



Les maladies vectorielles: le regard de l'entomologiste

Anna-Bella FAILLOUX

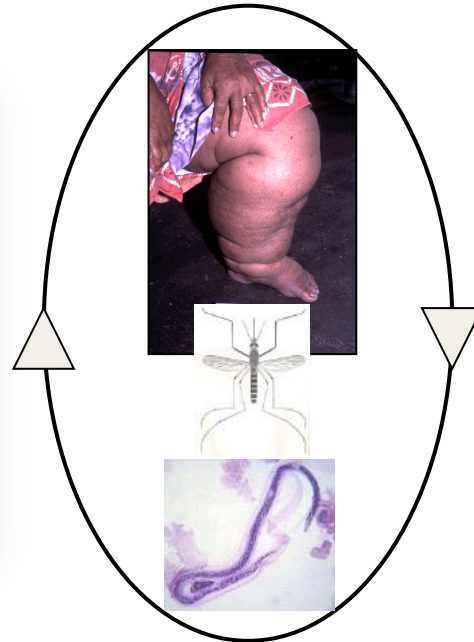
Arboviruses and Insect Vectors

Department of Virology



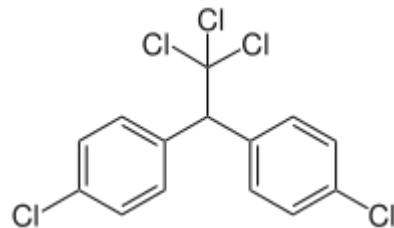
Medical entomology:

a discipline focused upon arthropods that impact human health



1877: Patrick Manson

Wuchereria bancrofti transmitted
by the mosquito *Culex pipiens*



1939: Paul Hermann Müller

DDT (Nobel Price 1948)

1877 **MANSON** : *Wuchereria bancrofti* in the mosquito *Cx. pipiens fatigans*

1881 **FINLAY** : *Ae. aegypti*, vector of yellow fever?

1897 **ROSS** : *Plasmodium* oocysts in *Anopheles* mosquitoes

1898 **SIMOND** : Experimental transmission of *Yersinia pestis* by fleas

1899 **BANCROFT** : Transmission *W. bancrofti* by *Culex*
GRASSI & coll : Transmission of malaria by *Anopheles*

1900 **REED & coll** : Transmission of yellow fever by *Ae. aegypti*










1903 **BRUCE & NAVARRO** : Transmission of *Trypanosoma* by *Glossina* flies

1909 **NICOLLE** : Transmission of typhus fever by lice
CHAGAS : Transmission of *Trypanosoma cruzi* by *Triatoma megista*.

1916 **CLELAND & coll** : Transmission of dengue virus by *Aedes aegypti*

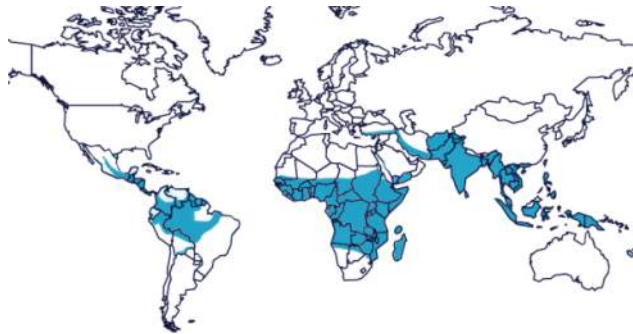
1926 **BLACKLOCK** : Transmission of *Onchocerca volvulus* by black flies

1939 **MULLER** : Insecticidal properties of DDT

Phylum	Class	Order	Family		Diseases	
Arthropods	Arachnids	Ixodida	Ixodidae (hard ticks)		Rickettsiosis, Tularemia, Lyme disease	
			Argasidae (soft ticks)		Borreliosis	
	Insects	Diptera	Siphonaptera	Pulicidae (fleas)		Plague, Rickettsiosis
			Phthiraptera	Pediculidae (lice)		Borreliosis, Bartonella, Rickettsioses
			Hemiptera	Reduviidae (bugs)		Chagas
				Simulidae (black flies)		Onchocerciasis (river blindness)
				Tabanidae (horse flies)		Loa Loa filariasis (eye worm)
				Psychodidae (sandflies)		Leishmaniasis
			Glossinidae (tsetse fly)		African trypanomiasis (sleeping sickness)	
			Culicidae (mosquito)			

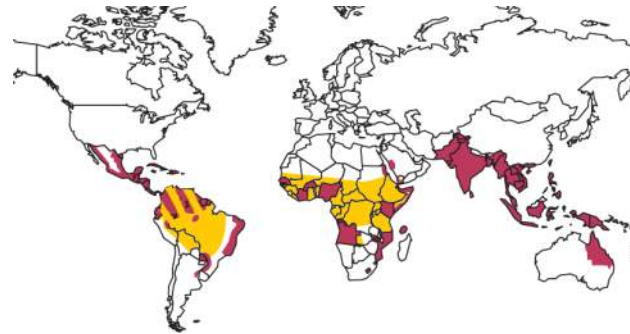
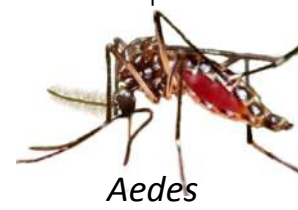
Fontaine & Almeras (2011)

Family: Culicidae



Malaria

300 millions cases/yr
1 million deaths/yr

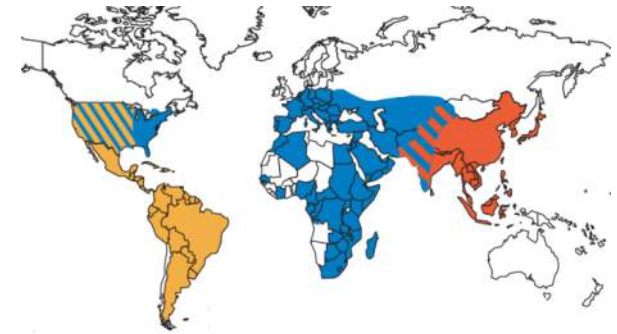


Dengue

50 millions cases/yr
20 000 deaths/yr

Yellow fever

200 000 cases/yr
30 000 deaths/yr



Japanese encephalitis

50 000 cases/yr
10 000 deaths/yr

St Louis encephalitis

50 000 cases/yr

West Nile

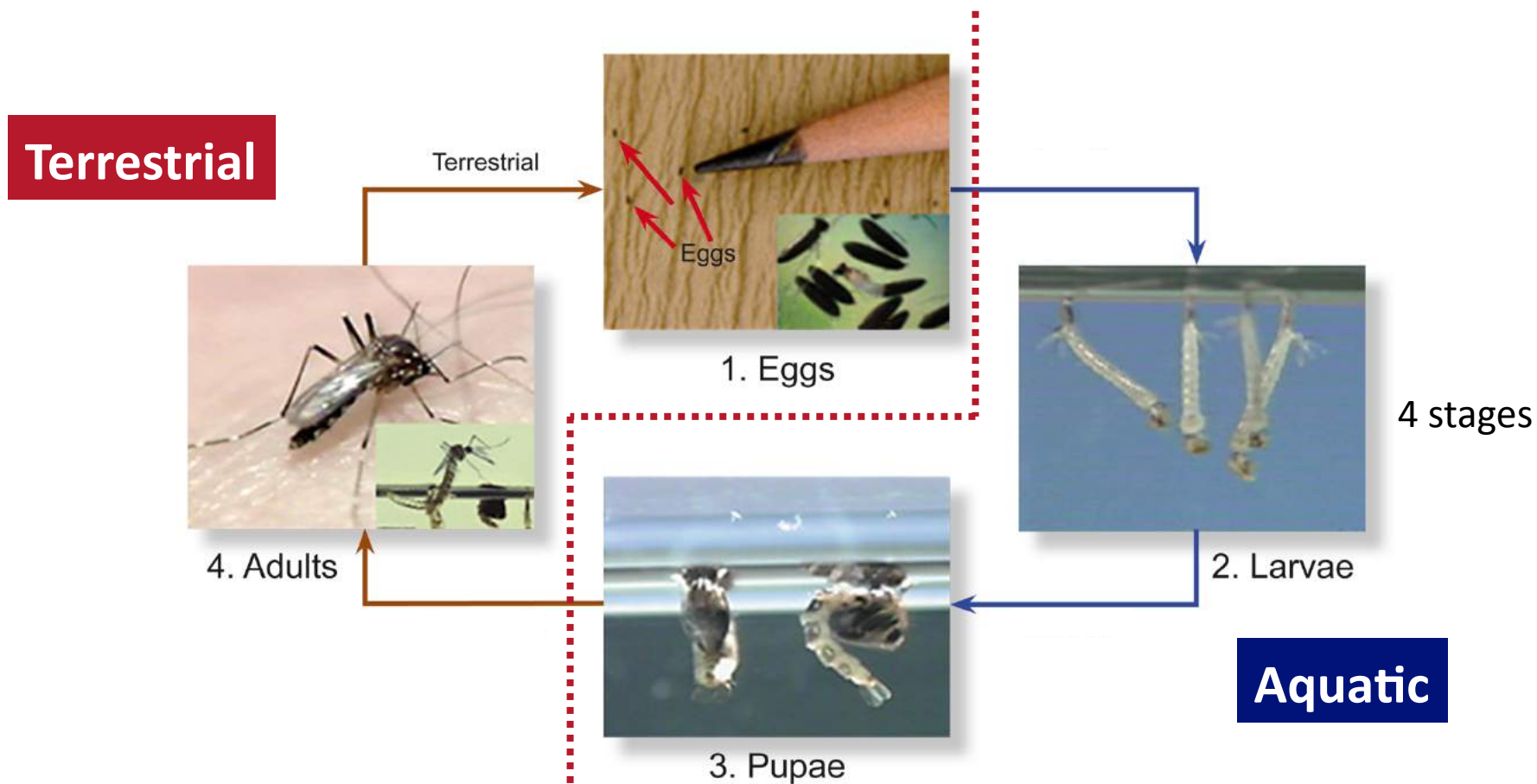
3 630 cases in 2007 in U.S.

Fontaine & Almeras (2011)

Chiffres de l'OMS et du CDC, cartes: Roberts, L., 2002, *Science*, photo: vectorbase.org

Developmental cycle

Mean duration: 8 - 12 days



From www.cdc.gov/dengue/entomologyEcology/m_lifecycle.html.

Urdanetta-Marquez and Failloux. *Infect Genet Evol* (2011)

Gonotrophic cycle



Unique mating

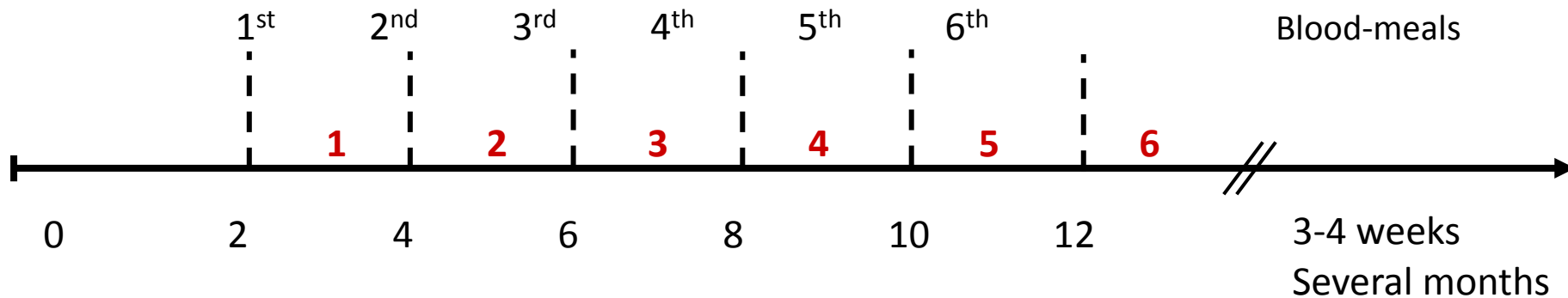


Blood feeding



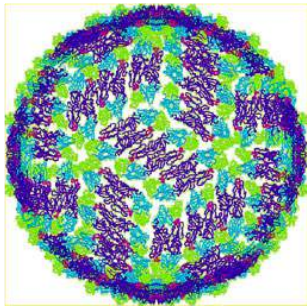
Eggs

Gonotrophic cycle



Arboviruses

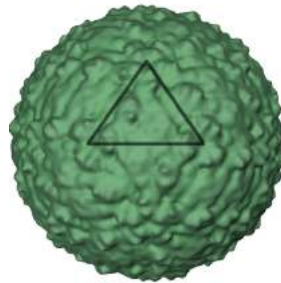
- ✓ 80 families of viruses
- ✓ 4000 virus species
- ✓ **500-600** arboviruses described
- ✓ 265 transmitted by mosquitoes
- ✓ 100 pathogen to humans
- ✓ Most are RNA virus
(except African swine plague, dsDNA, Asfarviridae)
- ✓ Enveloped virus



