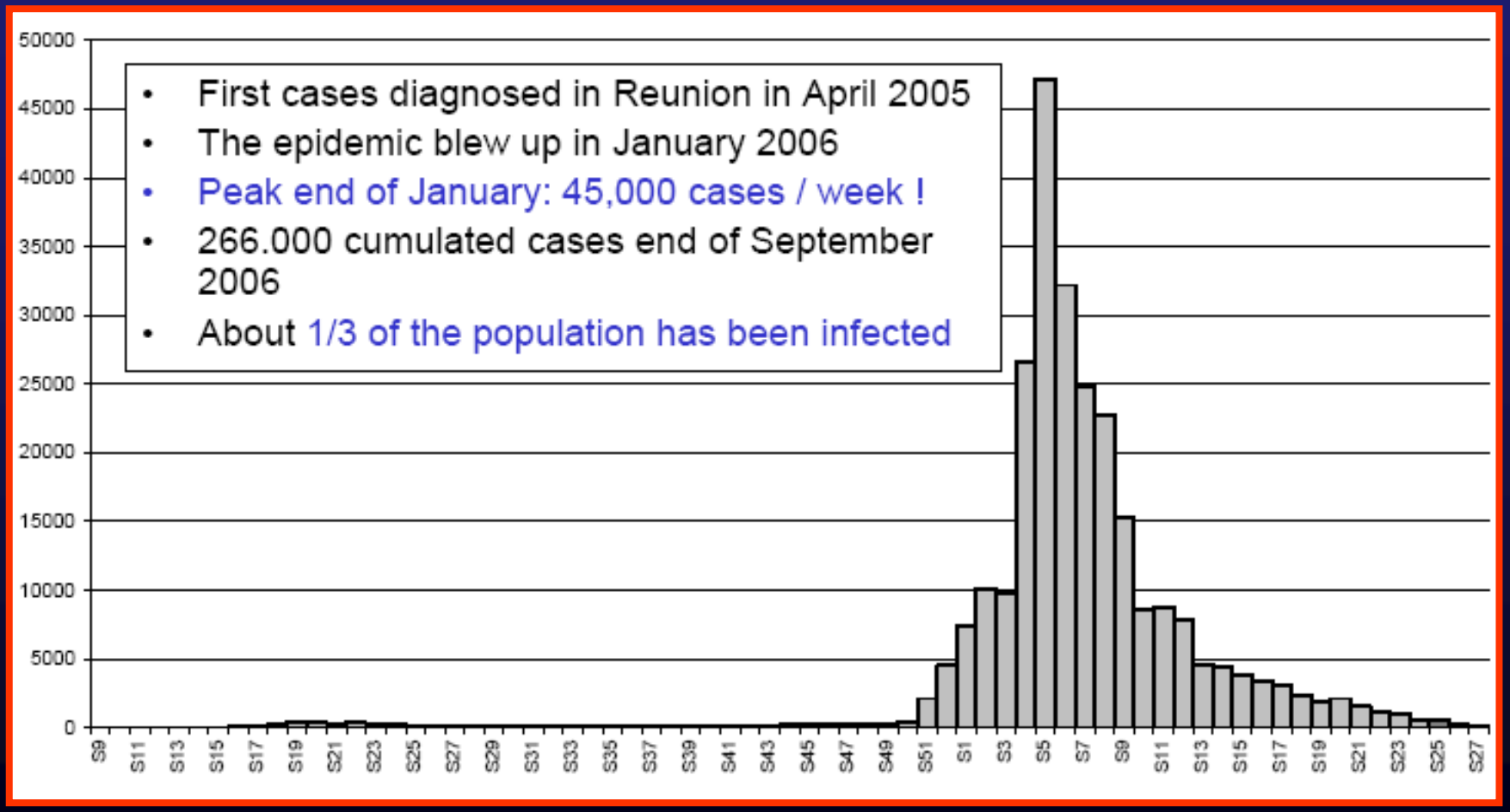
# Il grande outbreaks (2004/2006)

- Reunion e Oceano Indiano: 266,000 casi riportati, vettore *Aedes albopictus*
- India: 1.400,000 casi riportati, vettore Aedes aegypti
- I *clades* virali nelle due epidemie sono risultati correlati, differenti dai *clades* prima presenti in India

# 2004-2006 : THE GIANT OUTBREAK !



# CHIKV IN REUNION ISLAND




www.invs.sante.fr

Boelle & Flahault. Vect Born Zoon Dis 2007

# Infection with chikungunya virus in Italy: an outbreak in a temperate region

**2007**

G Rezza*, L Nicoletti*, R Angelini, R Romi, A C Finarelli, M Panning, P Cordioli, C Fortuna, S Boros, F Magurano, G Silvi, P Angelini, M Dottori, M G Ciufolini, G C Majori, A Cassone, for the CHIKV study group† Lancet 2007; 370: 1840–46

## Summary

**Background** Chikungunya virus (CHIKV), which is transmitted by *Aedes* spp mosquitoes, has recently caused several outbreaks on islands in the Indian Ocean and on the Indian subcontinent. We report on an outbreak in Italy.

**Methods** After reports of a large number of cases of febrile illness of unknown origin in two contiguous villages in northeastern Italy, an outbreak investigation was done to identify the primary source of infection and modes of transmission. An active surveillance system was also implemented. The clinical case definition was presentation with fever and joint pain. Blood samples were gathered and analysed by PCR and serological assays to identify the causal agent. Locally captured mosquitoes were also tested by PCR. Phylogenetic analysis of the CHIKV E1 region was done.

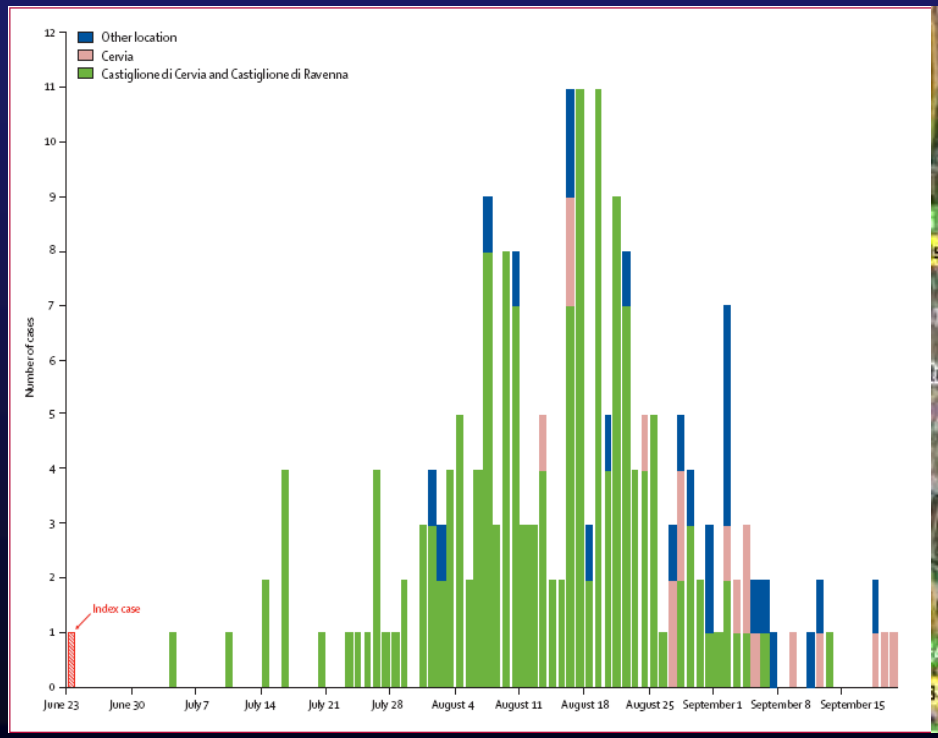
**Findings** Analysis of samples from human beings and from mosquitoes showed that the outbreak was caused by CHIKV. We identified 205 cases of infection with CHIKV between July 4 and Sept 27, 2007. The presumed index case was a man from India who developed symptoms while visiting relatives in one of the villages. Phylogenetic analysis showed a high similarity between the strains found in Italy and those identified during an earlier outbreak on islands in the Indian Ocean. The disease was fairly mild in nearly all cases, with only one reported death.

**Interpretation** This outbreak of CHIKV disease in a non-tropical area was to some extent unexpected and emphasises the need for preparedness and response to emerging infectious threats in the era of globalisation.

# Epidemia di Chikungunya in Romagna

205 casi (175 confermati in lab.) tra il 4 Luglio ed il 27 settembre 2007
Presunto caso indice, un immigrato di ritorno da visita a parenti in India

Date di comparsa di casi Chikungunya per luogo d'infezione





Rezza G et al., Lancet 2007; 370: 1840-6

**Era prevedibile una epidemia da Ckikungunya in Italia ed è possibile che possa ripetersi?**

# Condizioni indispensabili perché possa verificarsi una epidemia

- **Importazione del virus (turisti ed immigrati)**
- **Presenza del vettore (*Aedes albopictus)***
- **Fitness virale (Variante A226V)**
- **Condizioni climatiche favorevoli**

# Travelers

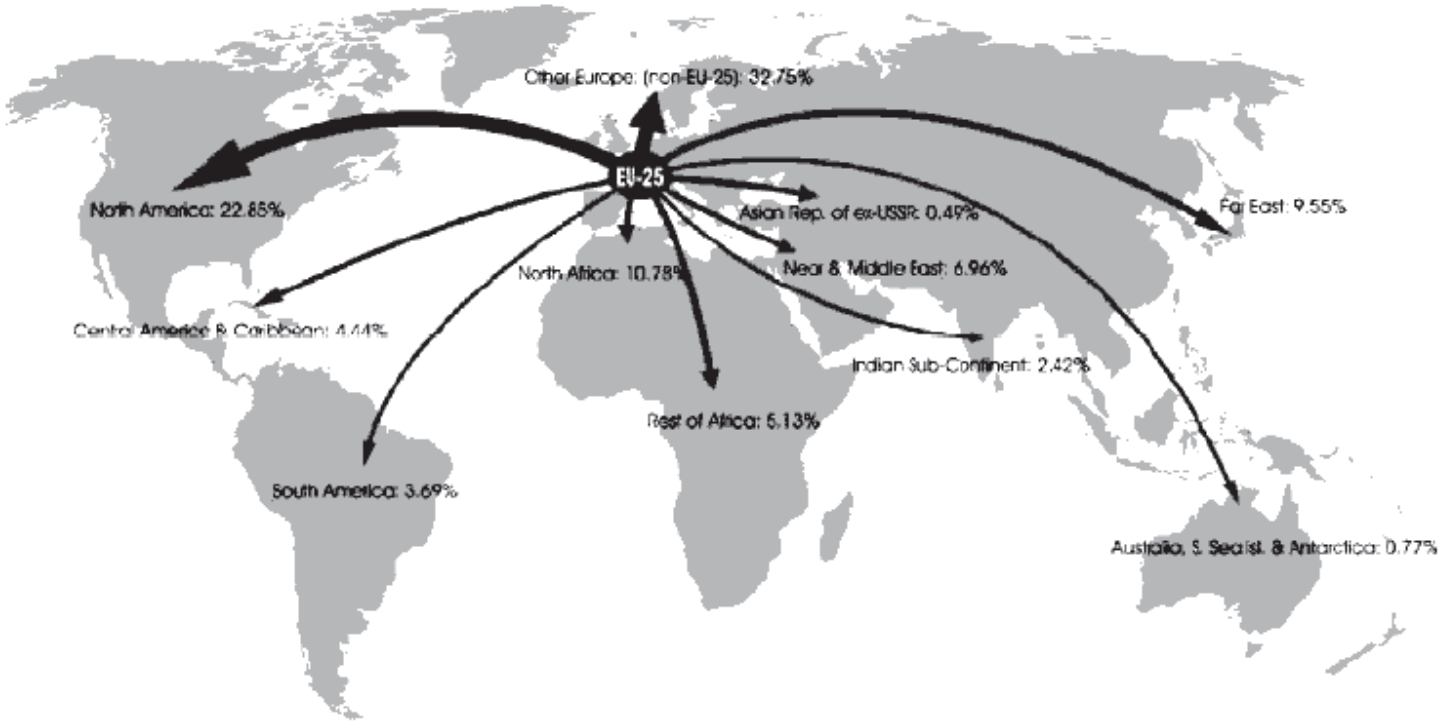
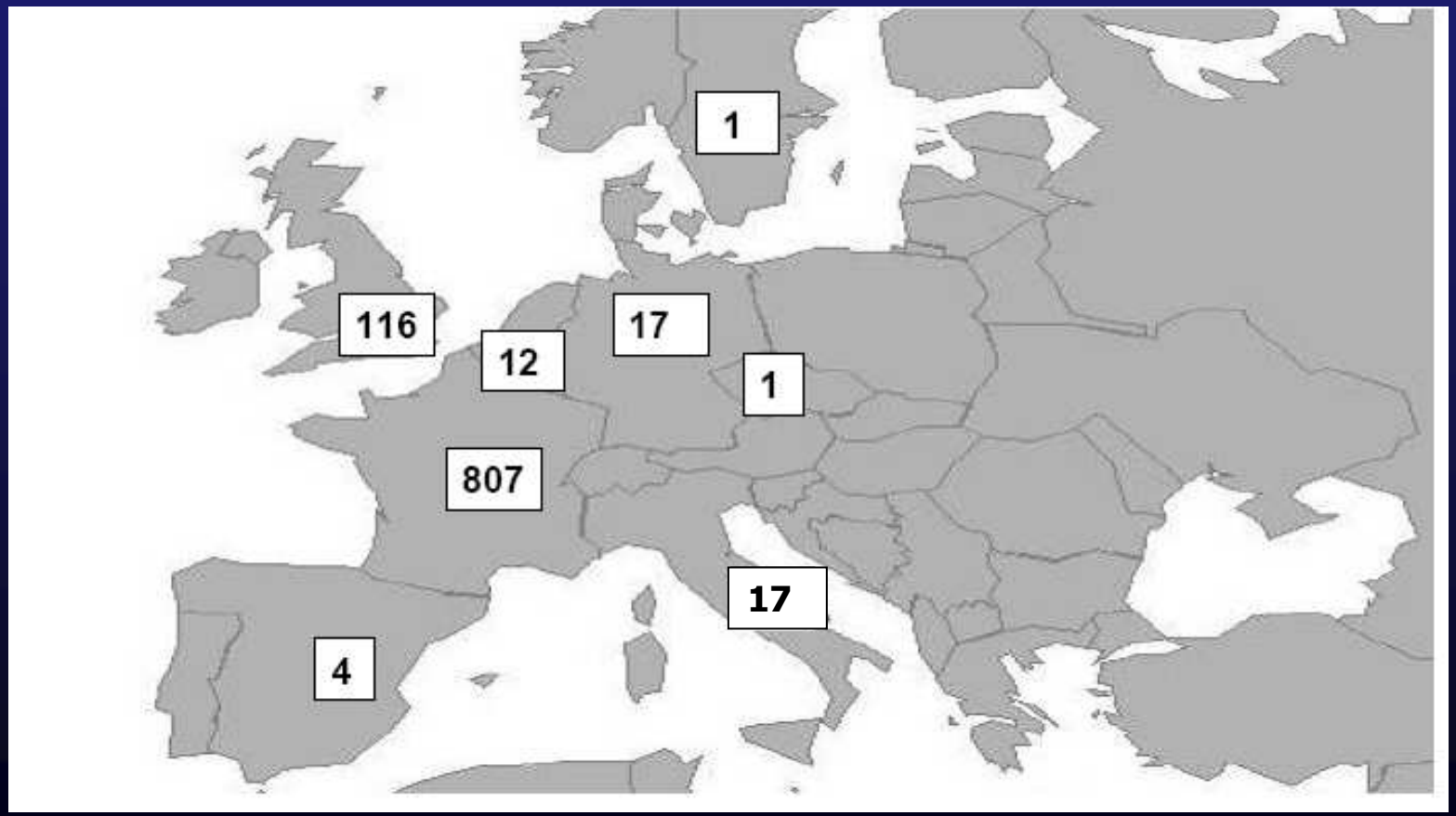



*Figure 2. Extra-EU-25 transport of passengers: share in world regions in % of total extra-EU-25 transport in 2005. From De la Fuente Layos (2006).*

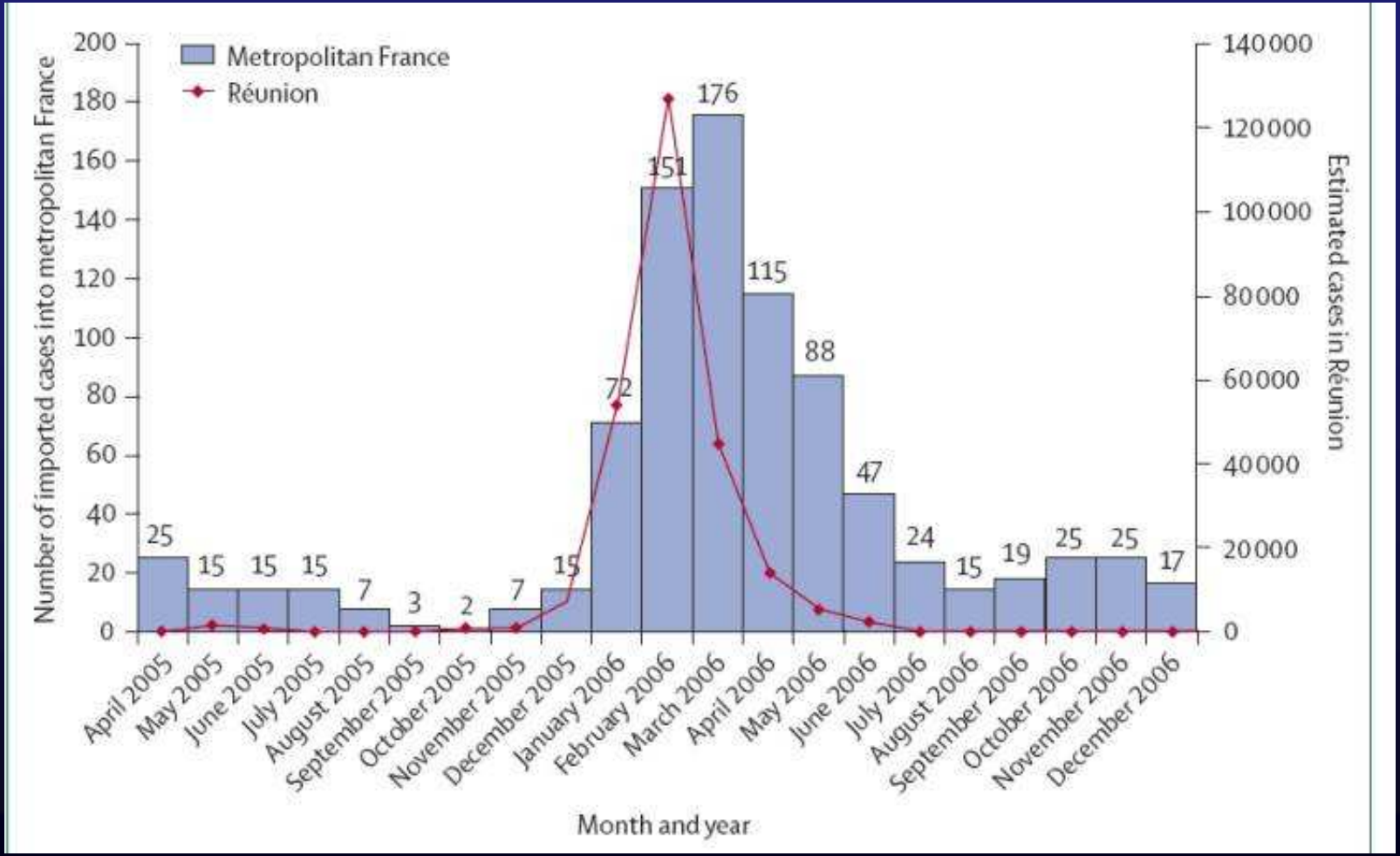
In 2005, the total number of passengers transported by air in the European Union (EU) rose to more than 700 million. Of them 35% were carried on external –EU flights.

# CHIKV INFECTION
# AN EMERGING DISEASES IN TRAVELERS




Eurosorveilance 2006

# CHIKV INFECTION IN FRANCE




**Pialloux et al. Lancet Infect Dis. 2007;13:319- 27**

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Emerging Infectious Diseases

Volume 13, Number 8–August 2007

*Letter*

# Imported Chikungunya Infection, Italy

**Anna Beltrame,* ✉ Andrea Angheben,† Zeno Bisoffi,† Geraldo Monteiro,† Stefania Marocco,† Guido Calleri,‡ Filippo Lipani,‡ Federico Gobbi,‡ Francesca Canta,‡ Francesco Castelli,§ Maurizio Gulletta,§ Sara Bigoni,§ Veronica Del Punta,§ Tiziana Iacovazzi,¶ Roberto Romi,# Loredana Nicoletti,# Maria Grazia Ciufolini,# Giada Rorato,* Camilla Negri,* and Pierluigi Viale***

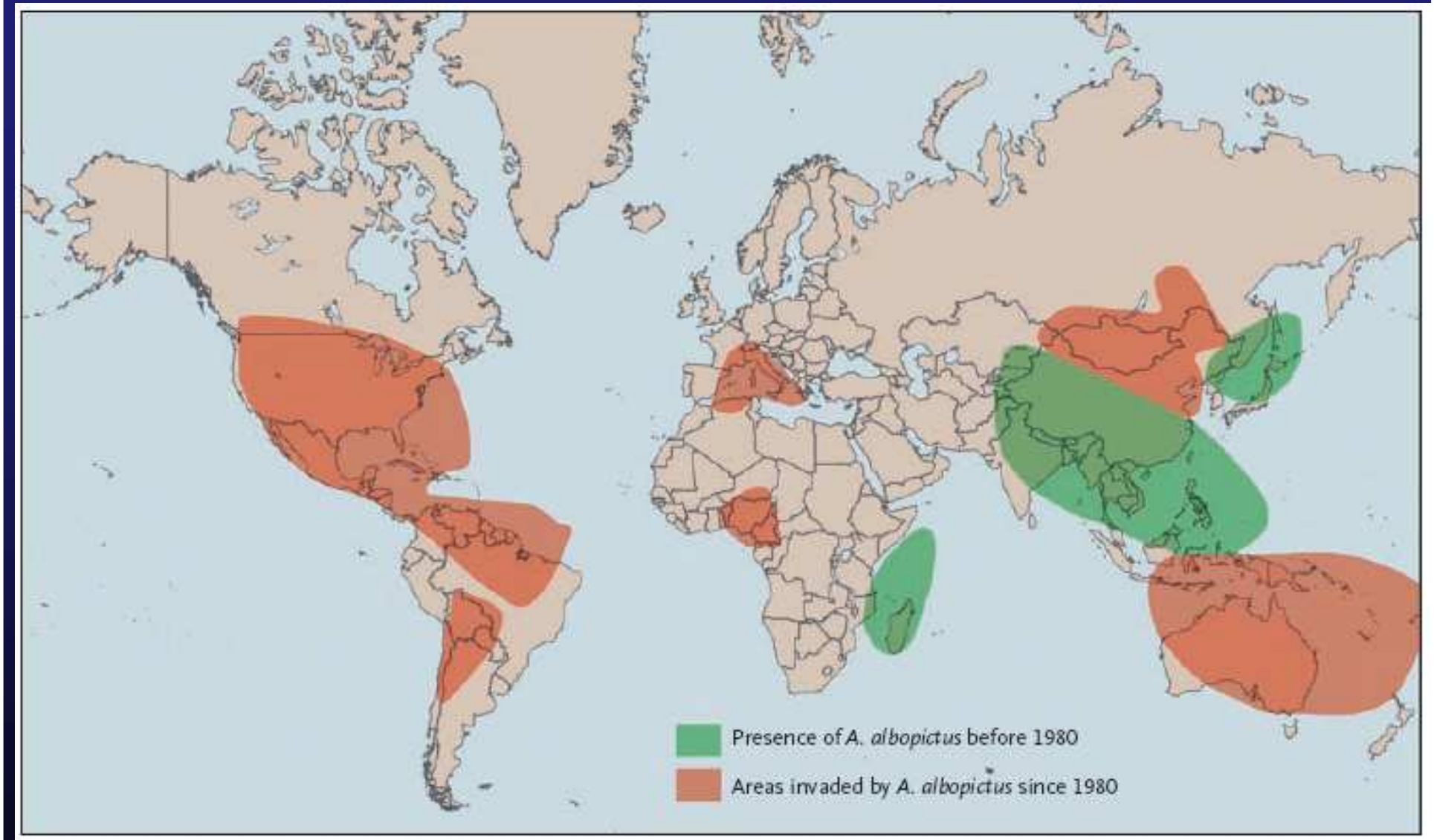
*Clinic of Infectious Diseases at University of Udine, Udine, Italy; †Sacro Cuore Hospital, Negrar, Italy; ‡Amedeo di Savoia Hospital, Torino, Italy; §University of Brescia, Brescia, Italy; ¶F. Fallacara Hospital, Triggiano, Italy; and #Istituto Superiore di Sanità, Roma, Italy

17 confirmed cases of CHIKV infection observed in travelers from July to September 2006 at 5 GISPI centers.