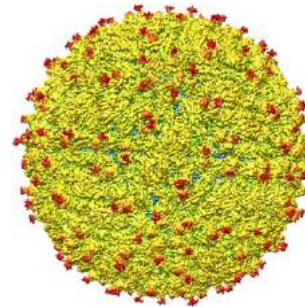
Dengue



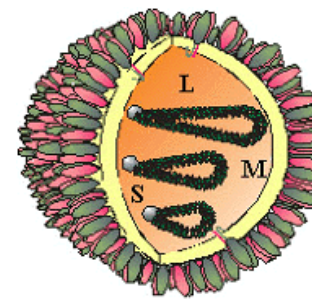
Fièvre jaune



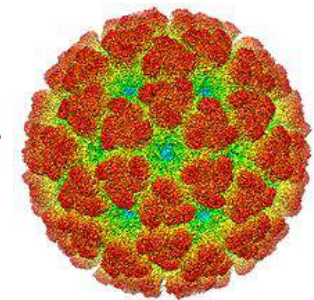
West-Nile



Zika

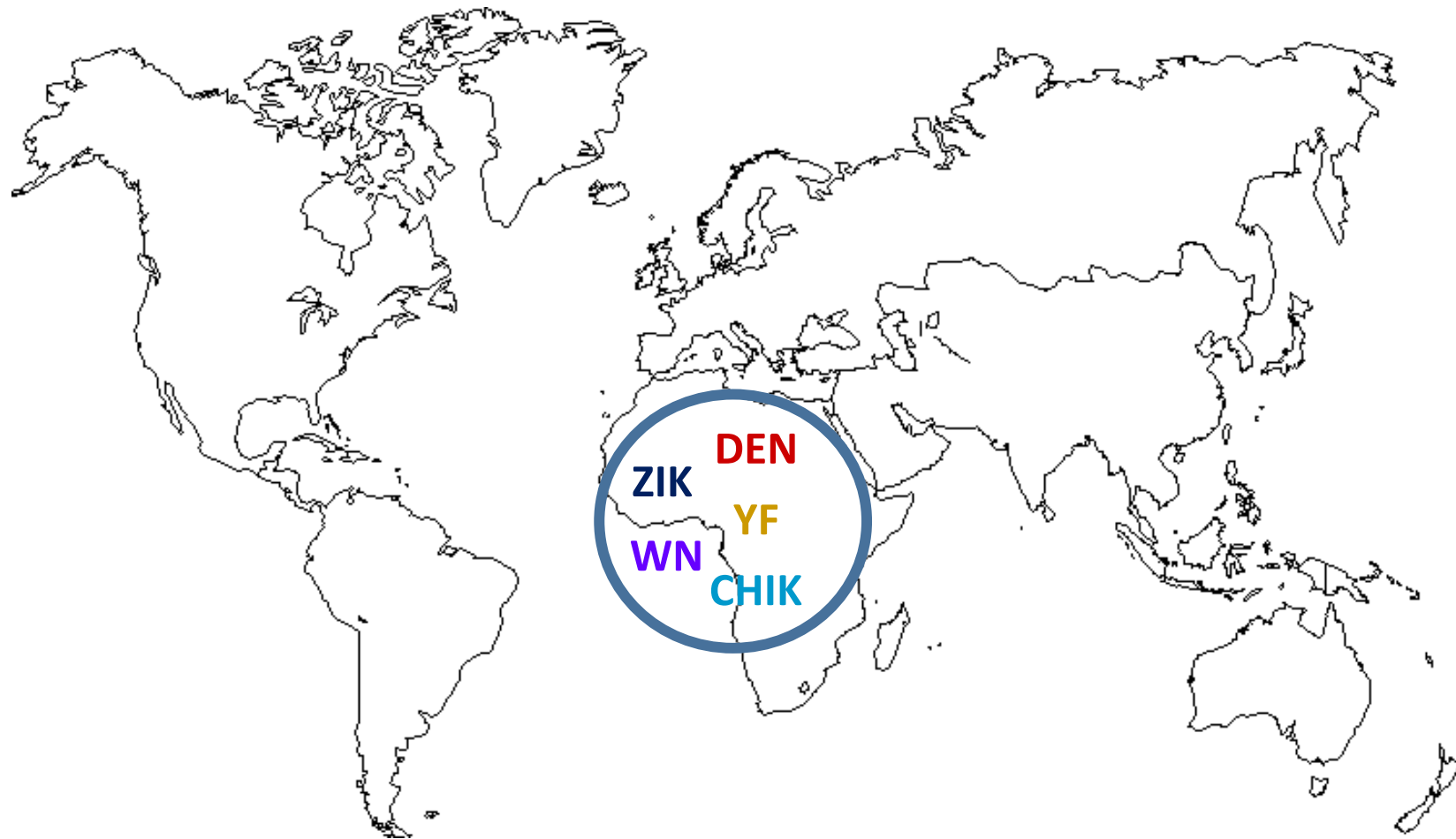


Fièvre de la Vallée du Rift



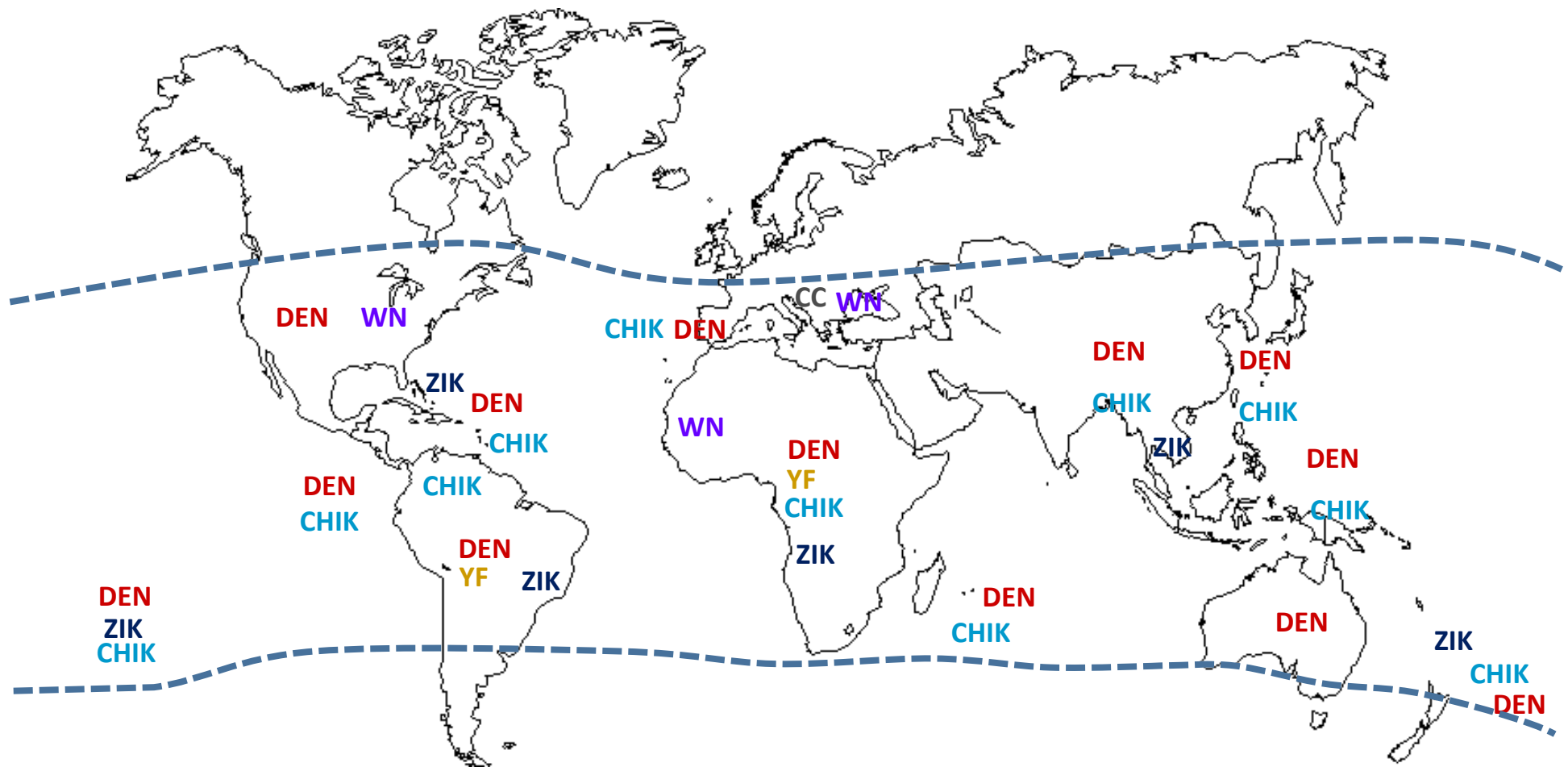
Chikungunya

First detections



Flavivirus / **DEN**: dengue; **YF**: Yellow fever; **WN**: West-Nile; **ZIK**: Zika
Alphavirus / **CHIK**: Chikungunya

Worldwide expansion



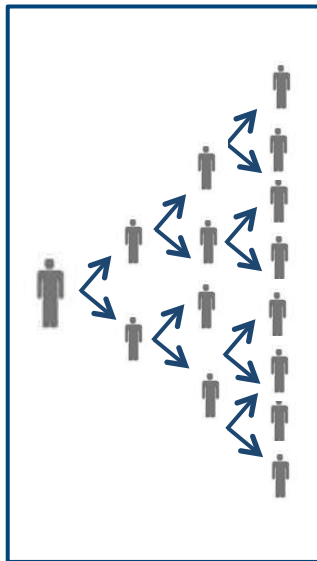
Flavivirus / **DEN**: dengue; **YF**: Yellow fever; **WN**: West-Nile; **ZIK**: Zika
Alphavirus / **CHIK**: Chikungunya

The basic reproductive number (R0)