# *Aedes albopictus*

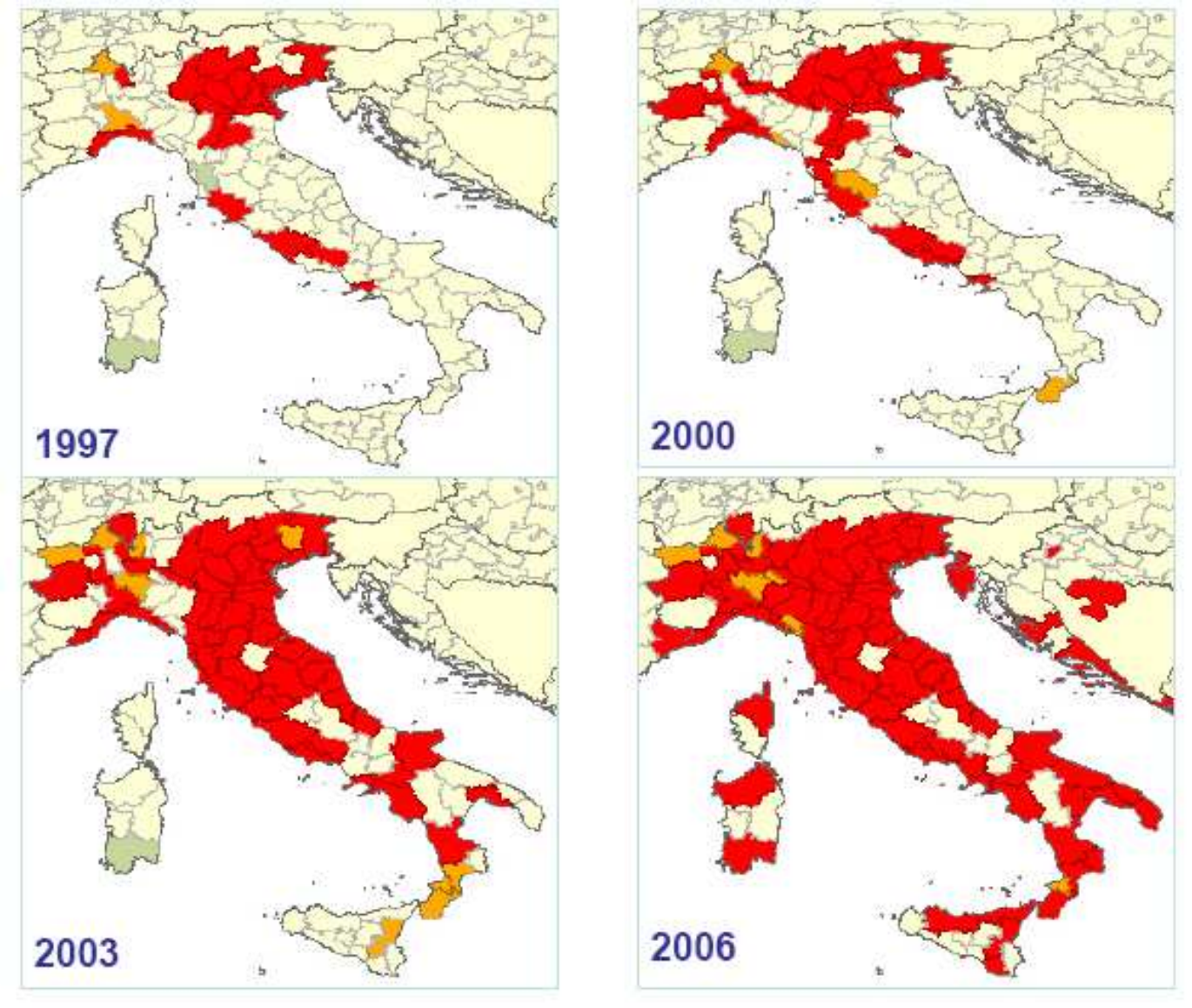

**La zanzara tigre *Aedes albopictus* : il vettore in causa nella epidemia di CHIK nell'isola di La Reunion**

**Comoros, Mauritius, Seychelles: *Aedes aegypti* ?**




**World Distribution of the *Aedes albopictus* Mosquito.**

# Aedes albopictus in Italia



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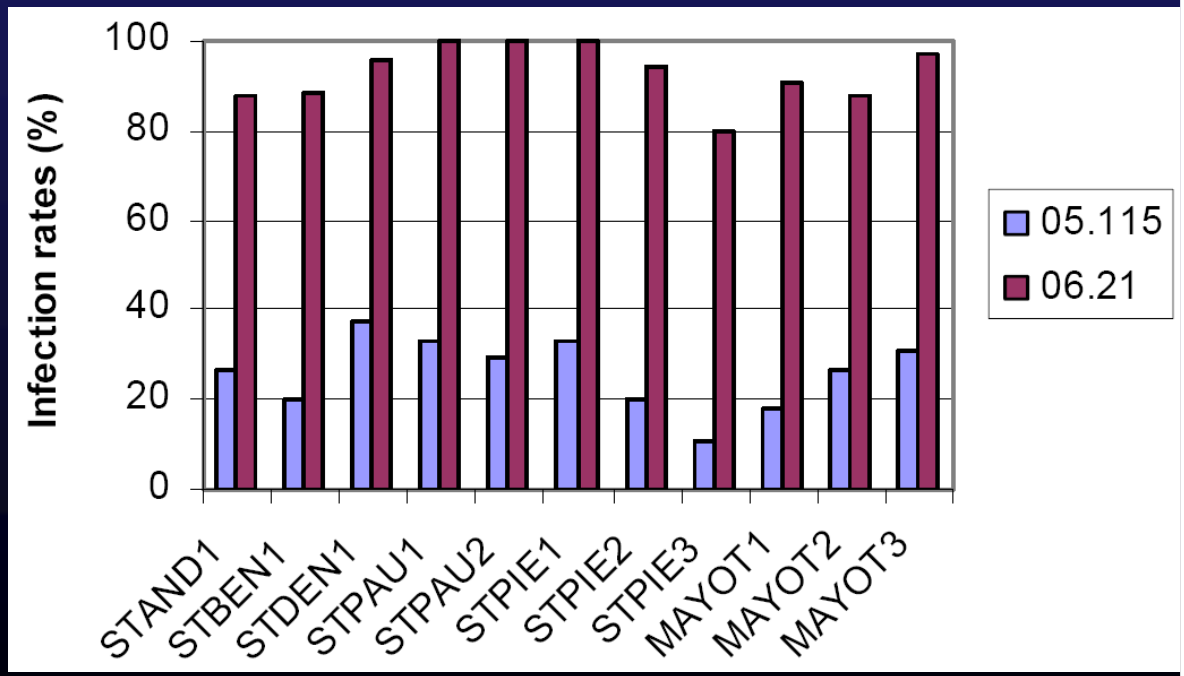
PLoS one

# Two Chikungunya Isolates from the Outbreak of La Reunion (Indian Ocean) Exhibit Different Patterns of Infection in the Mosquito, *Aedes albopictus*

Marie Vazeille[1], Sara Moutailler[2], Daniel Coudrier[2], Claudine Rousseaux[3], Huot Khun[4], Michel Huerre[4], Julien Thiria[5], Jean-Sébastien Dehecq[5], Didier Fontenille[6], Isabelle Schuffenecker[7], Philippe Despres[8], Anna-Bella Failloux[2]*

A highly competent vector *Ae. albopictus* which allowed an efficient replication and dissemination of CHIKV 06.21 (collected in November 2005 with a substitution A226V ).

Vertical transmission? Ovaries are infected at day 6 after experimental infection consequences ?



# Chikungunya in Emilia Romagna
## Elevata fitness virale per il vettore

- … the viral strain that caused the outbreak in Italy is thought to be better adapted to A.albopictus than are other variants *(Rezza G, et al. Lancet 2007; 370: 1840)*

- "… contained a mutation in the E1 glycoprotein which was responsible for a single amino acid substitution (A226V) able to increase the infectivity of the virus for A. albopictus" at the Reunion island *(Rezza G . European Journal of Public Health, 2009 1–2)*

OPEN ACCESS Freely available online

PLoS one

# Two Chikungunya Isolates from the Outbreak of La Reunion (Indian Ocean) Exhibit Different Patterns of Infection in the Mosquito, *Aedes albopictus*

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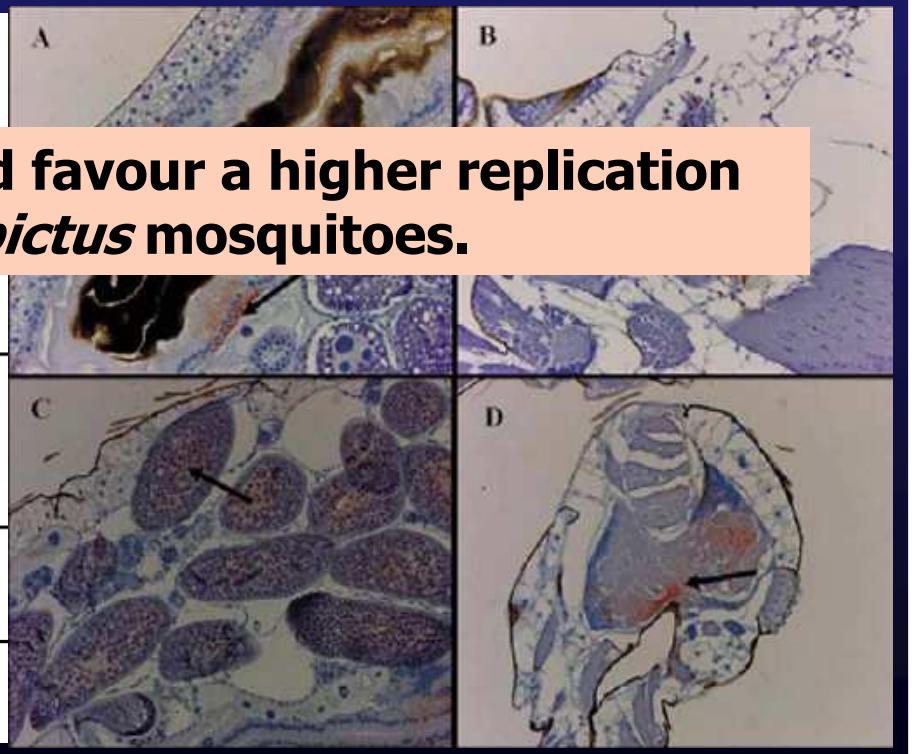
| CHIK isolate | Date | Localisation | E1-226 | E1-284 |
|---|---|---|---|---|
| 05.115 | | | | |
| 06.21 | Nov. 2005 | La Réunion | Val | Asp |
| 06.111 | Feb. 2006 | Mayotte | Val | Asp |
| 06.117 | 1999-2000 | RDC | Ala | Glu |

**The A 226 substitution would favour a higher replication rate in *Aedes albopictus* mosquitoes.**




PLoS ONE. 2007 Nov 14;2(11):e1168

# Chikungunya: clinica

**Una malattia con due facce**

- ***Arbovirosi*** – sindrome algo-febbrile acuta
  - diffusione epidemica (*Ae. albopictus e A226V-CHIKV)*
- ***Alfavirosi*** – potere artritogeno
  - evoluzione clinica cronica

# Chikungunya: clinica

- Incubazione: 1-12 giorni
- Viremia: da - 48 ore a  +10 gg dalla comparsa dei sintomi.
- Elevata carica virale:
  - contagio interumano
  - trasmissione verticale
  - rischio per le donazioni

# Fase acuta (G1-G10)

- **Febbre** (96%)
- **Artralgie/artriti** (95-100%) : bilaterali, simmetriche, distali, >10 art.
- **Rash morbilliforme** (40-51%)
- **Complicazioni:** encefalite, miocardite, epatite, trasmissione materno-fetale
- Mortalità < 1/1000 (> 75 anni, co-patologie)

*Borgherini G et coll. Clin Infect Dis 2007;44:1401-7  Simon F et coll. Medicine 2007;86: 123-37 Josseran L et coll. Emerg Infect Dis 2006:12:1994-*

# Frequenza di manifestazioni cliniche nell' epidemia dell' Emilia Romagna, 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%) |

*Mandatory in the case definition. †Not mandatory if diagnosis is laboratory confirmed.

***Table 2:*** **Distribution of symptoms**

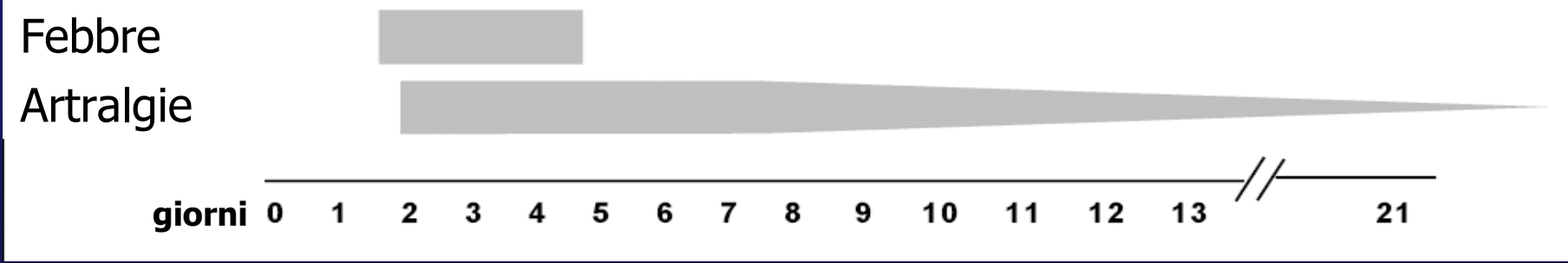
Rezza G et al., Lancet 2007; 370: 1840-6

# CHIKV: febbre

- Sovente con picchi sino a 40C°
- Spesso associata a:
  - cefalea, non intensa (50%)
  - iniezione congiuntivale, fotofobia
  - nausea,  vomito, dolore addominale)
  - linfoadenopatia generalizzata

# CHIKV: poliatralgia

- **Compare generalmente poco dopo la febbre**




- **Di grande intensità e temporaneamente invalidante**
- **Frequentemente localizzata alle spalle, piccole articolazioni delle mani, polsi, caviglie e piedi.**
- **In più della metà dei casi simmetrica**

# CHIKV: poliartralgia

- Può avere carattere carattere migrante, discontinuo e recidivante
- A volte associata a tumefazione articolare
- Più intensa al mattino
- Alleviata dall'esercizio lieve e peggiorata da quello intenso
- La pressione sul polso tende a scatenare un forte dolore

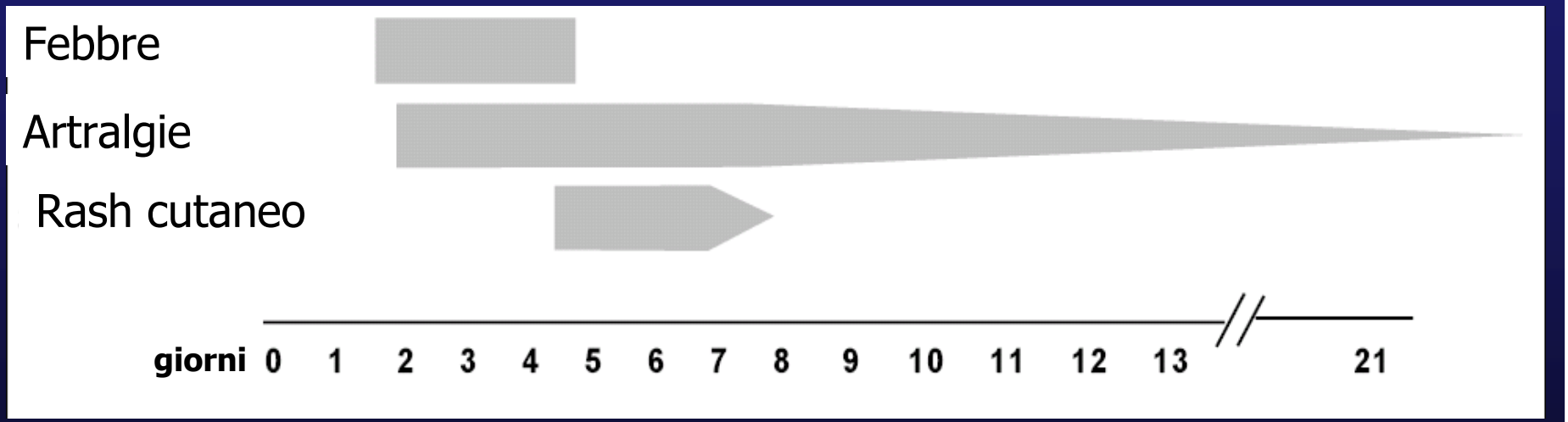
# CHIKV: Rash cutaneo

- Predominante al tronco e alle radici degli arti
- Associato ad enantema ed eritema palmare e plantare
- Nella metà dei casi associato a prurito
- Inizialmente eritematoso, quindi maculo-papulare (più raramente papulare)

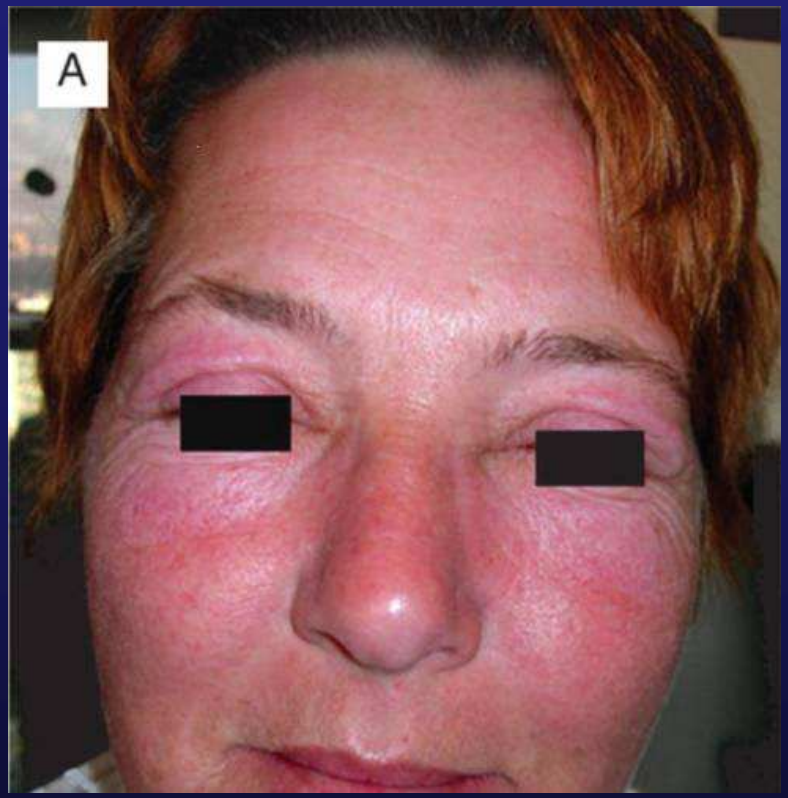
# CHIKV: altre manifestazioni cutanee

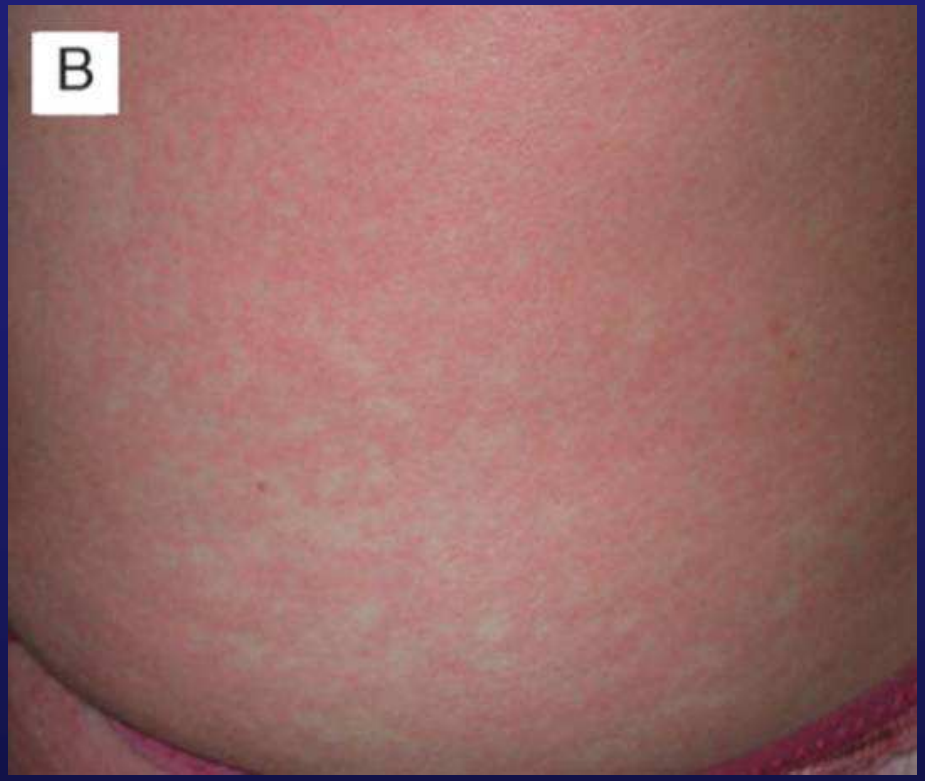
- Edema facciale
- Emorragie benigne a tipo gengivorragie ed epistassi,specie  nei bambini
- Nei bambini, rash bolloso

# CHIKV: Rash cutaneo



**Chikungunya: Rash maculo-papulare al tronco**





Medicine may 2007

# CHIKV: Infezioni asintomatiche

- 15% del totale nell’epidemia di Réunion *(Michault, Fritel)*

# CHIKV: forme severe

- Isola La Reunion : forme gravi = 0.02%; decessi 155 su 266.000 casi (Higgs 2006)
- Italia: 1 decesso (encefalite) su 205 casi

- Casi aneddotici di complicanze nell'adulto:
  - Epatite acuta grave, anche fulminante
  - Mielo-meningoencefalite
  - Poliradiculoneurite (Sindrome di Guillain-Barré)
  - Miocardite, pericardite

# CHIKV e gravidanza

- Donne gravide (n=159 a Reunion) 30/35 con infezione perinatale hanno trasmesso l'infezione al neonato.
- Oltre l'80% dei casi neonatali ha caratteristiche di gravità: encefalite e CID (Cordell H, 2006)
- Dimostrata (ma difficile da quantificare) la perdita fetale in gravide entro 22 W con chik (Touret Y, 2006)
- Rischio per viaggiatrici gravide in aree con attività epidemica di Chik

# Fase sub-acuta (G10-G90)

- **Miglioramento transitorio**
- **Rebound clinico (82%) e acme al M2-M3**
  - Poliartralgia/poliartrite
  - Tenosinovite
  - Acrosindrome
  - Astenia, stato depressivo

Simon F et coll. Medicine 2007;86: 123-37
Queyriaux B et col. Lancet Infect Dis 2008;8:2–3.

# CHIKV: decorso

- Nella maggior parte dei casi la malattia si risolve entro alcune settimane.
- La convalescenza si associa a profonda astenia.
- I dolori possono persistere in un terzo dei casi fino a 4 mesi e in alcuni casi per qualche anni.

# Fase cronica (> G90)

- A 3 mesi : 80 - 93%
- A 15 mesi : 57%
- A 24 mesi : 47%

- Fattori predittivi: età> 45 anni, co-morbidità articolari, gravità dell'episodio iniziale (dolore, CRP, carica virale iniziale)

*Moiton, M.P. et al. BEH thématique, 2008; 38-40 Sissoko D et al. PLoS Negl Trop Dis. 2009;3(3):389. Soumahoro M.K. et al. Rev Med Interne. 2008; 3371:S1-S55 Vivier E et coll., poster D-19 JNI 2010*

*Sissoko D et al. PLoS Negl Trop Dis. 2009;3(3):389. Hoarau JJ et coll. J Immunol 2010;184:5914-27.*

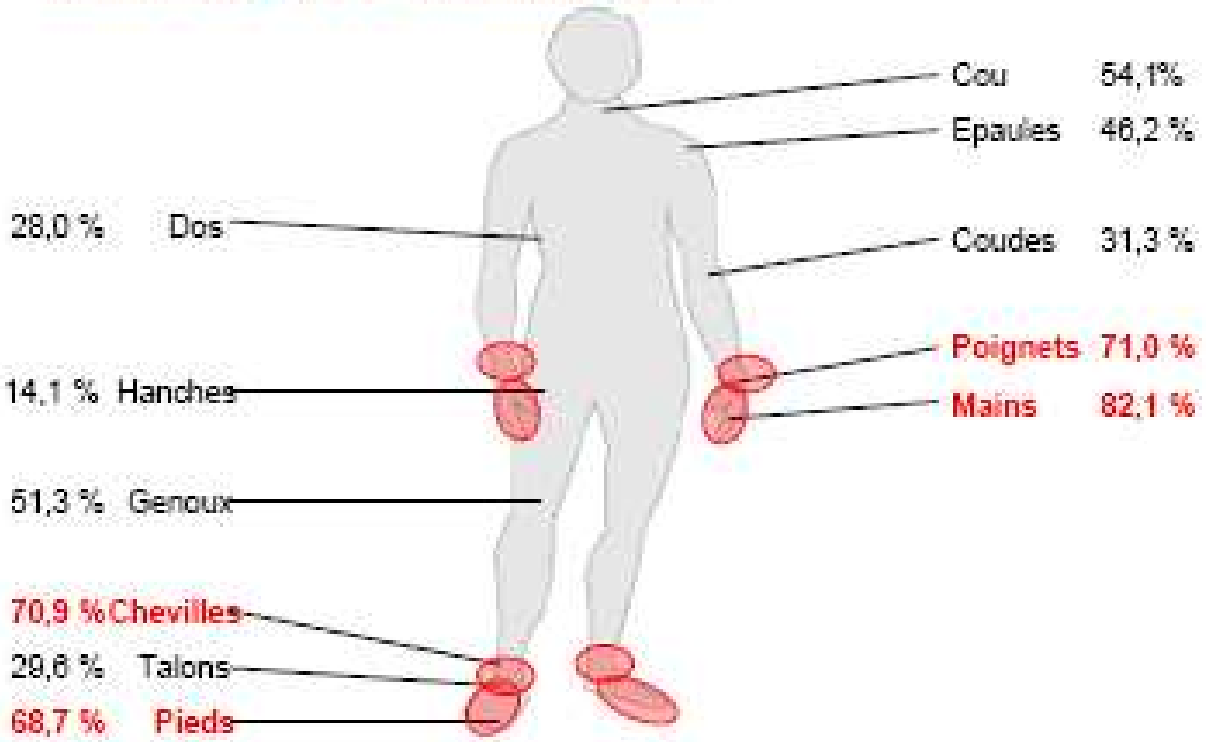
# Arthralgies chroniques

757 gendarmes,
Réunion 2006

**A 6 mois**
672 répondeurs
*H: 95%, méd: 40 ans*

→126 CHIK+

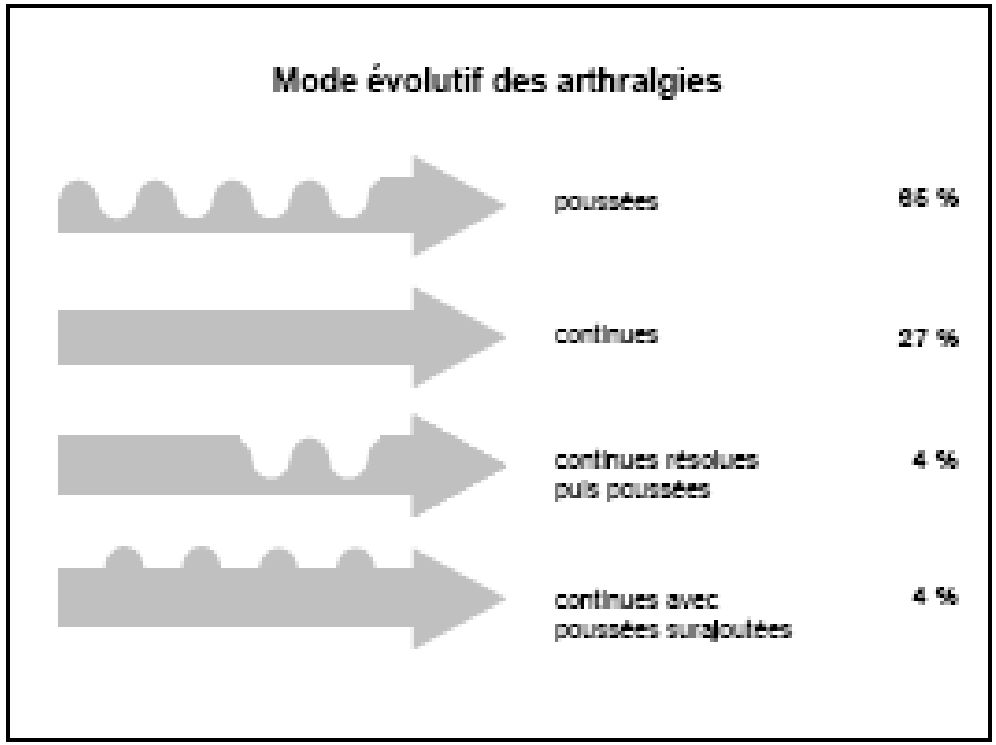
***86% chroniques***




*Simon F, données personnelles*

# Arthralgies chroniques (2)

- ***Type inflammatoire***
  - Dérouillage matinal (32%)
- ***Fluctuations***
  - « rechutes »
  - Sensibilité au froid




*Simon F, données personnelles*

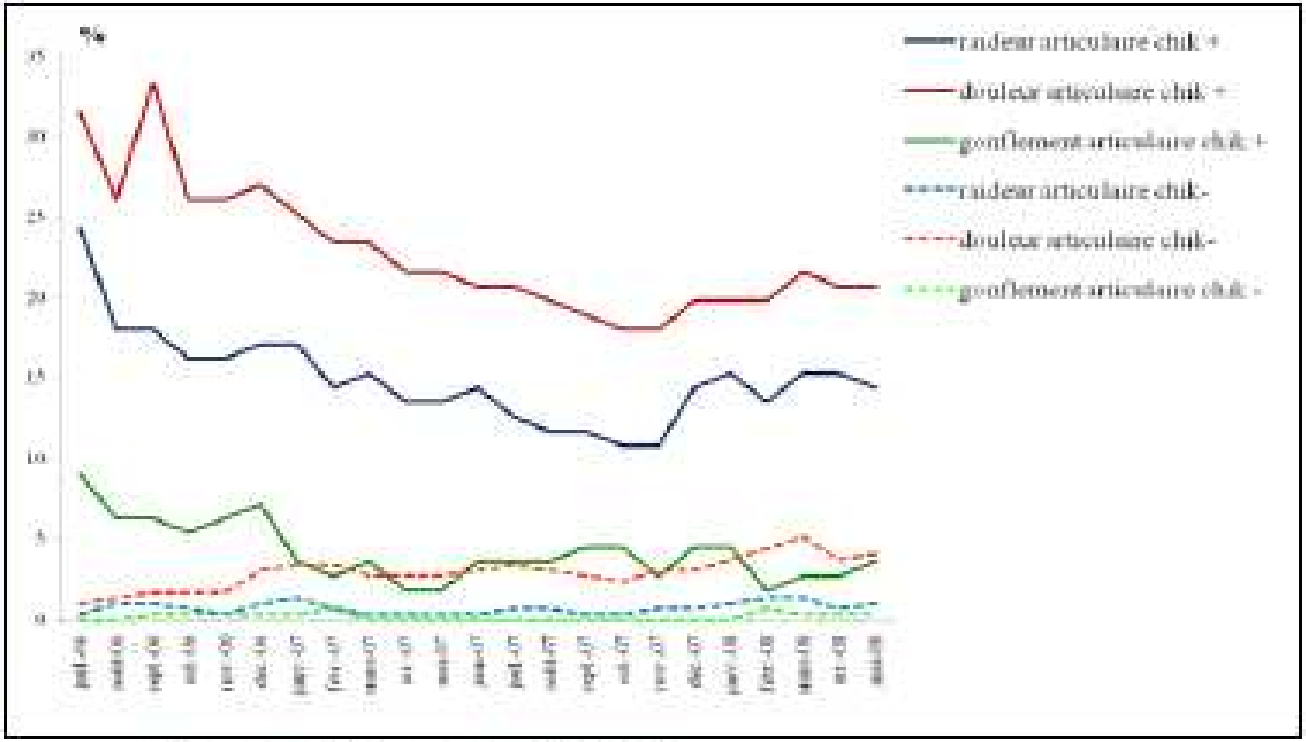
# Symptômes articulaires périphériques chroniques