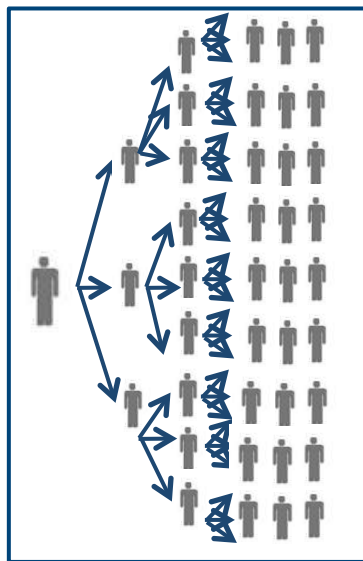


R0 < 1

$$R_0 = \frac{ma^2 \cdot p^n}{-\ln \cdot p} \cdot b \cdot c \cdot \frac{1}{r}$$



R0 = 2

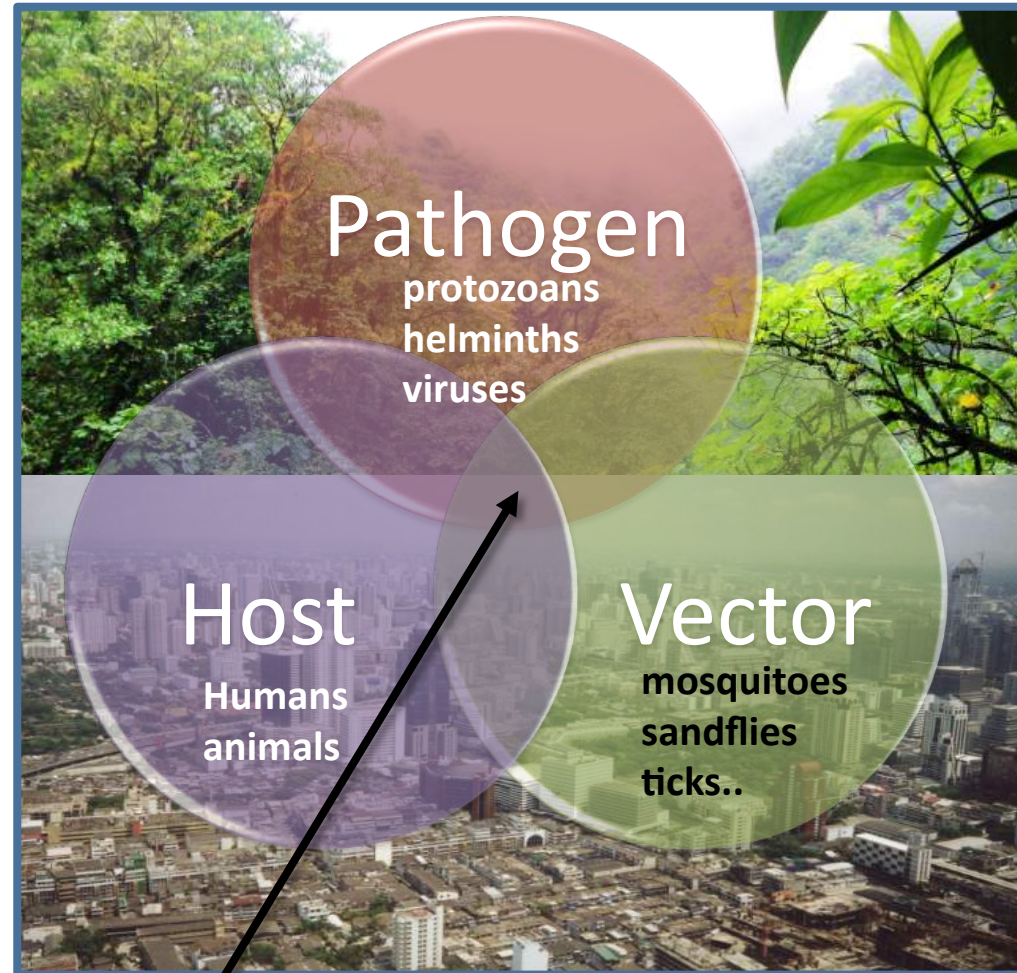
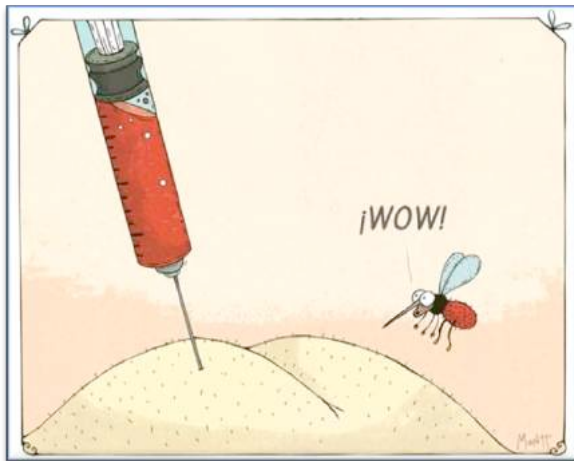


R0 = 3

- m:** Vector density
- a:** Human biting rate
- p:** Daily survival rate of mosquitoes
- n:** **Extrinsic Incubation Period**
- b:** **Vector competence**
- c:** Transmission efficiency from an infected human to a mosquito
- 1/r:** Human infectious period




Vectorial system

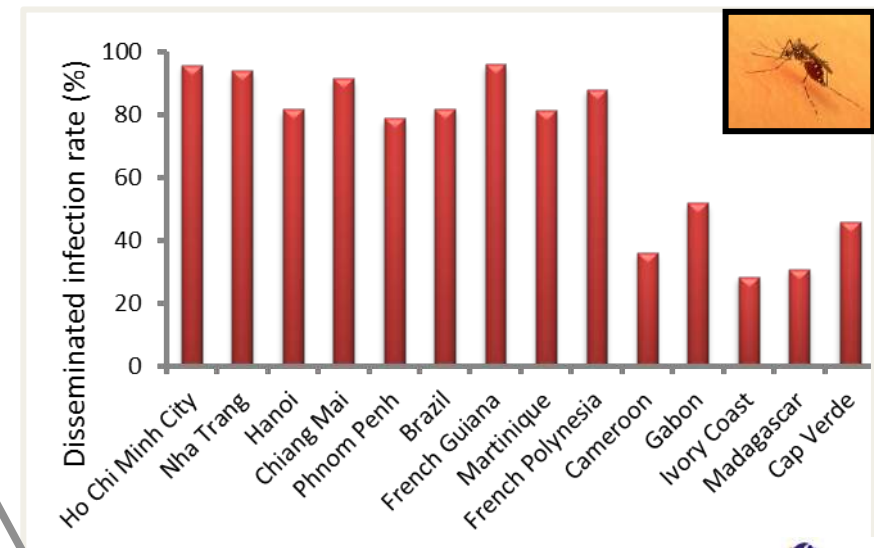
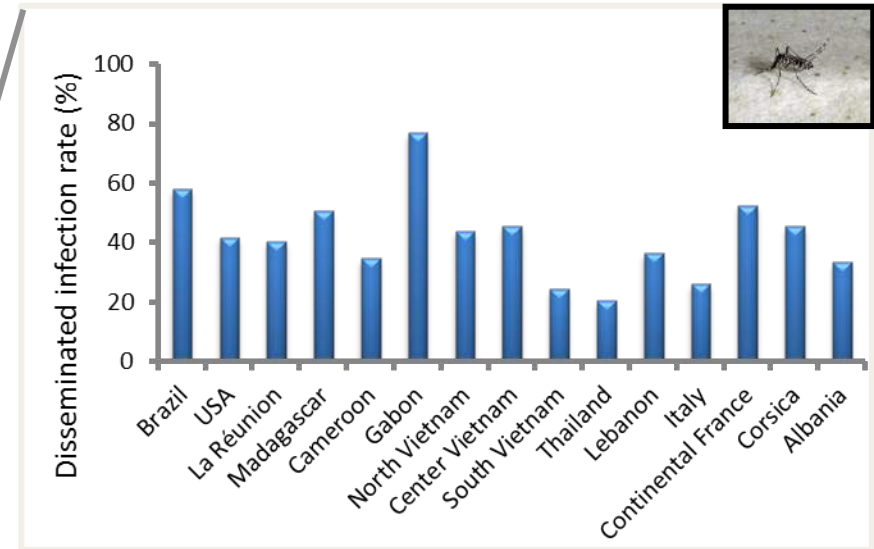
The mosquito is not a needle!



Transmission is possible

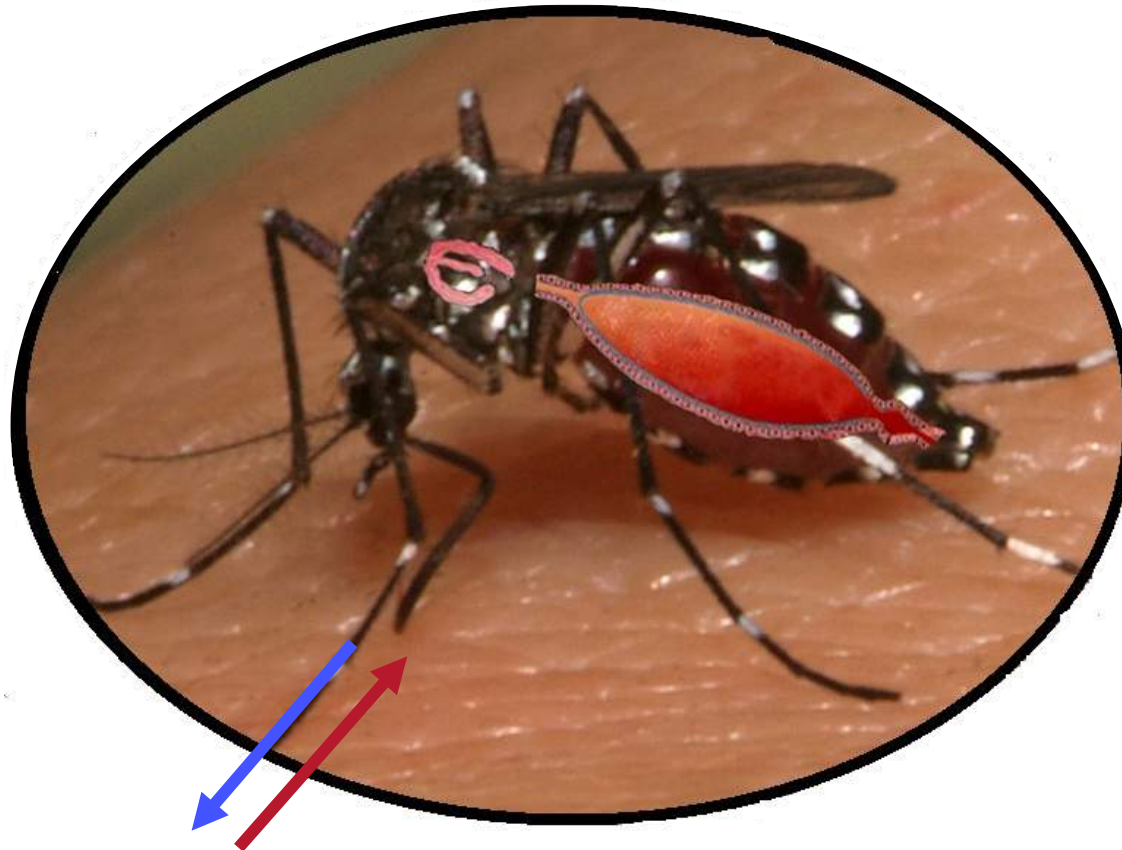
All mosquitoes are not able to transmit all viruses

	RVF	CHIK	DEN
 <i>Culex pipiens</i>	+	-	-
 <i>Aedes albopictus</i>	-	+	+
 <i>Aedes aegypti</i>	-	+	+