662 gendarmes,
Réunion 2006

**A deux ans**
404 répondeurs
*H: 95%, méd: 43 ans*

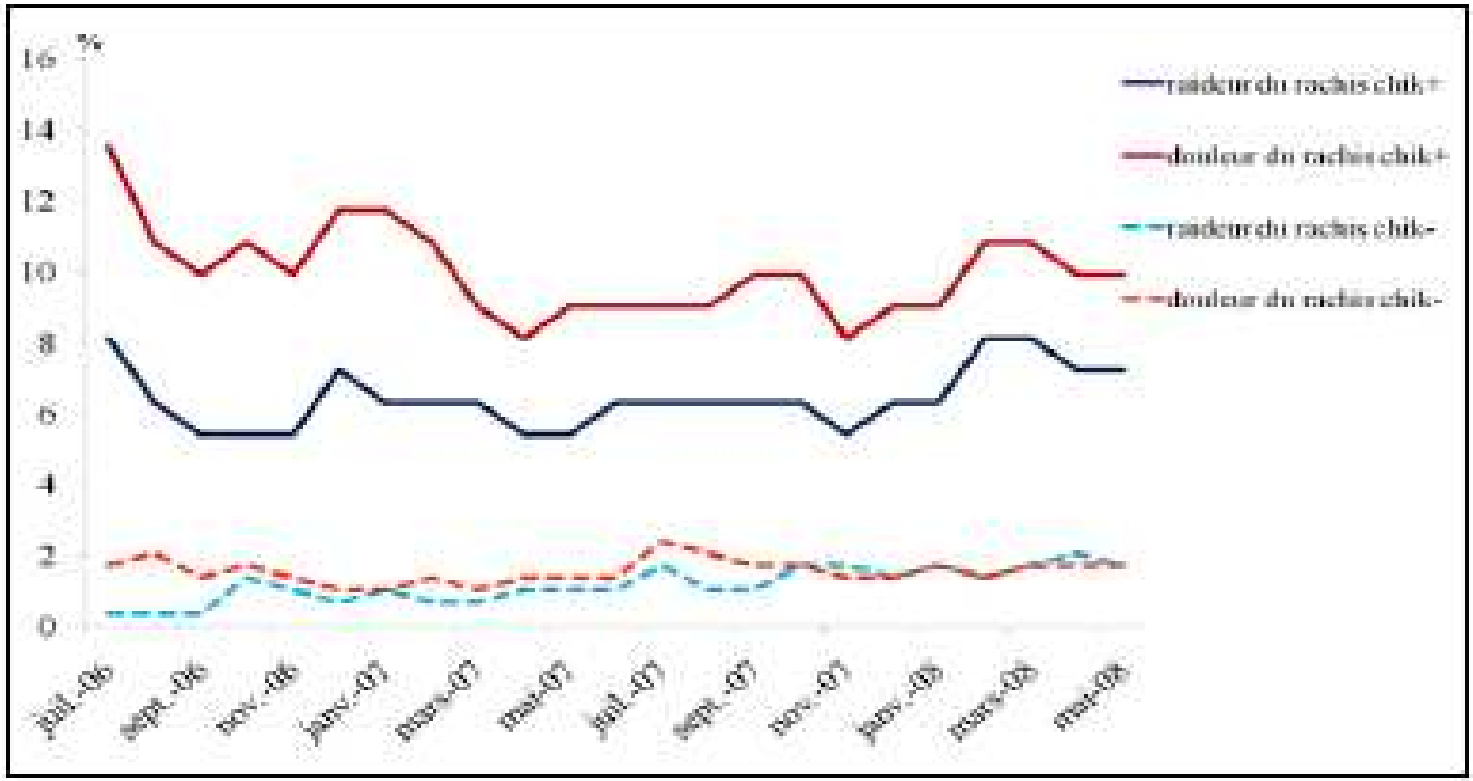
→297 CHIK-
→101 CHIK+

***47% guéris,***
***37% non guéris,***
***16% indéterminés***




*Vivier E et coll., poster D-19 JNI 2010*

# Symptômes rachidiens chroniques




*Vivier E et coll., poster D-19 JNI 2010*

# Laboratory diagnosis of CHIKV

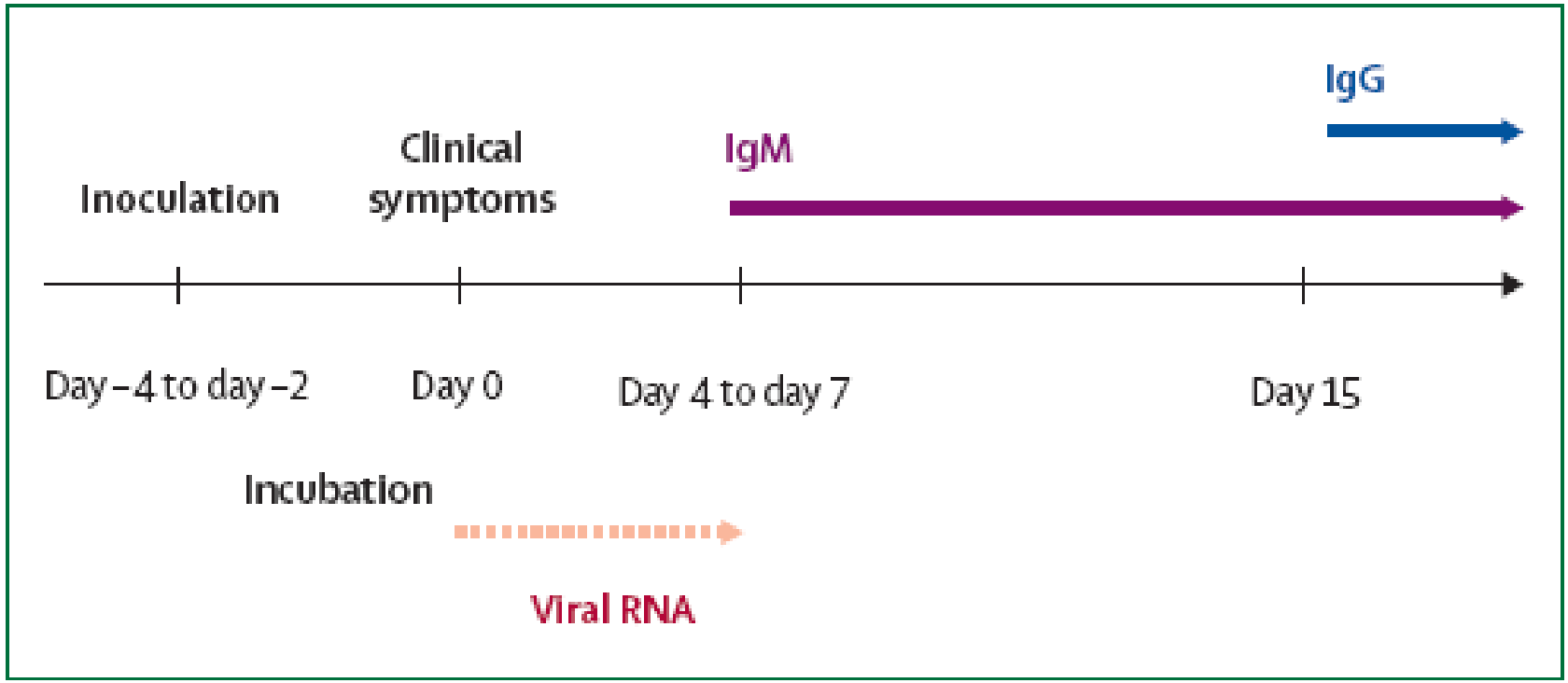


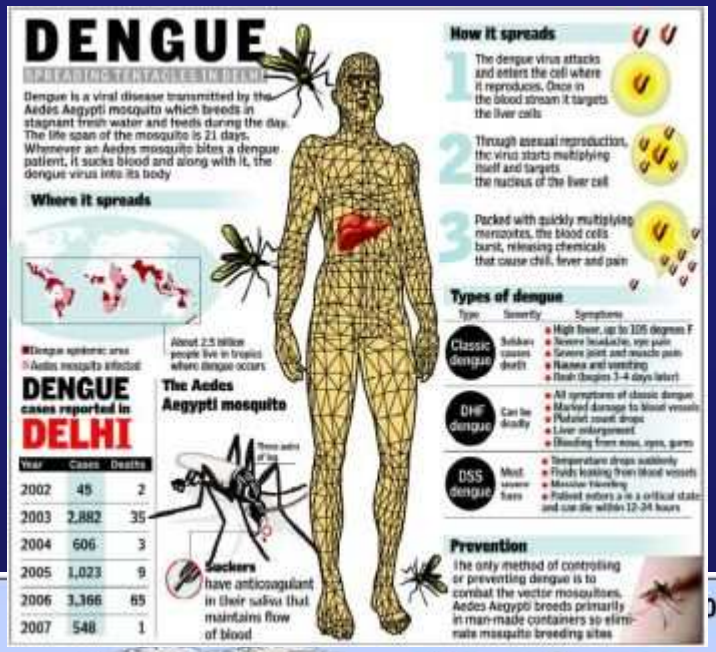

*Figure 6:* Biological diagnosis of chikungunya

Pialoux G, 2007; Lancet Infect Dis 7:319

# CHIV: terapia

- Sintomatica: FANS (non ASA), paracetamolo
- Evitare i salicilati, per la tendenza emorragica
- Evitare possibilmente antibiotici e corticosteroidi
- Sia la febbre sia la sintomatologia algica sono però poco sensibili FANS e paracetamolo


HOJE É DIA
DE COMBATER A DENGUE
CUMPRA SEU DEVER. A DENGUE PODE MATAR.
Encha de areia até a borda os pratinhos dos vasos de planta.
Guarde garrafas sempre de cabeça para baixo.
Jogue no lixo todo objeto que possa acumular água.
Mantenha bem tampad tonéis e barris d'água.
Lave semanalmente por dentro com escova e sabão os tanques utilizados para armazenar água.
Mantenha a caixa d'água sempre fechada com tampa adequada.
Entregue seus pneus velhos ao serviço de limpeza urbana ou guarde-os sem água em local coberto e abrigados da chuva.
Remova folhas, galhos e tud possa impedir a água d correr pelas calhas.
Não deixe a água da chuva acumulada sobre a laje.
Evite água parada.
Proteja sua família.
SUS
Secretaria Estadual de Saúde
Secretaria Municipal de Saúde
Disque Dengue 156
CCZ 3314.5000
Coloque o lixo em sacos plás mantenha a lixeira bem fec


DENGUE
Dengue is a viral disease transmitted by the Aedes Aegypti mosquito which breeds in stagnant fresh water and feeds during the day. The life span of the mosquito is 21 days. Whenever an Aedes mosquito bites a dengue patient, it sucks blood and along with it, the dengue virus into its body
Where it spreads
About 2.5 billion people live in tropics where dengue occurs
DENGUE cases reported in DELHI
Year Cases Deaths
2002 45 2
2003 2,882 35
2004 606 3
2005 1,023 9
2006 3,366 65
2007 548 1
The Aedes Aegypti mosquito
Suckers have anticoagulant in their saliva that maintains flow of blood
How it spreads
1 The dengue virus attacks and enters the cell where it reproduces. Once in the blood stream it targets the liver cells
2 Through asexual reproduction, the virus starts multiplying itself and targets the nucleus of the liver cell
3 Packed with quickly multiplying merozoites, the blood cells burst, releasing chemicals that cause chill, fever and pain
Types of dengue
Classic dengue
DHF dengue
DSS dengue
Prevention
The only method of controlling or preventing dengue is to combat the vector mosquitoes. Aedes Aegypti breeds primarily in man-made containers so eliminate mosquito breeding sites


Jan. isoth. 10.C
Jul. isoth. 10.C
Hawaii
Galapagos Islands
Easter Island
Sudan
Nepal
Bhutan
Hong Kong SAR
Macao SAR
Madagascar - La Reunion
Geographic extension of dengue, 2000-2006
Risk of dengue transmission
World Health Organization
Data Source: WHO
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization

# Dengue

# Eziologia

- Flavivirus  (RNA a singola elica)
- 4 sierotipi:  D-1, D-2, D-3, D-4.

# Sierotipi della dengue

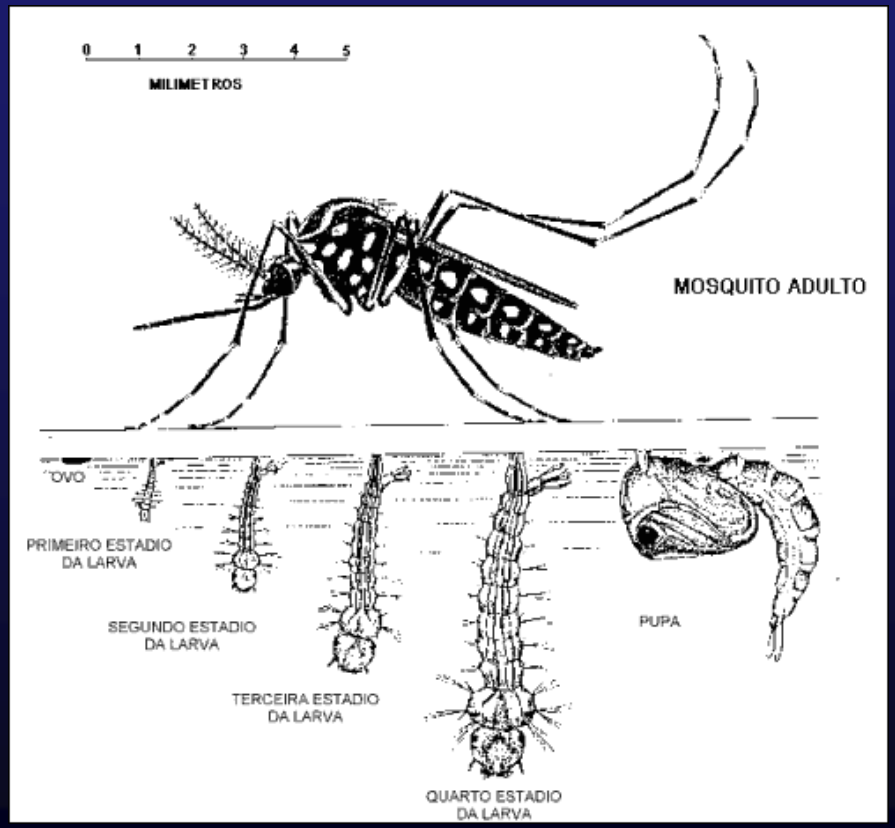
- Ogni sierotipo determina immunità specifica permanente e cross-immunità di breve durata.
- Tutti i sierotipi possono determinare manifestazioni cliniche gravi e fatali.
- All'interno di un sierotipo, alcuni sottotipi sono associati a quadri clinici più o meno severi.
  - Quadri clinici severi (DHF, DSS) associati a sottotipi di GT 2 e GT 3 nel Sud Est asiatico
  - Quadri clinici non gravi nelle sovrainfezioni in Perù

# Vettore e reservoir

- **Vettori:** *Aedes aegypti*, *Aedes albopictus*

- **Reservoir**: primati selvatici (probabile rilevanza limitata) e uomo (+++ in outbreaks)

# Vettore: *Aedes aegypti*




## Ciclo biologico

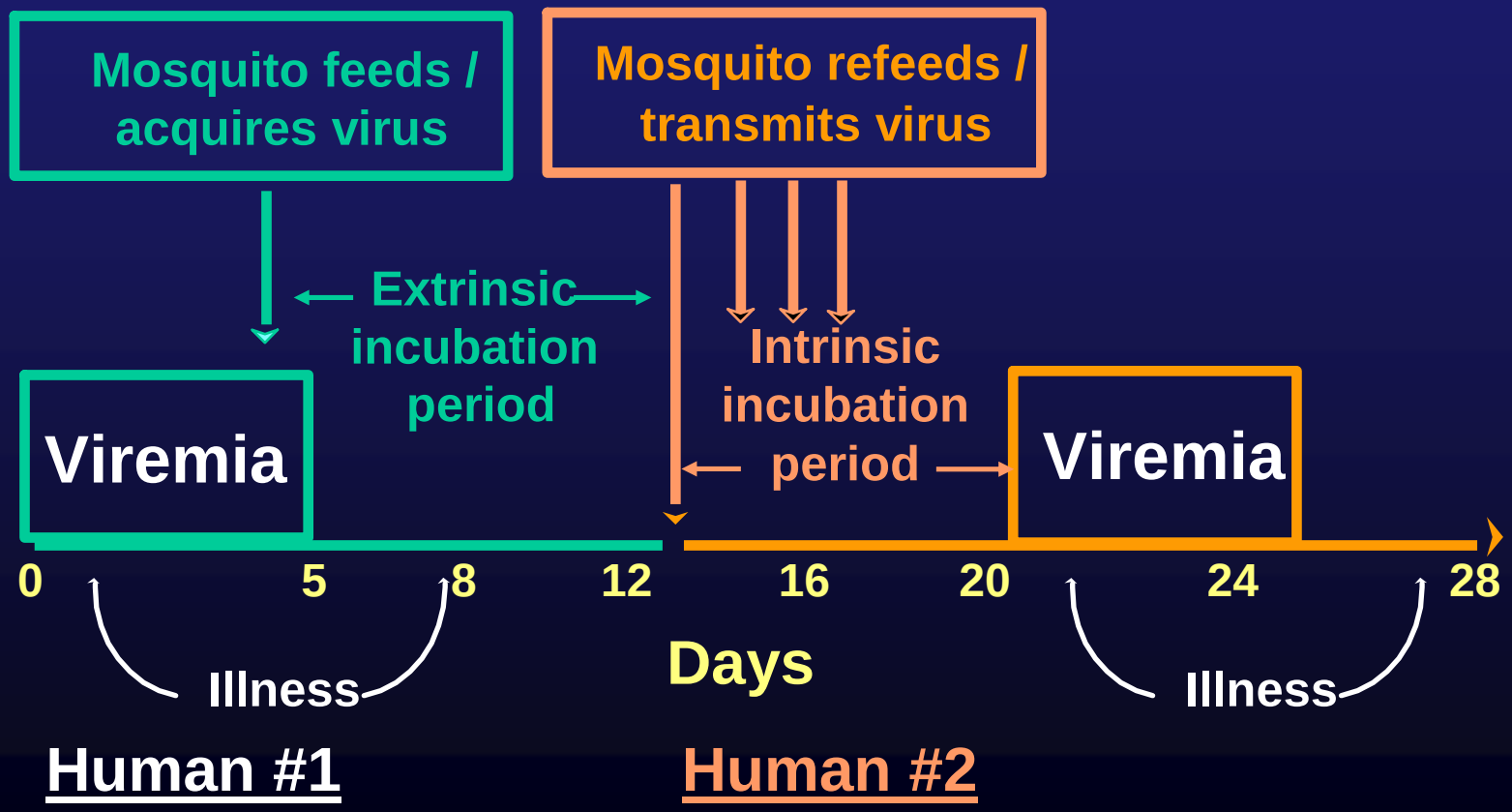
Uova

Larva

Pupa

Adulto

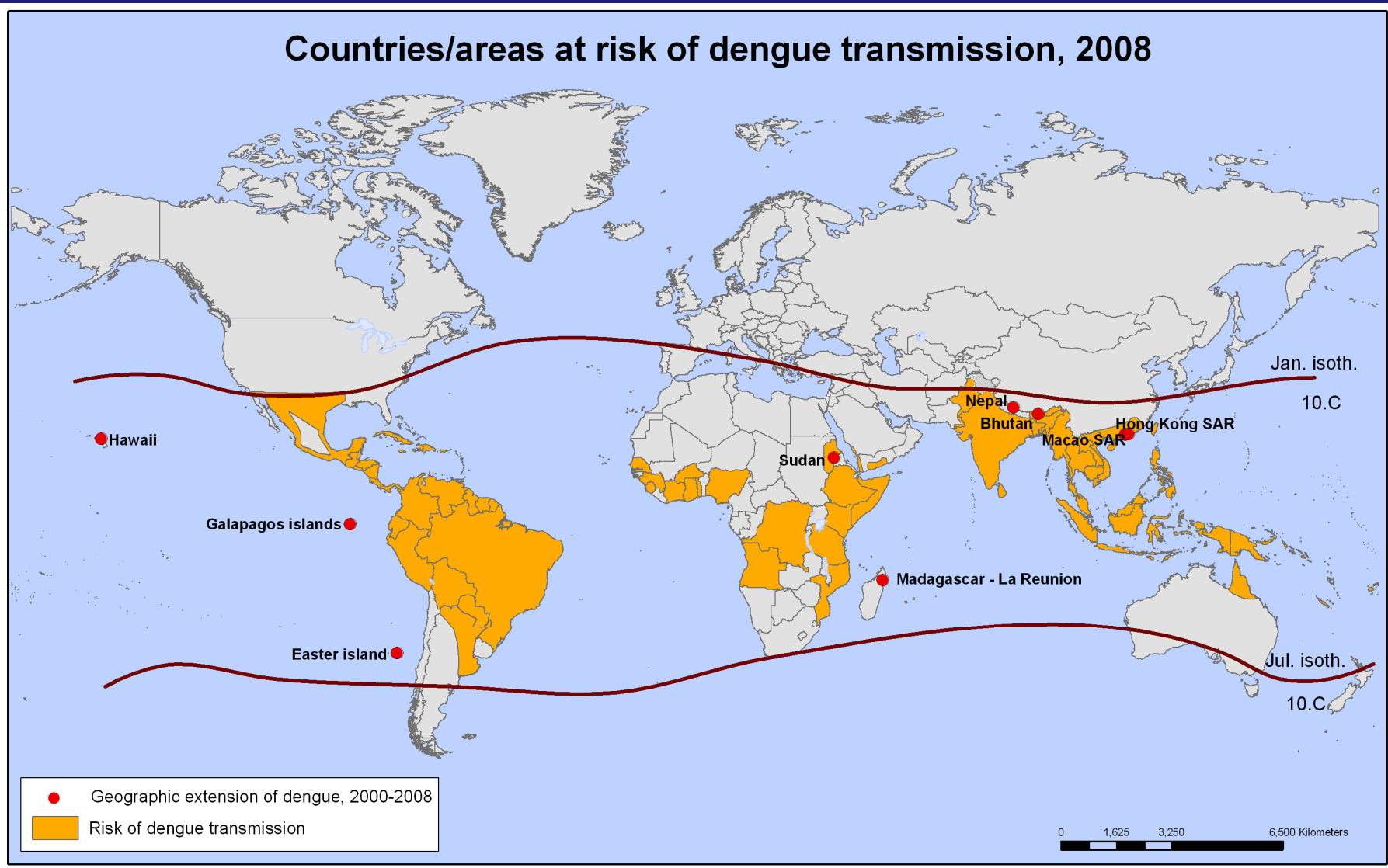
# Transmission of dengue virus by *Aedes aegypti*




# Epidemiology of dengue

- **The most common arboviral disease :**
  - 2.5 billion people living in endemic areas;
  - 100 million annual cases of DF
  - 250,000 annual cases od DHF
  - 25,000 deaths per year.
- **Dengue cases reported in > 100 countries.**

# Countries/areas at risk of dengue transmission, 2008

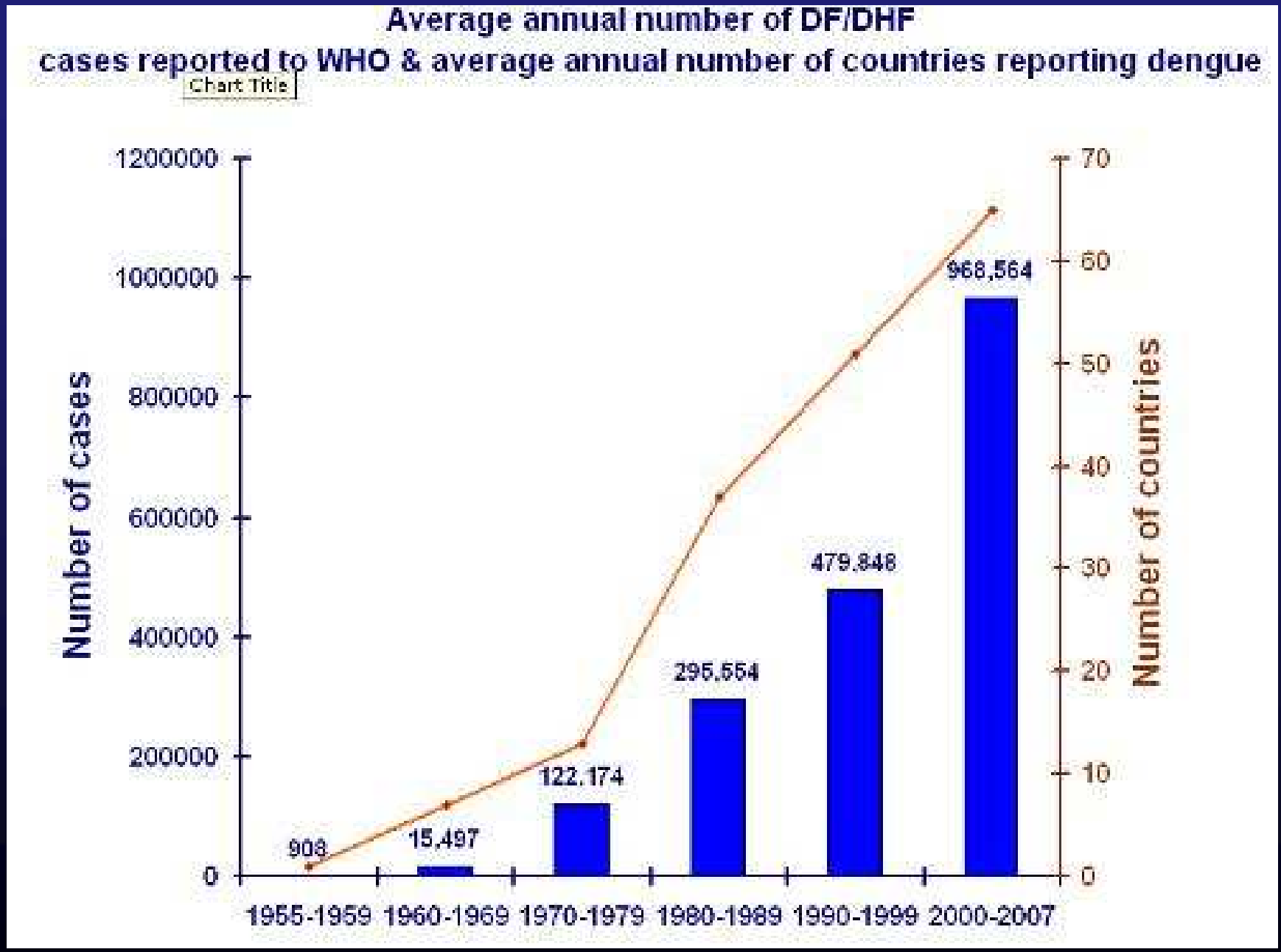



World Health Organization

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 the World Health Organization 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 lines on maps represent approximate border lines for which there may not yet be full agreement.



Data Source: DengueNet, World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)

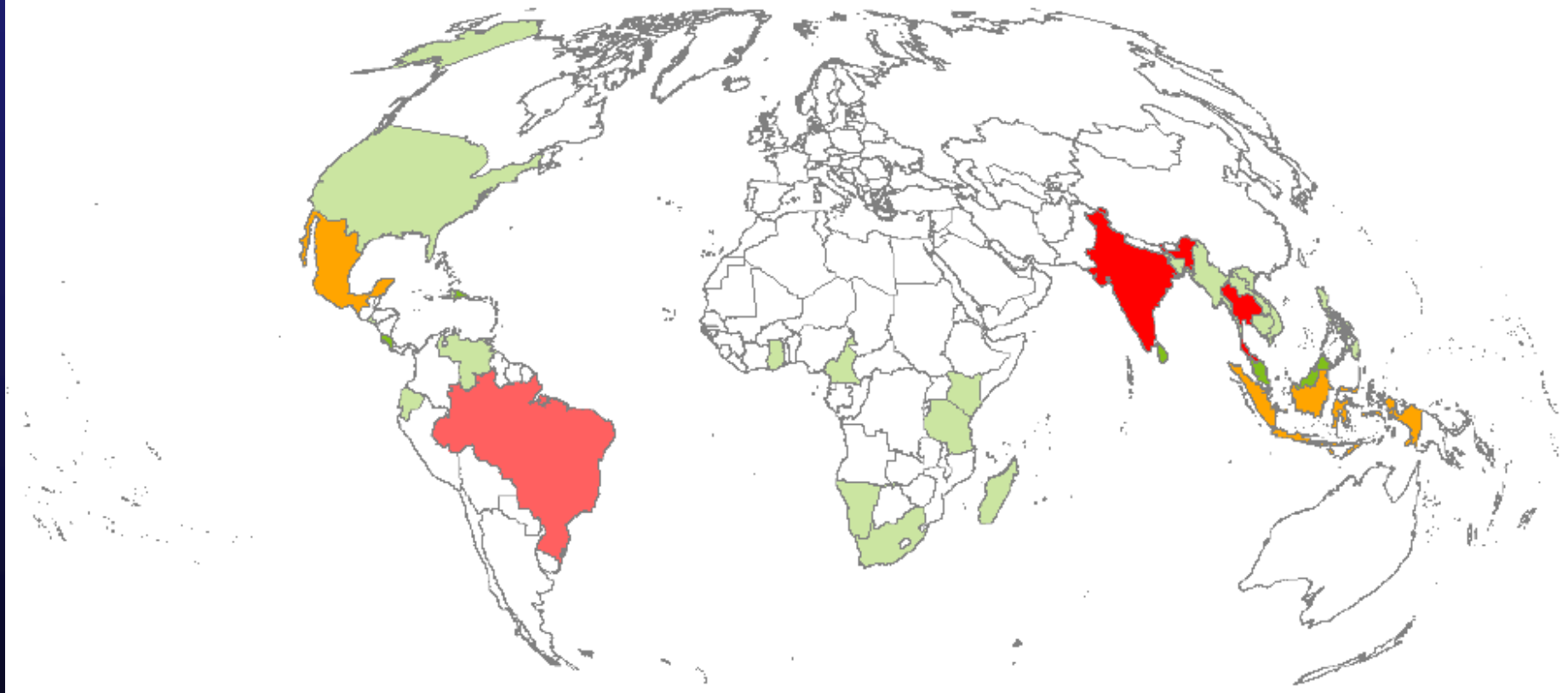

Average annual number of DF/DHF
cases reported to WHO & average annual number of countries reporting dengue
Chart Title
Number of cases
Number of countries
1200000
1000000
800000
600000
400000
200000
0
70
60
50
40
30
20
10
0
908
15,497
122,174
295,554
479,848
968,564
1955-1959
1960-1969
1970-1979
1980-1989
1990-1999
2000-2007