Vector competence

2. Wings/Legs/Heads
Dissemination rate

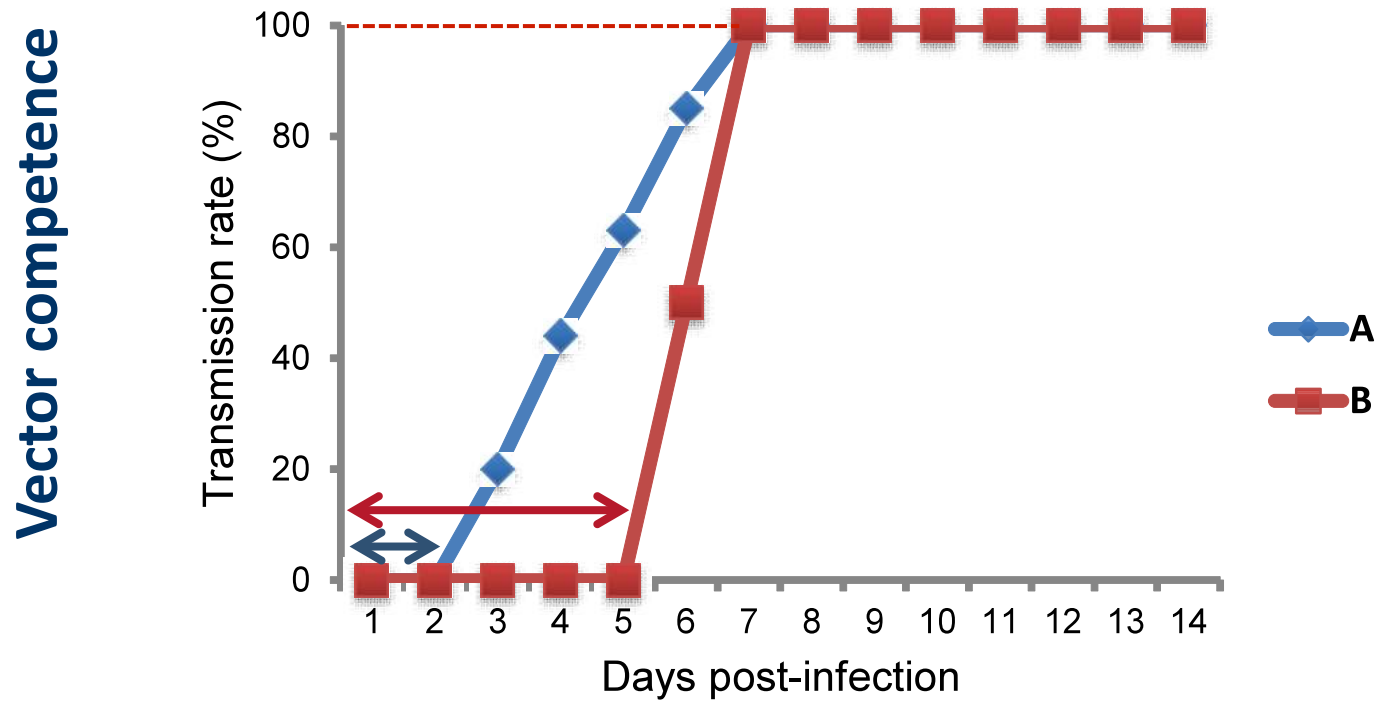


3. Saliva
Transmission rate

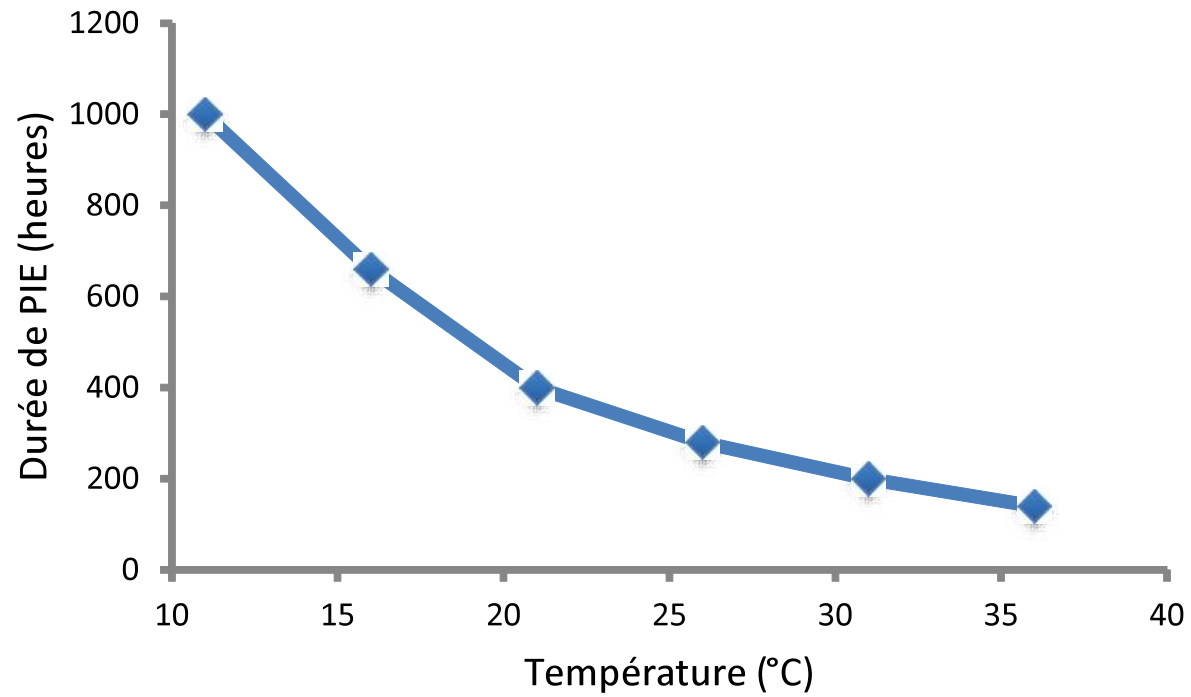
← Extrinsic incubation period (EIP)

1. Midgut
Infection rate

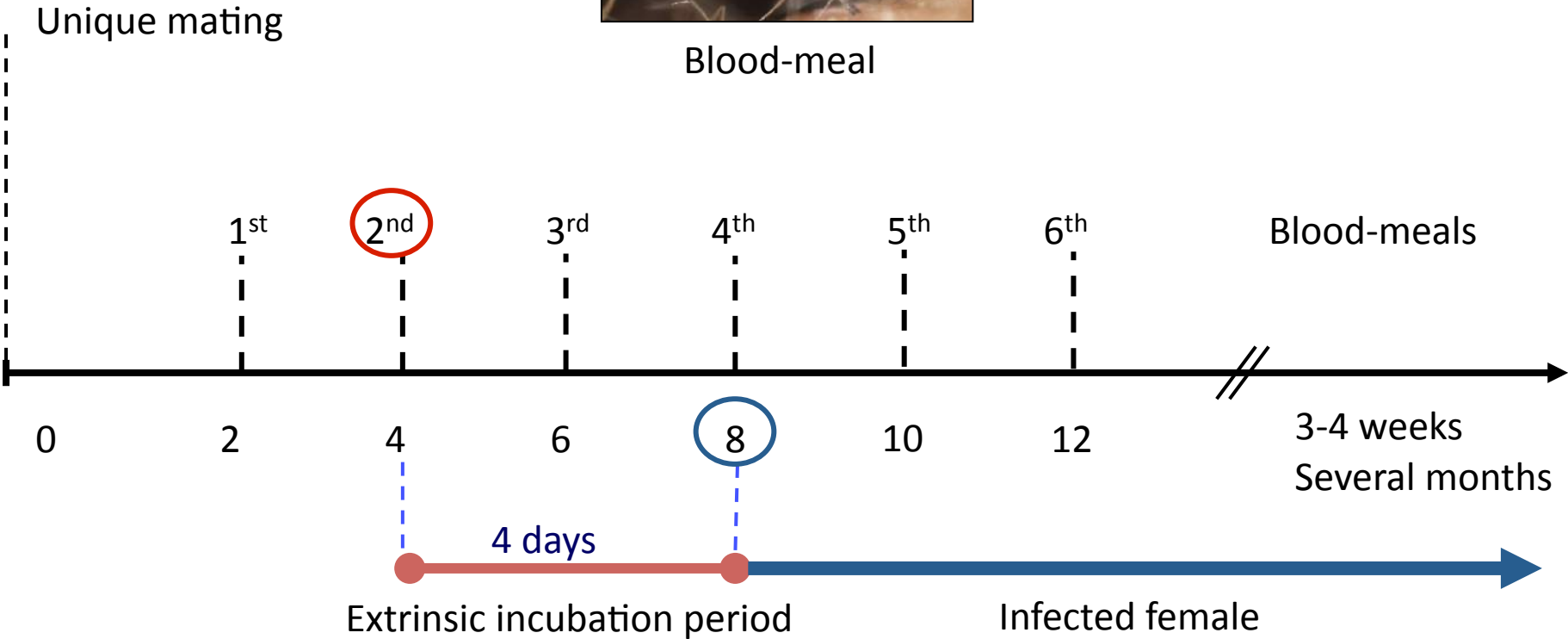
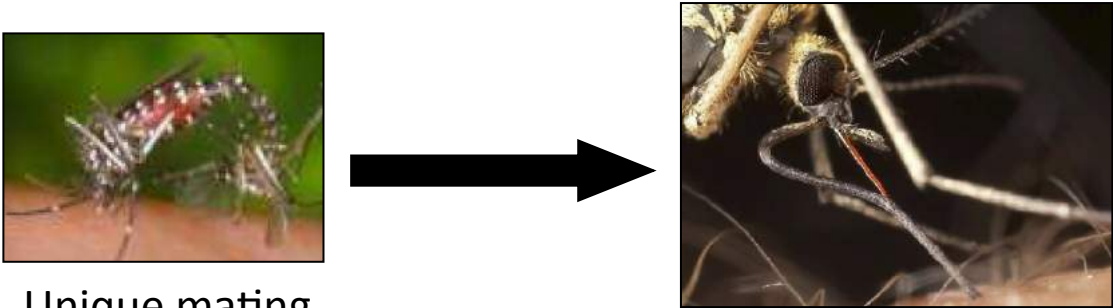
Extrinsic incubation period (EIP)



EIP according to T°

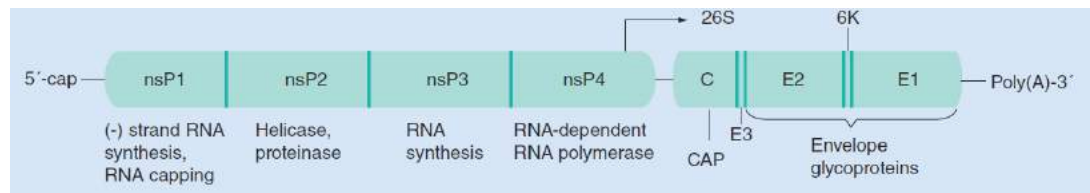


Once infected, she remains infected all her life



Chikungunya

Togaviridae - Alphavirus

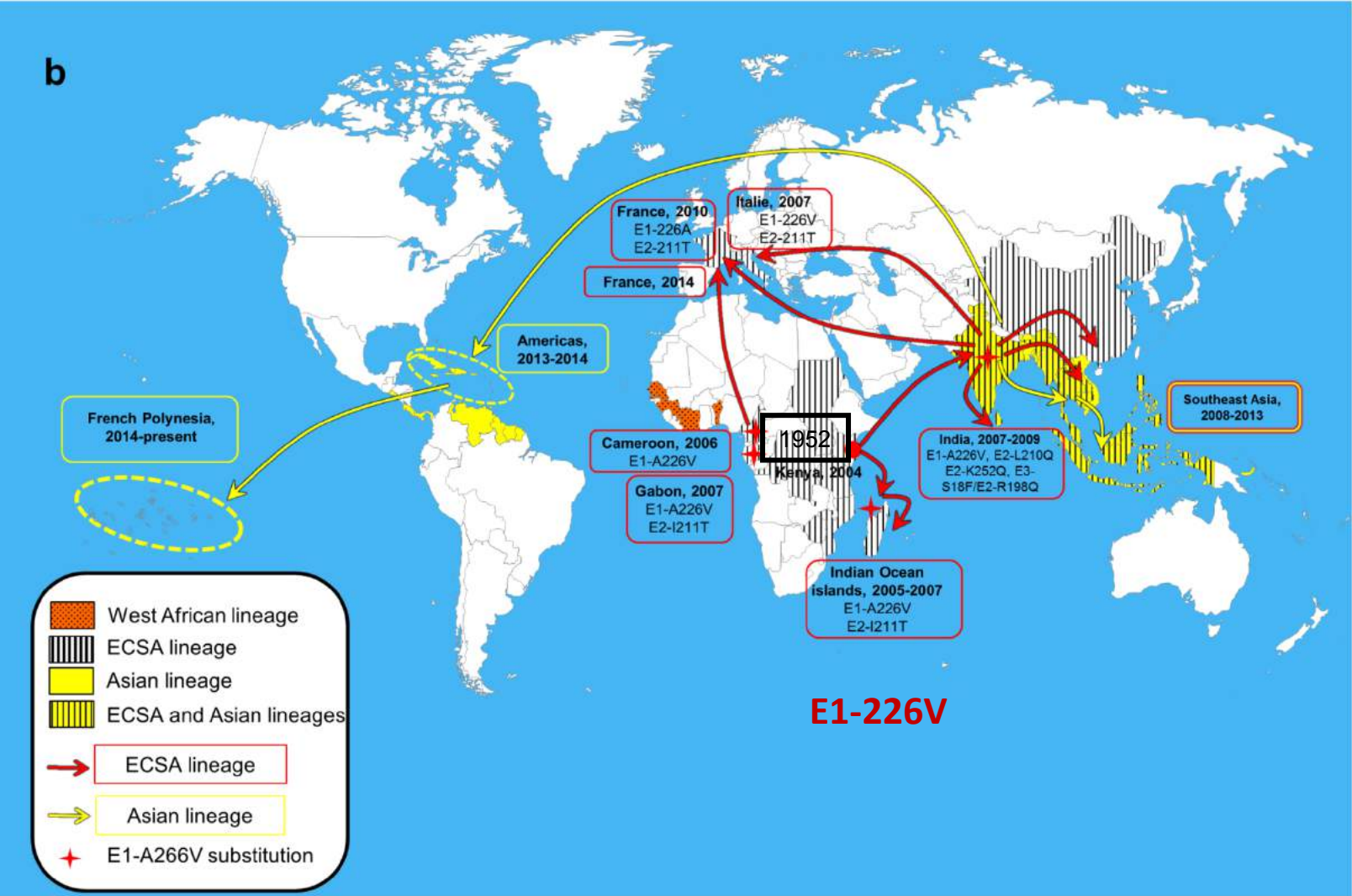


Coffey et al. *Future Microbiol* (2013)