# Epidemiology of dengue

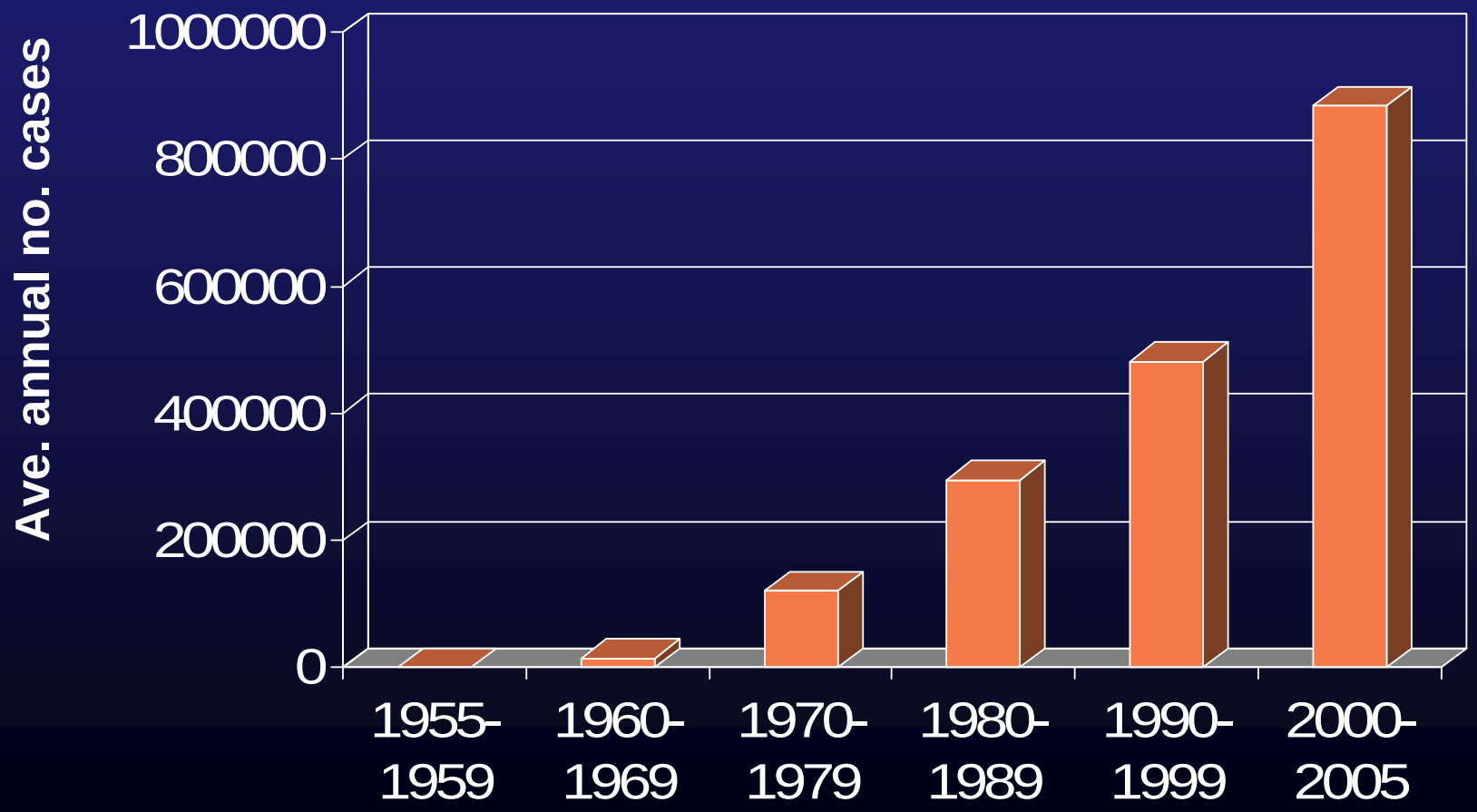
- Most cases of DHF are reported from Asia.
- Since 1980s dramatic expansion of epidemic DF and DHF from Southeast Asia to South Pacific Islands, Caribbean and Latin America.
- Latin America showed the most dramatic increas in dengue activitiy (30 countris with > 1 million cases of DF in 2001)
- Latin America has changed from nonendemic (no serotypes present) to hypoendemic (one serotype present) or hyperendemic (multiple serotypes present).

Stephenson JR, Trans R Soc Trop Med Hyg 2005;

# Dengue in TropNet 2006
# Place of infection (n=105)

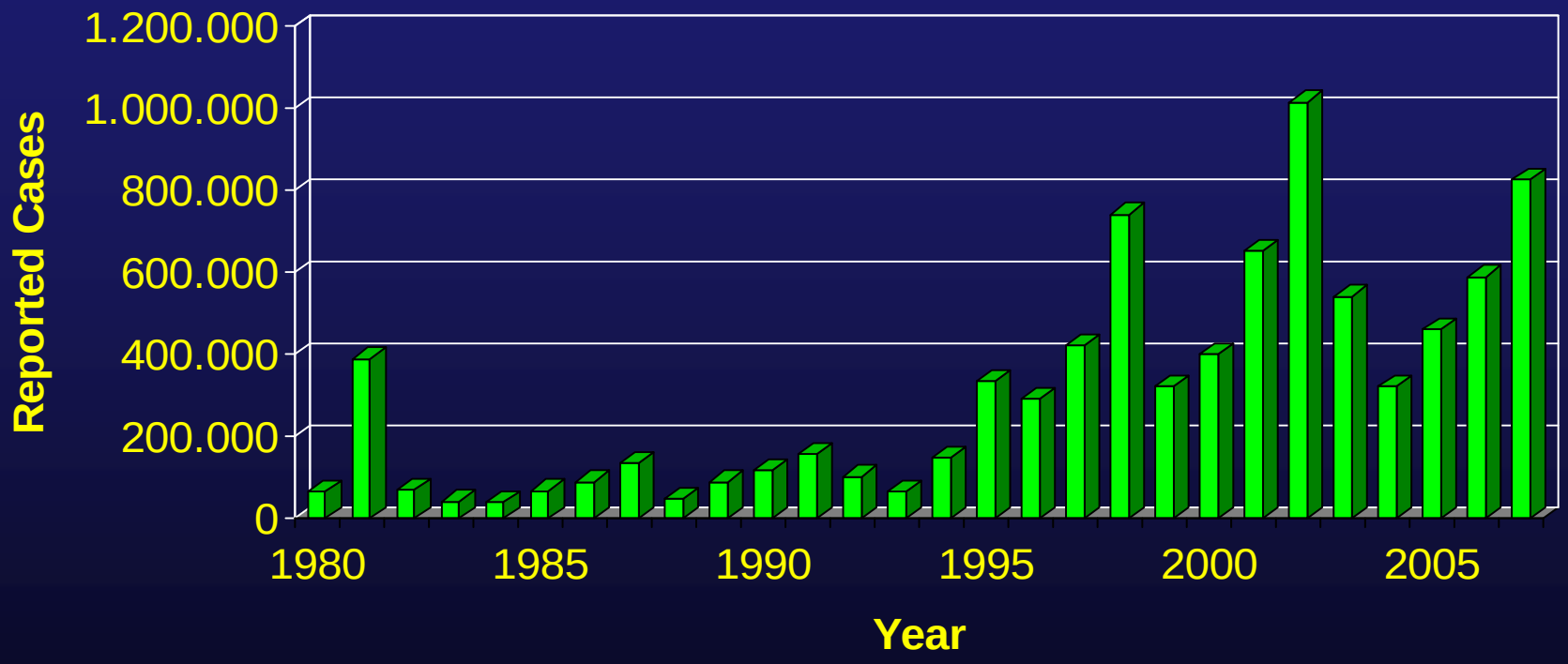


# Dengue/DHF cases reported to the WHO 1955-2005*




* Source: WHO, Sep. 2006

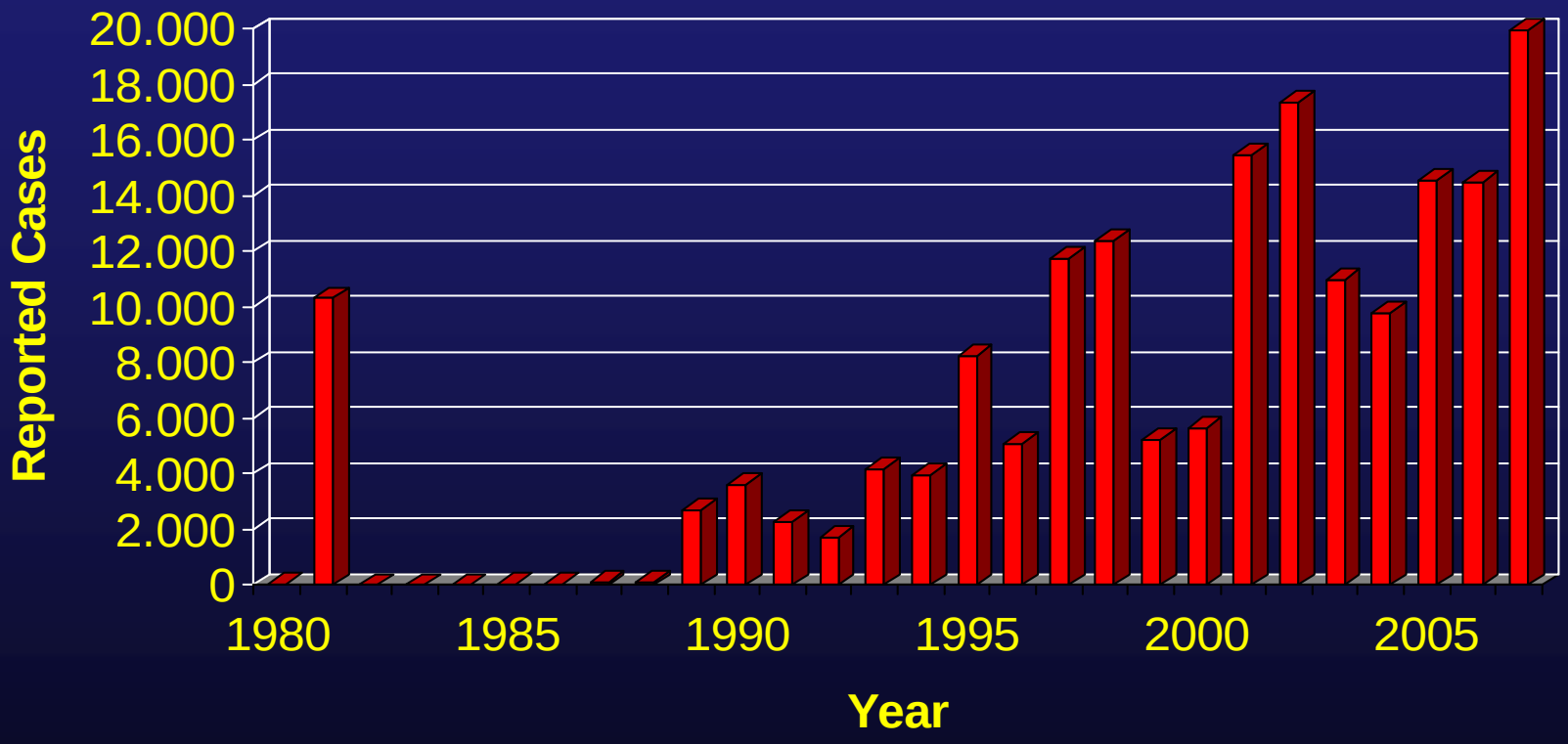
# Reported Cases of Dengue in the Americas, 1980 – 2007 *




* Data: PAHO (Nov. 30, 2007)

CDC
Centers for Disease Control and Prevention

# Reported Cases of DHF in the Americas, 1980 – 2007 *




* Data: PAHO (Nov. 30, 2007)

CDC
Centers for Disease Control and Prevention

# Dengue classica in America 1960 - 2007

**Nicaragua**
1985 DEN 1
1990 DEN 2 e 4

**Caribi e Venezuela**
1963 –1964 DEN 3
1968 – 1969 DEN 2 e 3
1980 DEN 1

**Jamaica**
1977 DEN 1

**Colombia** 1970 DEN 2 e 3

**Brasile**
1982 DEN 3

1987 Río de Janeiro

**Paesi andini**
1995 DEN 3
1998 1999 2000 DEN 4

**Paraguay**
2001 DEN 2
2002 DEN 3

**PAESI SENZA DENGUE AUTOCTONA AL 2007**
CILE CONTINENTALE

# Evoluzione della DHF

# Dengue among travellers

- DF diagnosed among 2-16% of travellers with fever
- 3.4 / 1000 rate of self-reported DF among Israeli travellers to Thailand
- 1% DF serological incidence among travellers after 1 month of stay

Wilder-Smith A, N Engl J Med 2005; 353: 924

**Rischio di acquisire una patologia di importazione in un mese di soggiorno ai tropici senza profilassi**

| | |
|---|---|
| • Malaria (AFR occ) | 3,5% |
| • Dengue & Influenza | 3% |
| • Malaria (AFR centrale) | 0,2% |
| • Febbre tifoide | 1/100.000 |
| • Encefalite giapponese | 1/1.000.000 |
| • Meningite batterica | > 1/1.000.000 |