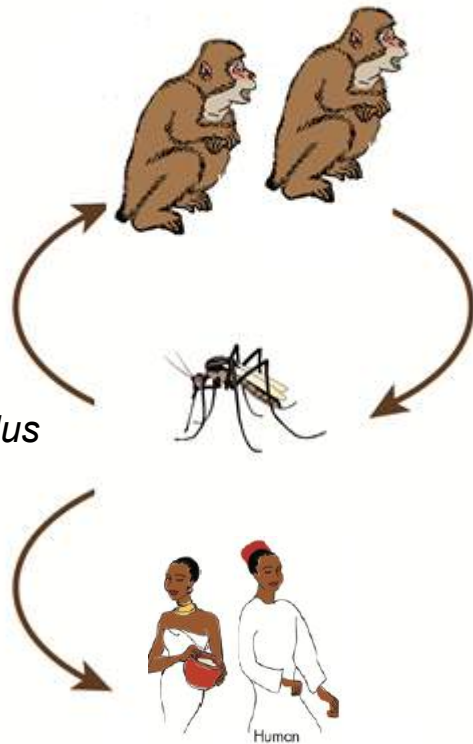
Aedes albopictus

CHIK in the world

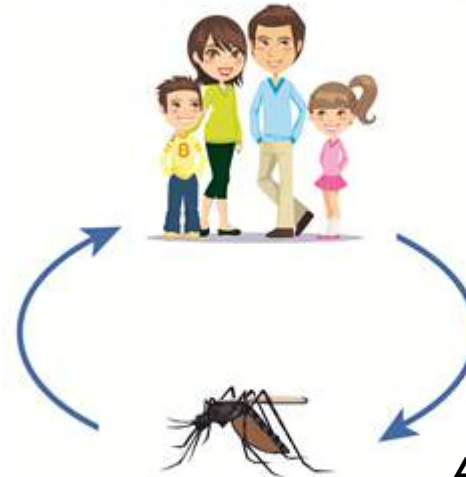


Zouache and Failloux. *Curr Opin Insect Sci* (2015)

Two transmission cycles



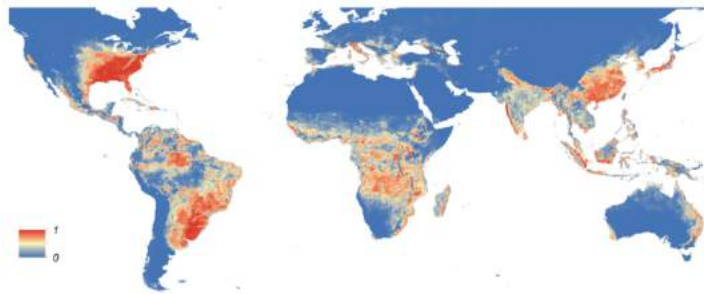
Sylvatic cycle



Epidemic cycle



Aedes albopictus



Kraemer et al. *eLife* (2015)

Country	Year	Vector	Genotype	E1-226 (A or V)
Kenya	2004	AA	ECSA	A
Comoros	2005	AA	ECSA	A
La Réunion	2005	AL	ECSA/IOL	V
Seychelles	2005	AL	ECSA/IOL	V
Mauritius	2006	AL	ECSA/IOL	V
Mayotte	2006	AA - AL	ECSA/IOL	V
Madagascar	2006	AL	ECSA/IOL	V
India	2006	AA - AL	ECSA/IOL	V
Sri Lanka	2006	AA - AL	ECSA/IOL	V
Maldives	2006	AA - AL	ECSA/IOL	V
Cameroon	2006	AL	ECSA/IOL	V
Equatorial Guinea	2006	AL	ECSA/IOL	V
Gabon	2007	AL	ECSA/IOL	V
Italy	2007	AL	ECSA/IOL	V
Singapore	2008	AA - AL	ECSA/IOL	V
Malaysia	2008	AA - AL	ECSA/IOL	V
Thailand	2008	AA - AL	ECSA/IOL	V
France	2010	AL	ECSA/IOL	A
China	2010	AL	ECSA/IOL	V
Cambodia	2011	AA - AL	ECSA/IOL	V
Congo	2011	AL	ECSA/IOL	V
Bhutan	2012	AA - AL	ECSA/IOL	A

Aedes albopictus (Skuse, 1894)



Native from Asia

Colonizes wide range of habitats

- Urban, suburban, rural areas, forests
- Natural and artificial breeding sites

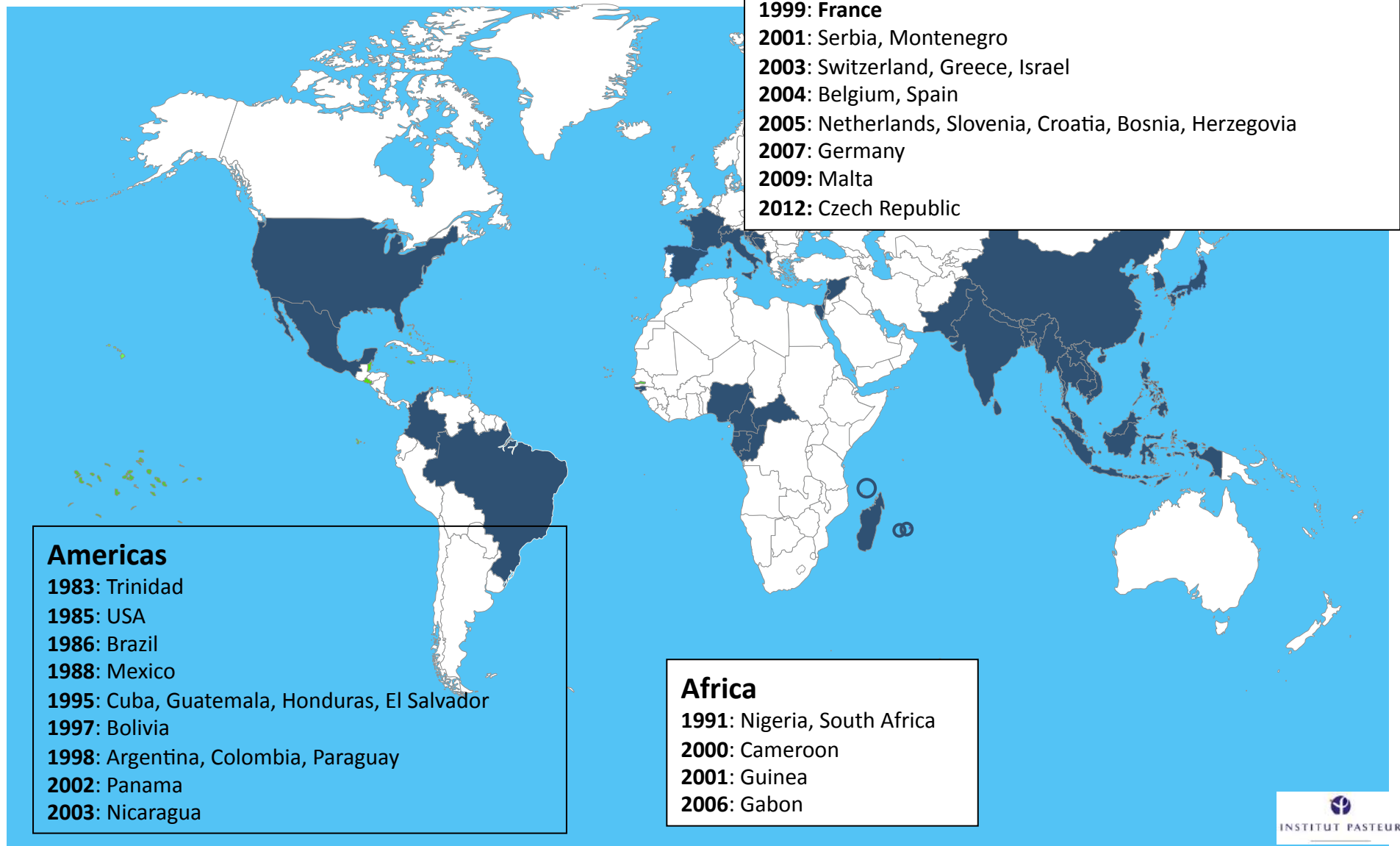


Two main biological characteristics:

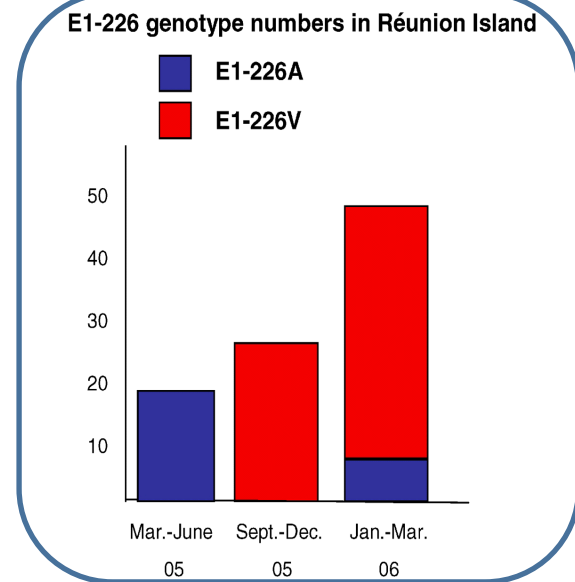
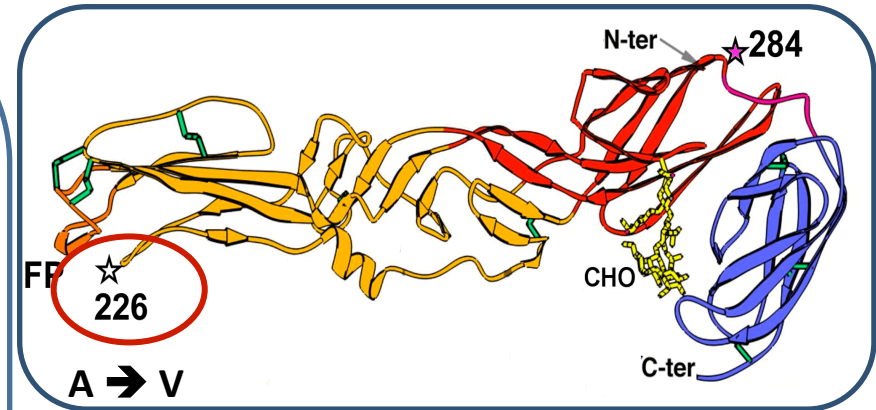
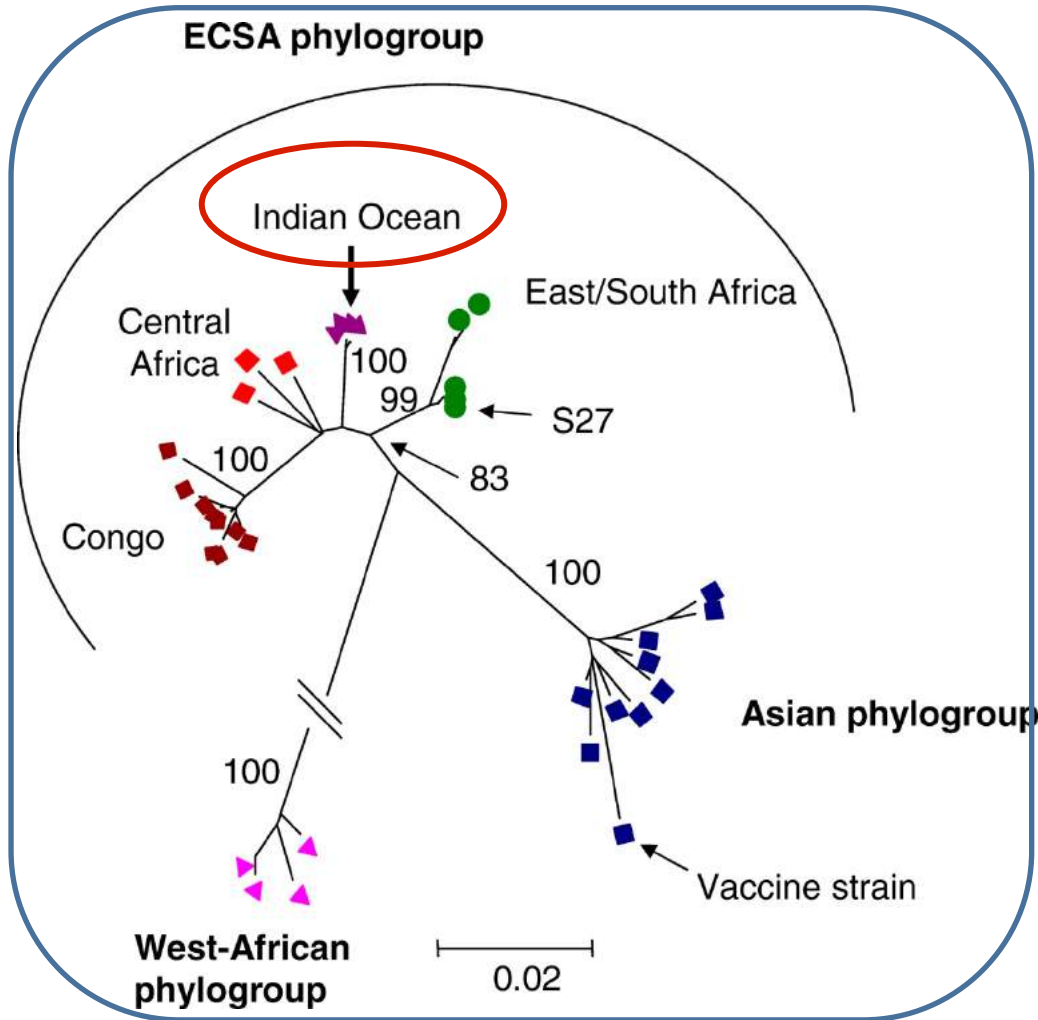
- desiccated eggs
- diapause during winter



Aedes albopictus: an invasive species

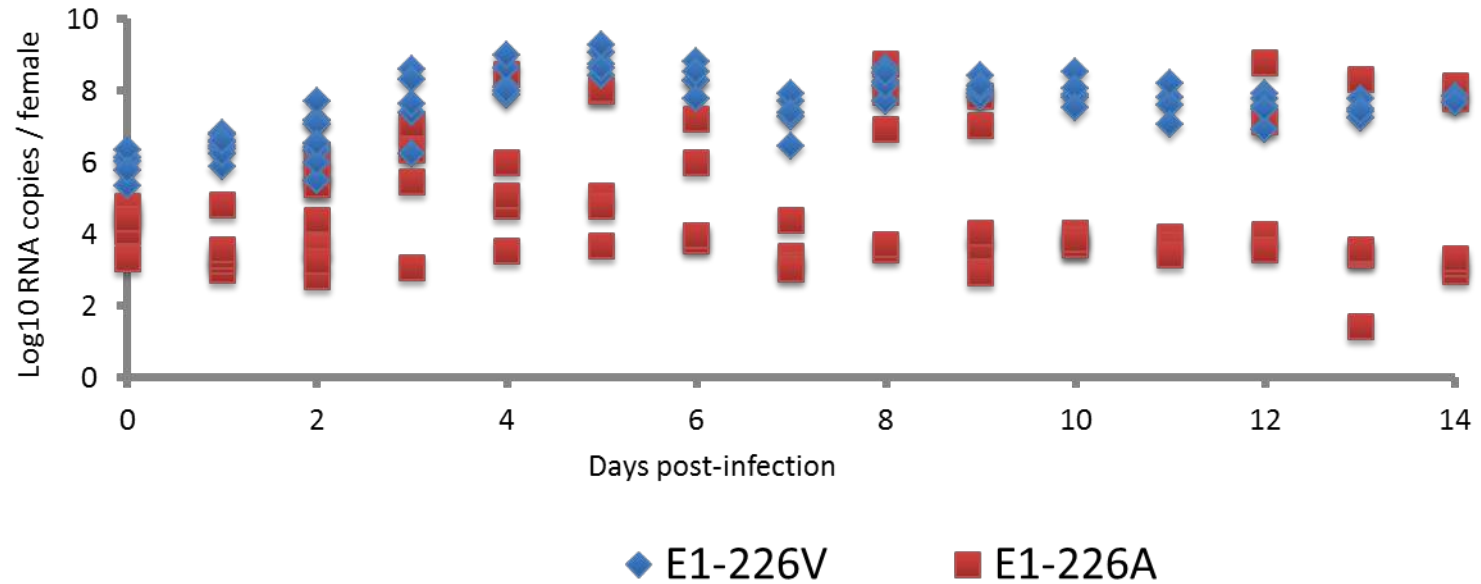


A new CHIK mutant



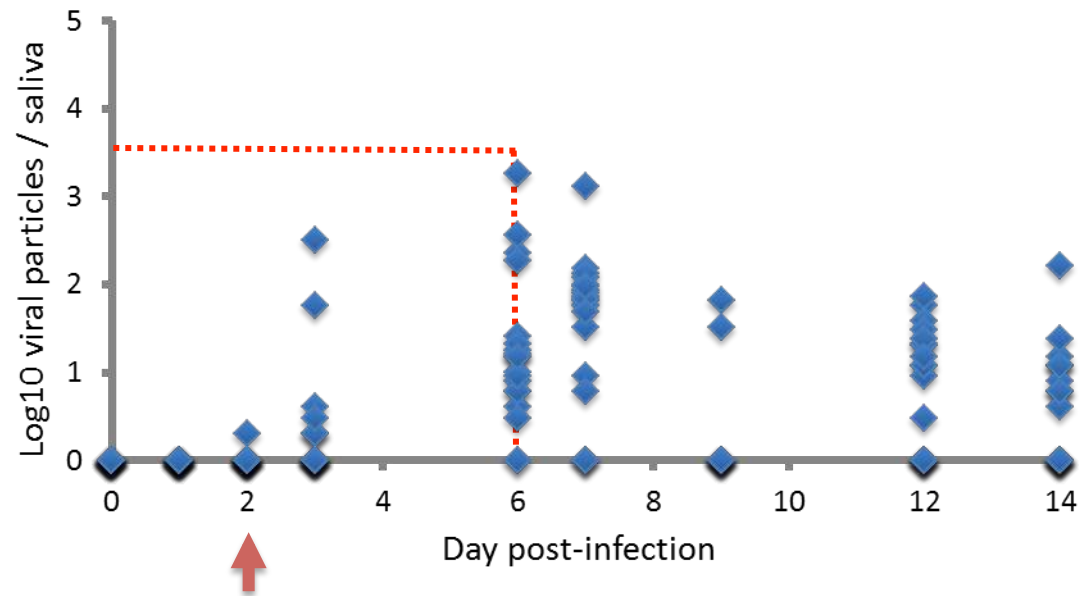
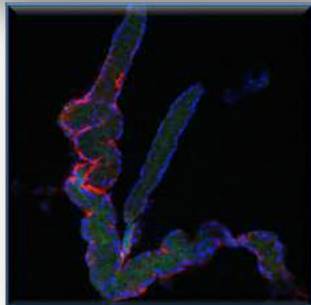
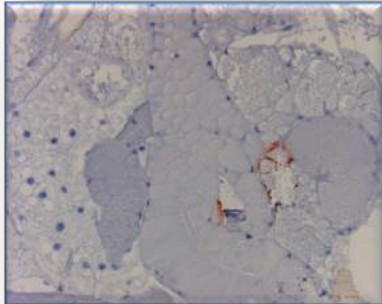
Schuffenecker et al. *PLoS Med* (2006)

Enhanced replication in *Aedes albopictus*



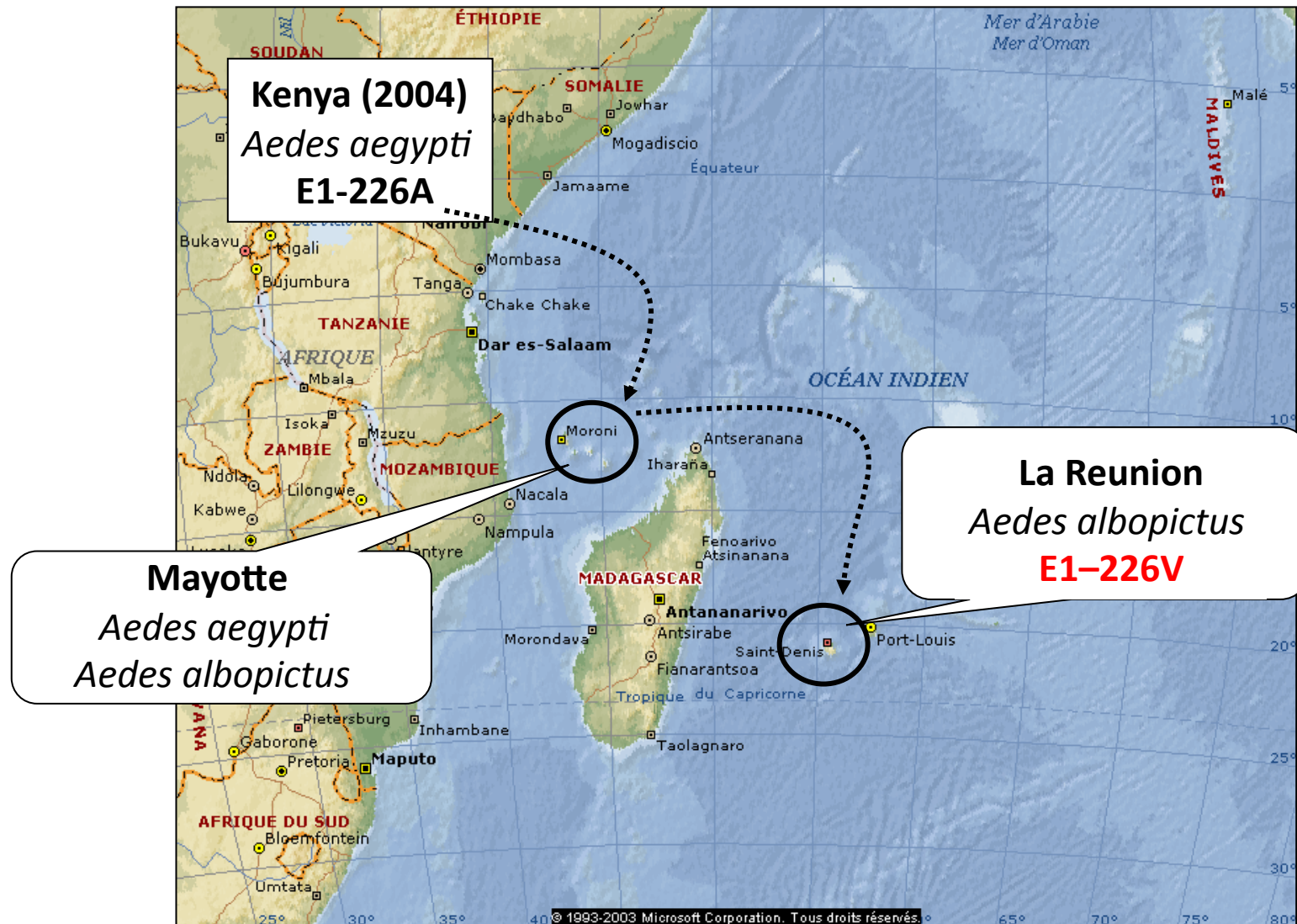
Vazeille et al. *PLoS ONE* (2007)

Saliva CHIKV-positive from day 2

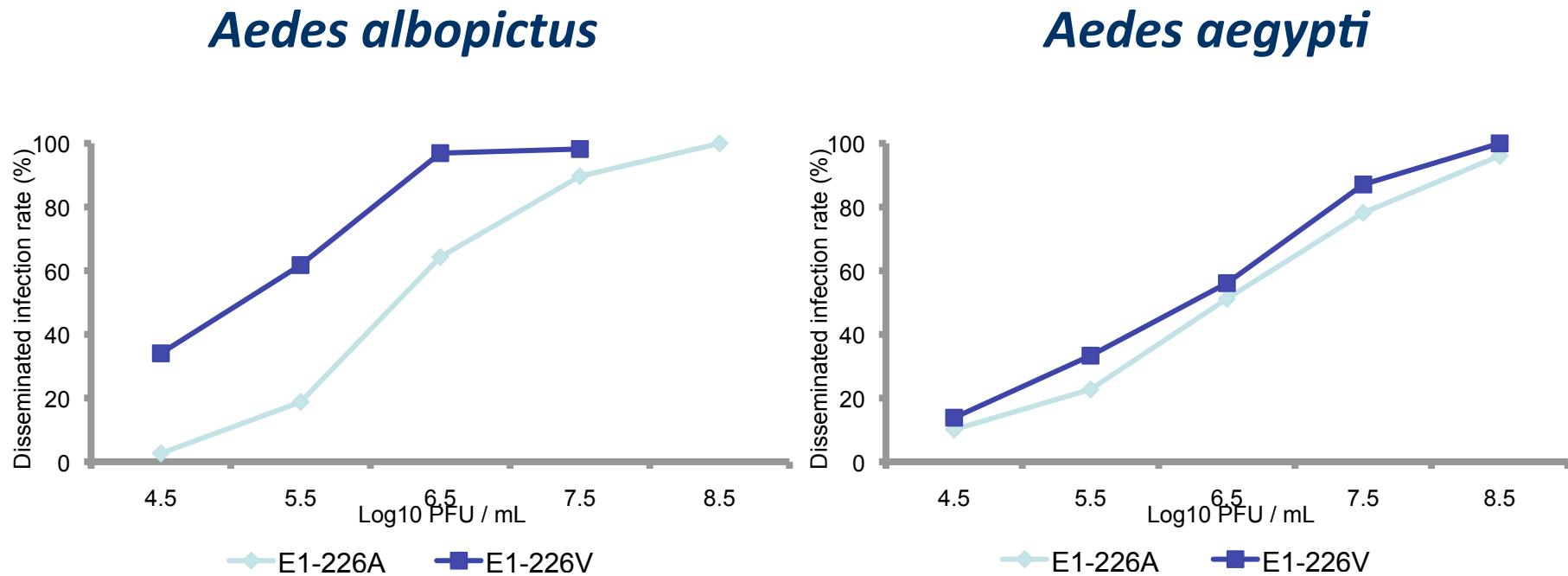


Dubrulle et al. *PLoS ONE* (2009)

Has *Aedes albopictus* contributed to select E1-226V?