Steffen, JTV 2008

# Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region

Table 3. **Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.***

| Syndrome and Cause | All Regions | Caribbean | Central America | South America | Sub-Saharan Africa | South Central Asia | Southeast Asia | Other or Multiple Regions† |
|---|---|---|---|---|---|---|---|---|
| | *number of cases per 1000 patients with syndrome* | | | | | | | |
| **Systemic febrile illness (n=3907)** | | | | | | | | |
| Specific pathogen or cause reported‡ | 594 | 459 | 527 | 446 | 718 | 522 | 547 | 454 |
| Malaria‡ | 352 | 65 | 133 | 133 | 622 | 139 | 130 | 234 |
| Dengue‡ | 104 | 238 | 123 | 138 | 7 | 142 | 315 | 35 |
| Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡ | 32 | 70 | 69 | 79 | 10 | 17 | 32 | 63 |
| Rickettsial infection‡ | 31 | 0 | 0 | 0 | 56 | 10 | 16 | 24 |
| *Salmonella typhi* or *S. paratyphi* infection‡ | 29 | 22 | 25 | 17 | 7 | 141 | 26 | 24 |
| No specific cause reported‡ | 406 | 541 | 473 | 554 | 282 | 478 | 453 | 546 |
| **Acute diarrhea (n=3859)** | | | | | | | | |
| Parasitic diarrhea‡ | 354 | 283 | 403 | 368 | 353 | 453 | 262 | 323 |
| Giardiasis‡ | 173 | 132 | 136 | 158 | 177 | 286 | 118 | 132 |
| Amebiasis‡ | 120 | 105 | 155 | 142 | 138 | 103 | 74 | 135 |
| Presumptive parasitic cause‡ | 35 | 9 | 45 | 52 | 33 | 55 | 33 | 13 |
| Bacterial diarrhea‡ | 268 | 260 | 190 | 253 | 250 | 294 | 369 | 227 |
| Campylobacter infection‡ | 85 | 46 | 32 | 90 | 73 | 87 | 180 | 57 |
| Shigella infection | 41 | 37 | 26 | 41 | 46 | 61 | 26 | 34 |
| Nontyphoidal salmonella infection‡ | 27 | 27 | 13 | 14 | 29 | 12 | 56 | 30 |
| Presumptive bacterial cause | 110 | 132 | 94 | 106 | 99 | 136 | 116 | 95 |
| Viral diarrhea‡§ | 9 | 23 | 32 | 5 | 7 | 4 | 5 | 7 |
| Unspecified acute diarrhea‡ | 385 | 457 | 377 | 376 | 397 | 289 | 393 | 451 |

Freedman, D. O. et al. N Engl J Med 2006;354:119-130

# Dengue: sindromi cliniche

- Febbre indifferenziata
- Dengue classica
- Dengue con sindrome emorragica (DHS)
- Dengue con shock syndrome (DSS)

# Dengue classica

- **Incubazione** di 7 - 10 giorni
- **Febbre**:  insorgenza improvvisa, durata 5-7 gg.
- **Cefalea**: intensa, retrorbitale
- **Mialgie ed atralgie**: intensi (febbre “spacca ossa”)
- **Esantema:** 50% dei casi; compare alla defervescenza della febbre; durata 2-4 gg; apetto maculare o maculo-papulare, confluente, ma con risparmio di isole di cute; pruriginoso (a volte) **.**
- **Altri segni/sintomi**: flushing faccia (prime 24-48 ore), linfoadenopatia, congiuntivite, iperemia faringea, sintomi gastrointestinali e respiratori modesti

# Dengue classica

- **Manifestazioni emorragiche:**
  - petecchie, ecchimosi o porpora;
  - tourniquet test +;
  - sanguinamento da mucose;
  - ematemesi o melena
- **Complicanze rare:**
  - Miocardite
  - Epatite
  - Encefalite e neuropatie
- **Alterazioni di laboratorio**
  - Piastrinopenia
  - Leucopenia con linfocitopenia
  - Elevazione transaminasi e LDH
  - iponatremia

# Dengue emorragica
## Definizione (WHO)

Diagnosi fatta sulla presenza della seguente triade di segni/sintomi:

1. Manifestazioni emorragiche (almeno uno tra):
   - tourniquet test +;
   - petecchie, ecchimosi o porpora;
   - anguinamento da mucose;
   - ematemesi o melena
2. Piastrinopenia (<=100.000)
3. Evidenza di perdita plasmatica (almeno uno tra:
   - Ht >=20% sulla “media”;
   - Ht >=20% in seguito a ripristino vol. plasmatico;
   - versamento pleurico e/o ascite e/o ipoproteinemia

# Dengue con shock syndrome

DHF più:

- Polso rapido e debole
- Ipotensione per l’età
- Cute fredda e umida, irrequietezza

- Mortalita > 40%

# Patogenesi (DHF/DSS)

Incremento dell'uptake virale in cellule mononucleate

↓

Aumento della permeabilità vascolare

↓

perdita di plasma

Deficit quali-quantitativo delle piastrine

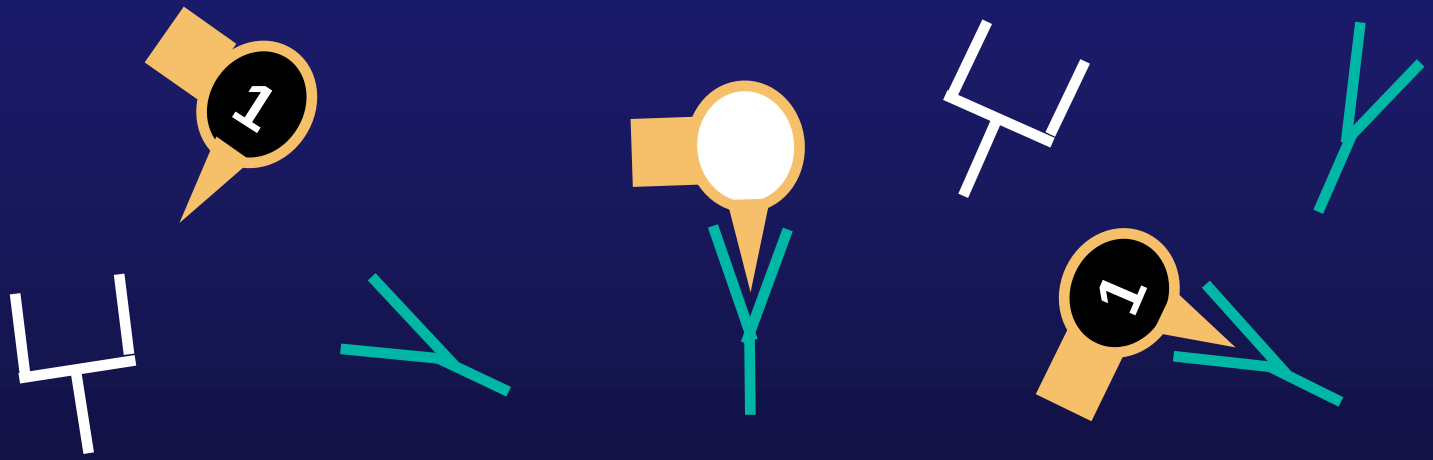
↓

emorragie

# Hypothesis on Pathogenesis of DHF (Part 1)

- Persons who have experienced a dengue infection develop serum antibodies that can neutralize the dengue virus of that same (homologous) serotype

# Homologous Antibodies Form Non-infectious Complexes

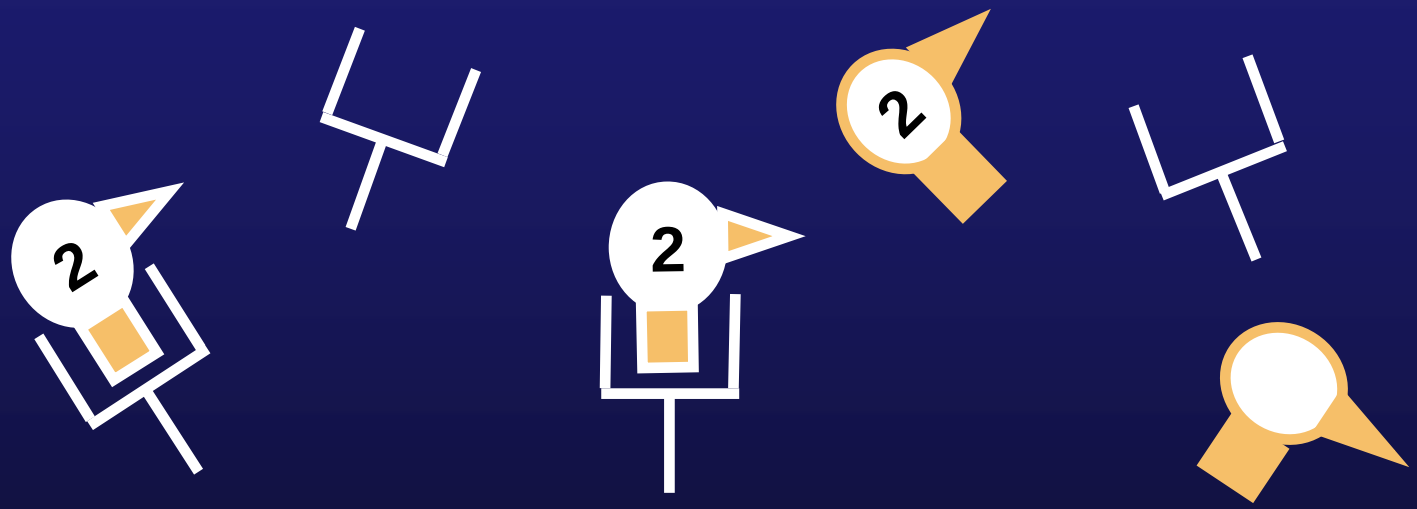



- Dengue 1 virus
- Neutralizing antibody to Dengue 1 virus
- Non-neutralizing antibody
- Complex formed by neutralizing antibody and virus

# Hypothesis on Pathogenesis of DHF (Part 2)

- In a subsequent infection, the pre-existing heterologous antibodies form complexes with the new infecting virus serotype, but do not neutralize the new virus

# Heterologous Antibodies Form Infectious Complexes




Dengue 2 virus

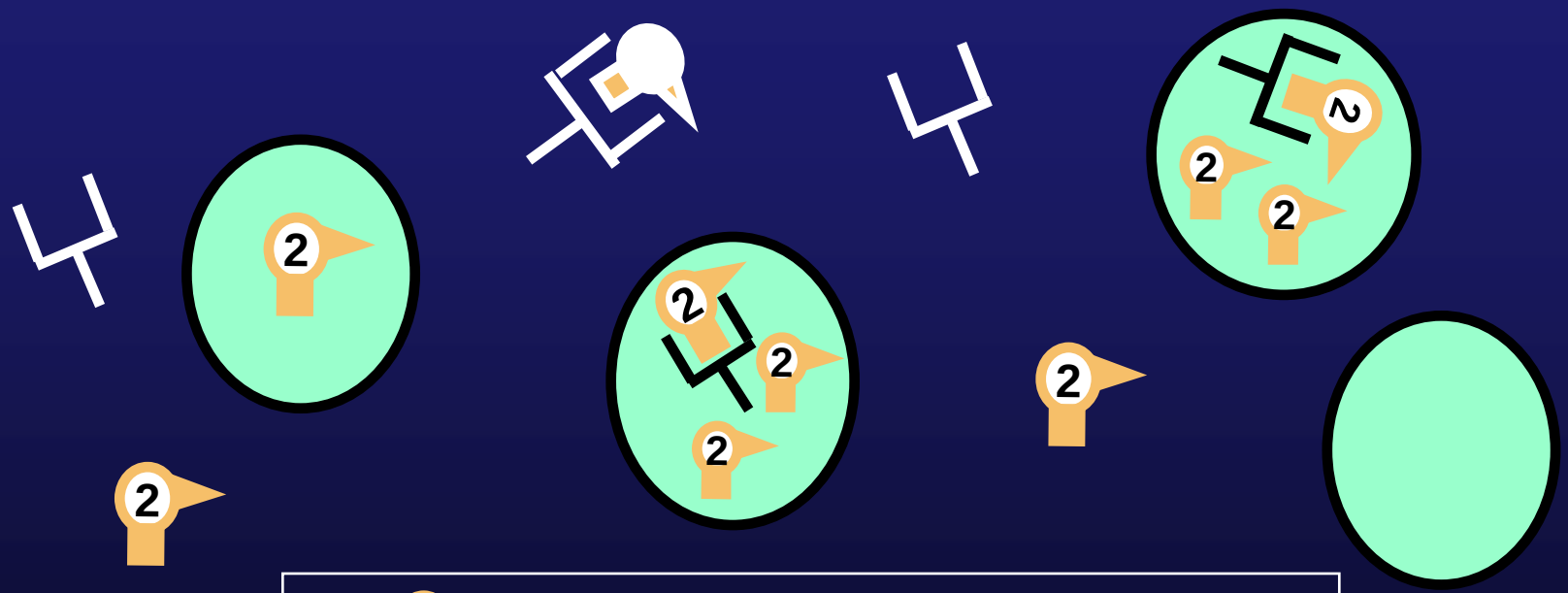
Non-neutralizing antibody to Dengue 1 virus

Complex formed by non-neutralizing antibody and virus

# Hypothesis on Pathogenesis of DHF (Part 3)

- Antibody-dependent enhancement is the process in which certain strains of dengue virus, complexed with non-neutralizing antibodies, can enter a greater proportion of cells of the mononuclear lineage, thus increasing virus production

# Heterologous Complexes Enter More Monocytes, Where Virus Replicates



# Hypothesis on Pathogenesis of DHF (Part 4)

- Infected monocytes release vasoactive mediators, resulting in increased vascular permeability and hemorrhagic manifestations that characterize DHF and DSS

**Table 2. Laboratory Diagnosis of Dengue.***

| Result of Diagnostic Test | Limitations |
|---|---|
| **Probable diagnosis** | |
| Positive IgM antibody test (IgM capture ELISA) | Negative early in disease; positive only 4–5 days after onset of symptoms |
| Single serum sample: titer ≥1280 with hemagglutination inhibition test, comparable IgG titer with enzyme-linked immunosorbent assay | Cross-reactivity to other flaviviruses (including previous vaccinations against Japanese encephalitis and yellow fever) |
| **Confirmed diagnosis** | |
| Isolation of dengue virus from serum or from samples obtained at autopsy | Sensitivity <50% and only early in disease; not commonly available |
| Increase by a factor of ≥4 in serum IgG and IgM (by hemagglutination inhibition test) specific for dengue virus | Requires convalescent serum; cross-reactivity to other flaviviruses (including previous vaccinations against Japanese encephalitis and yellow fever) |
| Detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or ELISA | Sensitivity <50% percent and only early in disease; test not commonly available |
| Detection of genomic sequences of dengue virus by reverse-transcription polymerase chain reaction | Sensitivity >90% in first few days of illness, with rapid decline to usually <10% 7 days after onset of symptoms; test not commonly available |