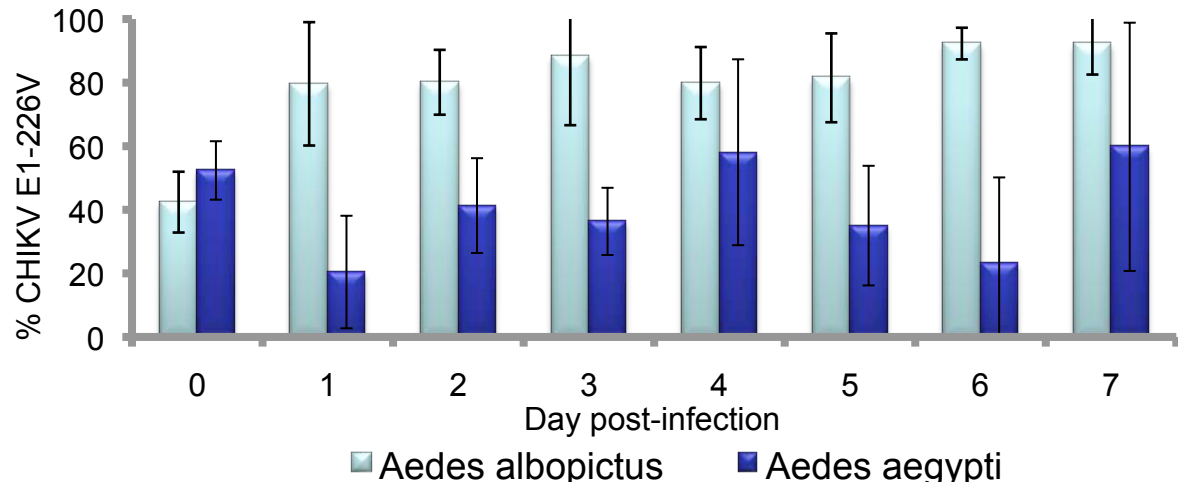
High dissemination of E1-226V in *Aedes albopictus*



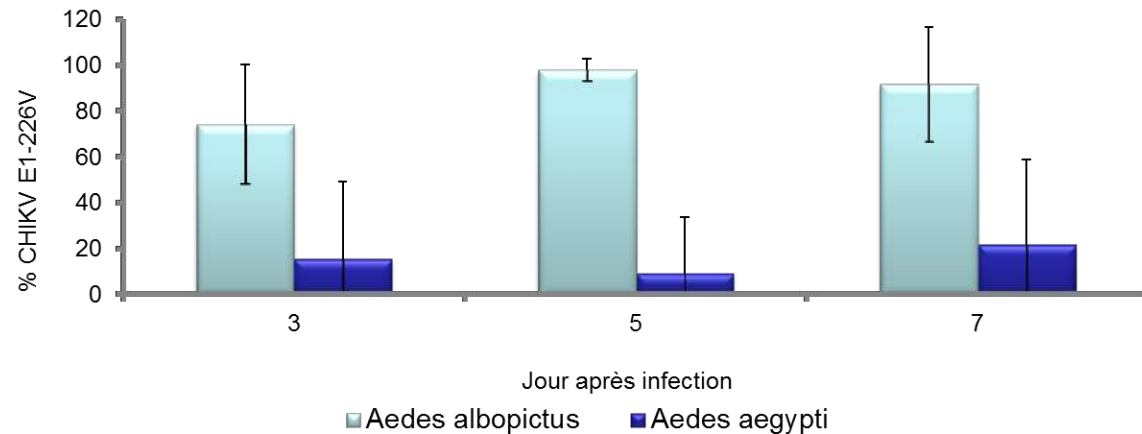
Martin et al. *BMC Ecol* (2010)

E1-226V predominates in *Aedes albopictus*

Midgut



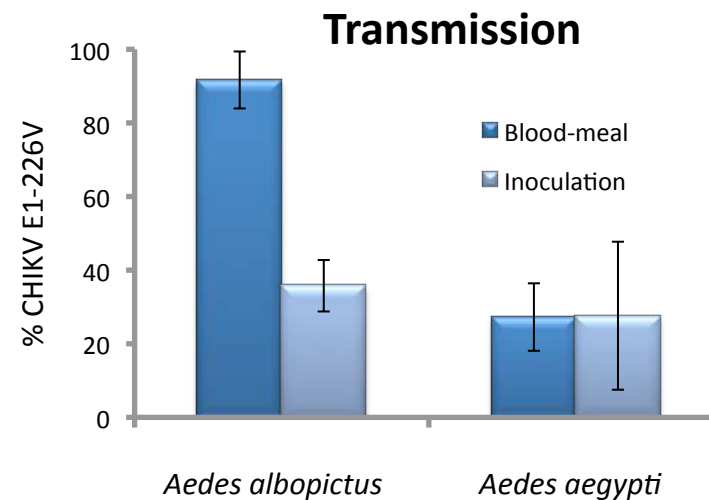
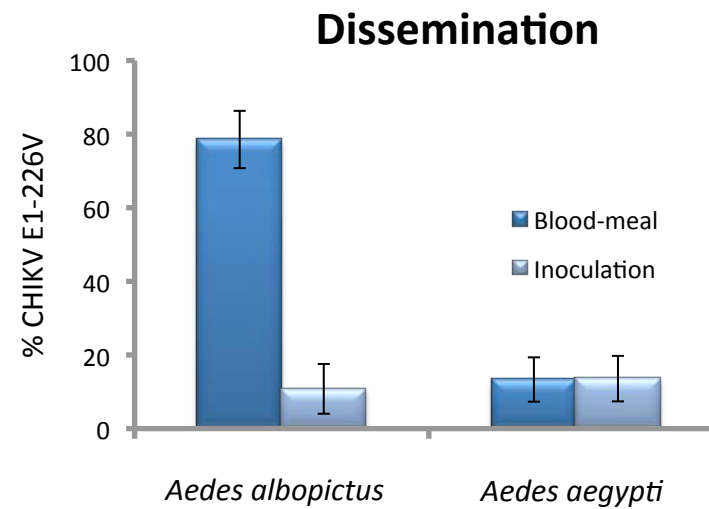
Saliva



The midgut plays a key role



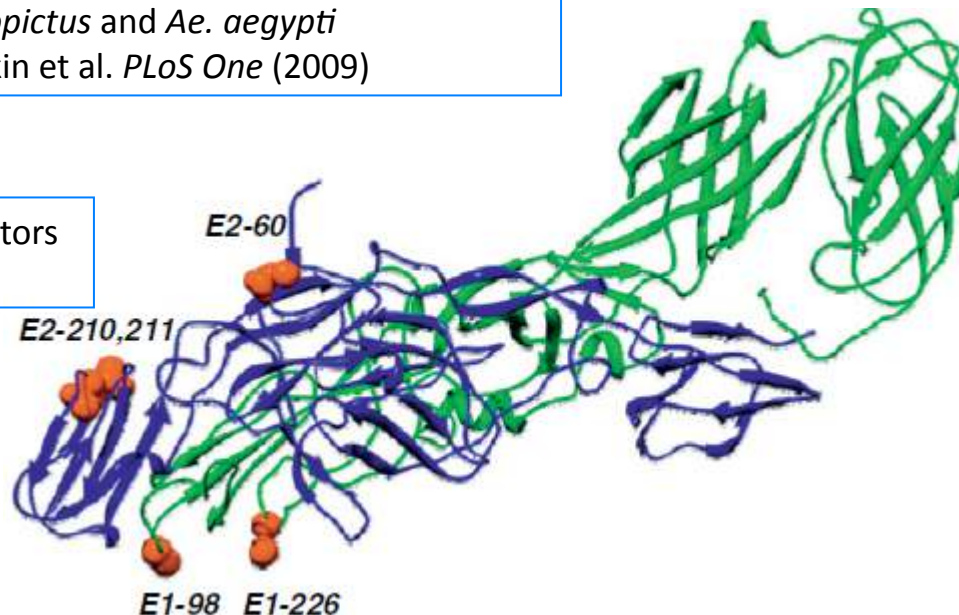
Arias-Goeta et al. *PLoS ONE* (2013)



Adaptation of CHIKV to *Ae. albopictus*

E2-60: Modulates CHIKV infectivity for both *Ae. albopictus* and *Ae. aegypti*
Tsetsarkin et al. *PLoS One* (2009)

E2-210,211: Interacts with cell receptors
Voss et al. *Nature* (2010)



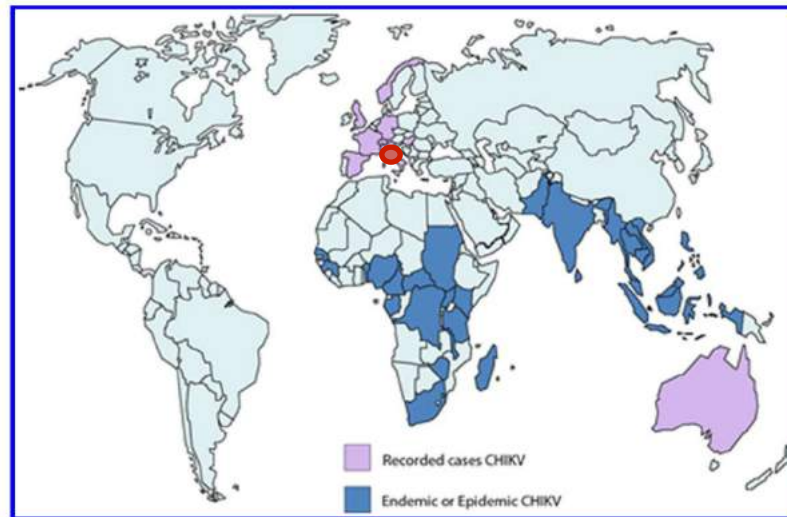
E1-98: Modulates the kinetics of the pH-dependent conformational changes and fusion reaction in endosomal compartment of *Ae. albopictus* cells
Tsetsarkin et al. *PNAS* (2011)

E1-226: Involved in viral entry via fusion with endosomal membranes

Tsetsarkin et al. *Curr Opin Virol* (2011)

Chikungunya emerging in temperate regions

Emergence of CHIK



Expansion of *Aedes albopictus*



Waldock et al. *Pathogens and Global Health* (2013)

Aedes albopictus in Europe

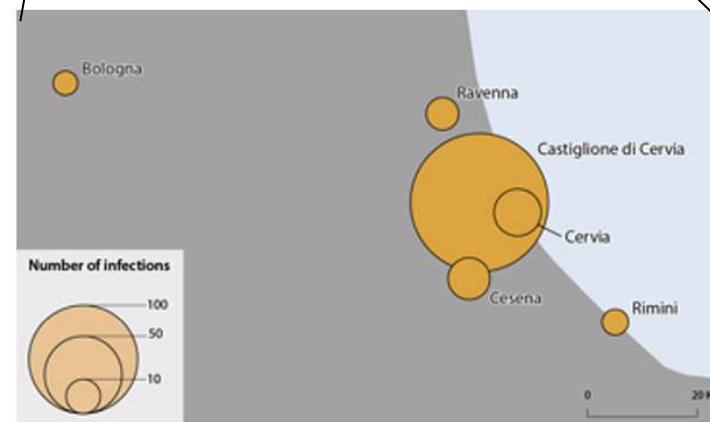


Medlock et al. *VBZD* (2012)

2007: CHIKV in Italy

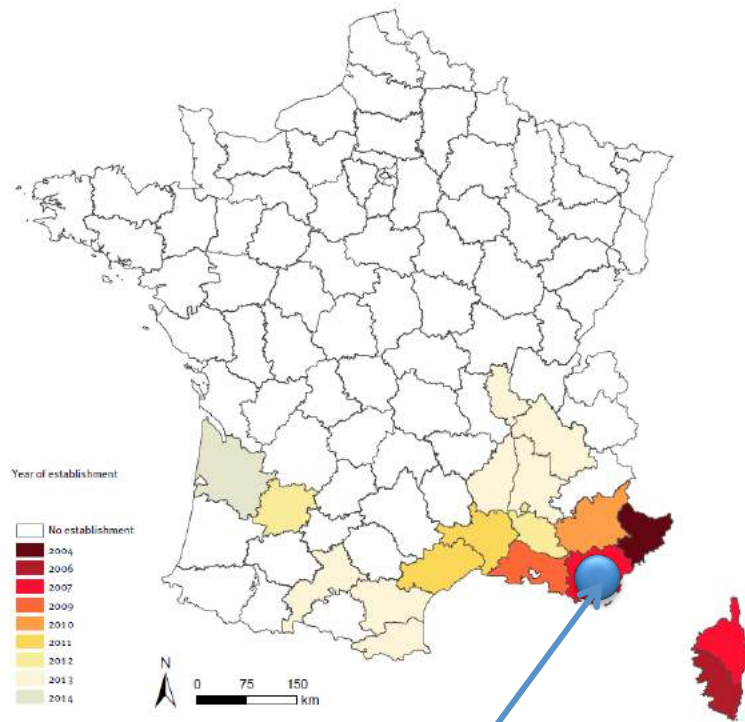


Emilia-Romagna
229 cases



Tomasello & Schlagenhauf. *Travel Med Inf Dis* (2013)

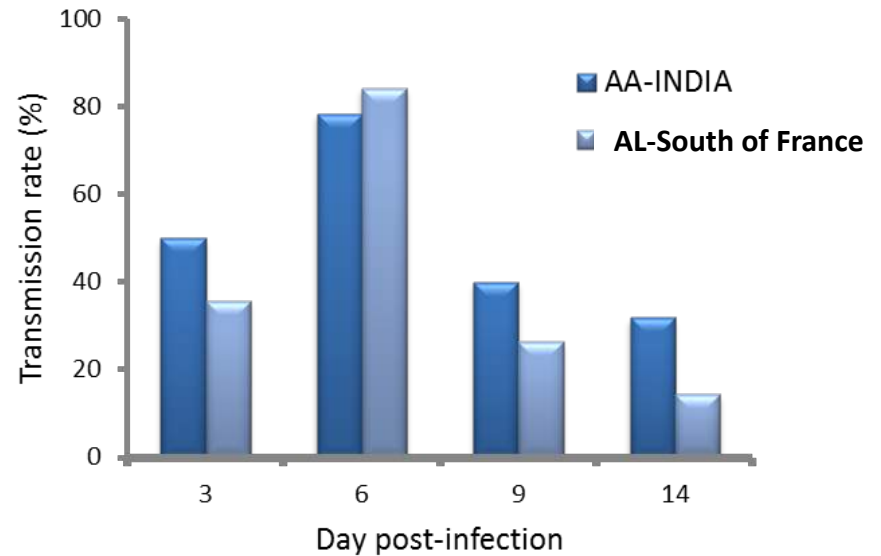
2010: CHIKV in France



Source: IGN-GéoFLA, 1999; French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS), 2014.

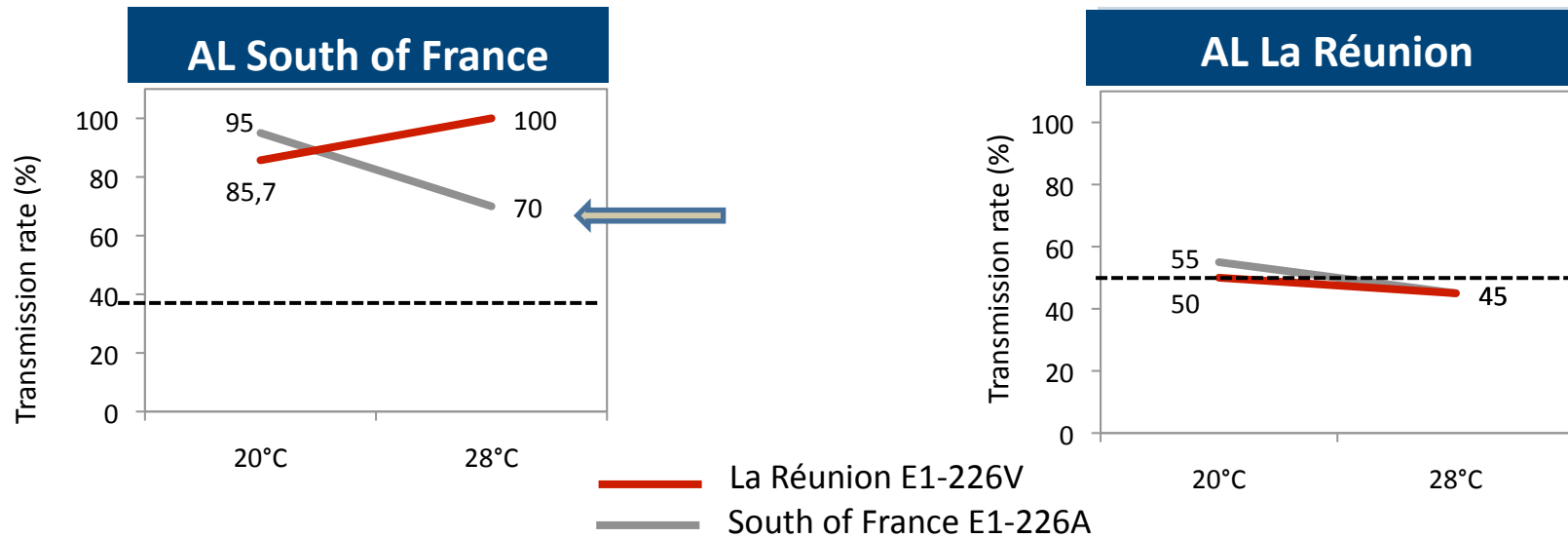
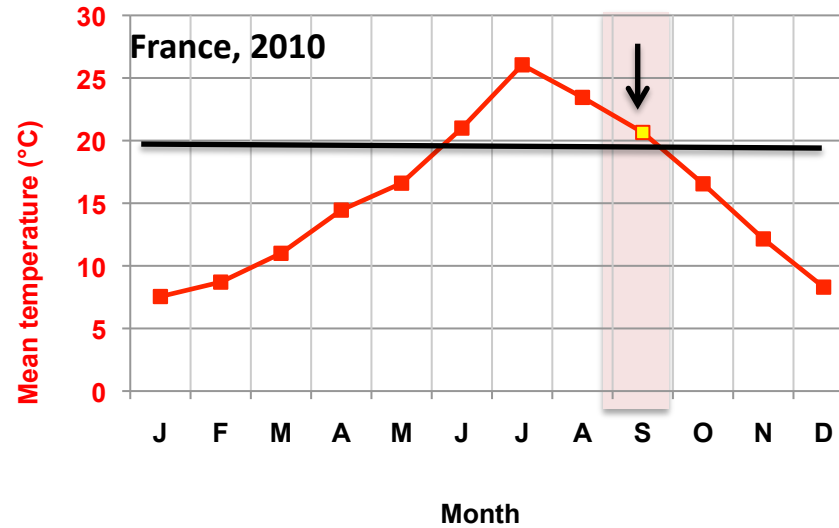
France
Fréjus (2010)

Paty et al. *Euro Surveill* (2014)



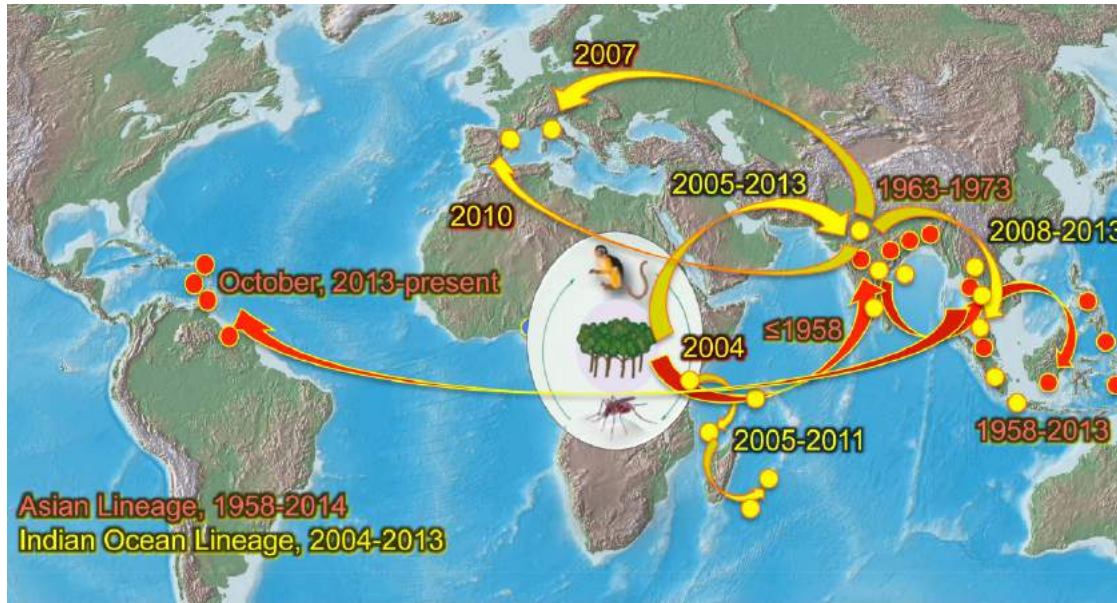
Vega-Rua et al. *PLoS ONE* (2013)

Lower transmission of CHIKV at 28°C

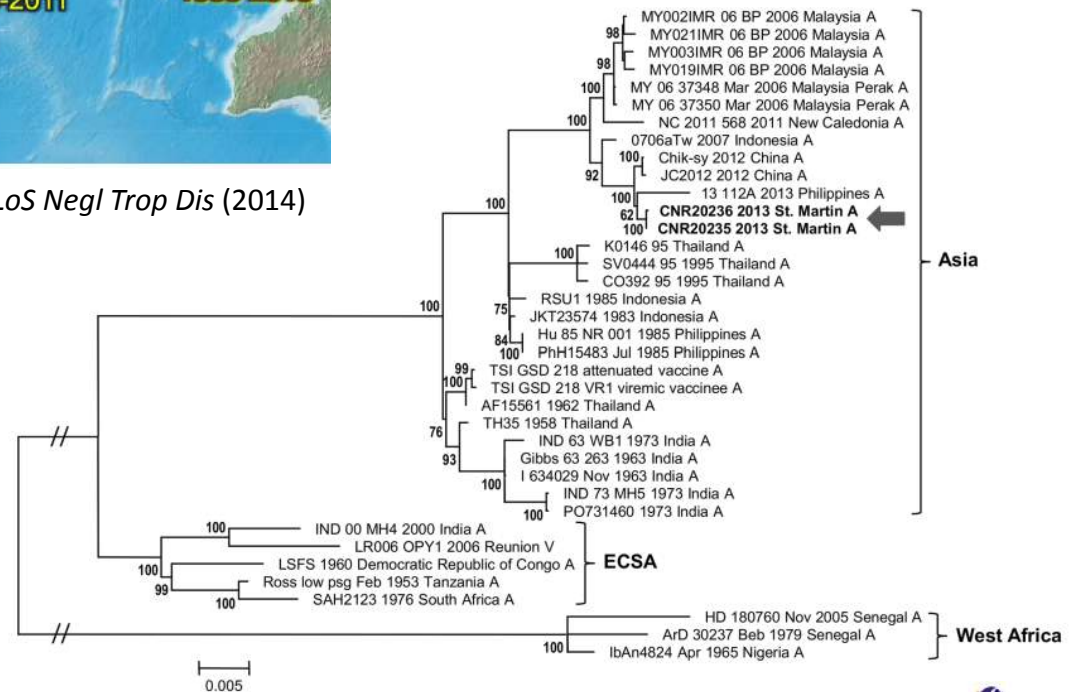


Zouache et al. *Proc Biol Sci* (2014)

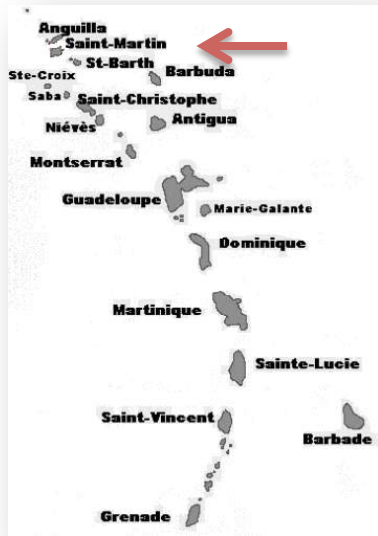
CHIK in America



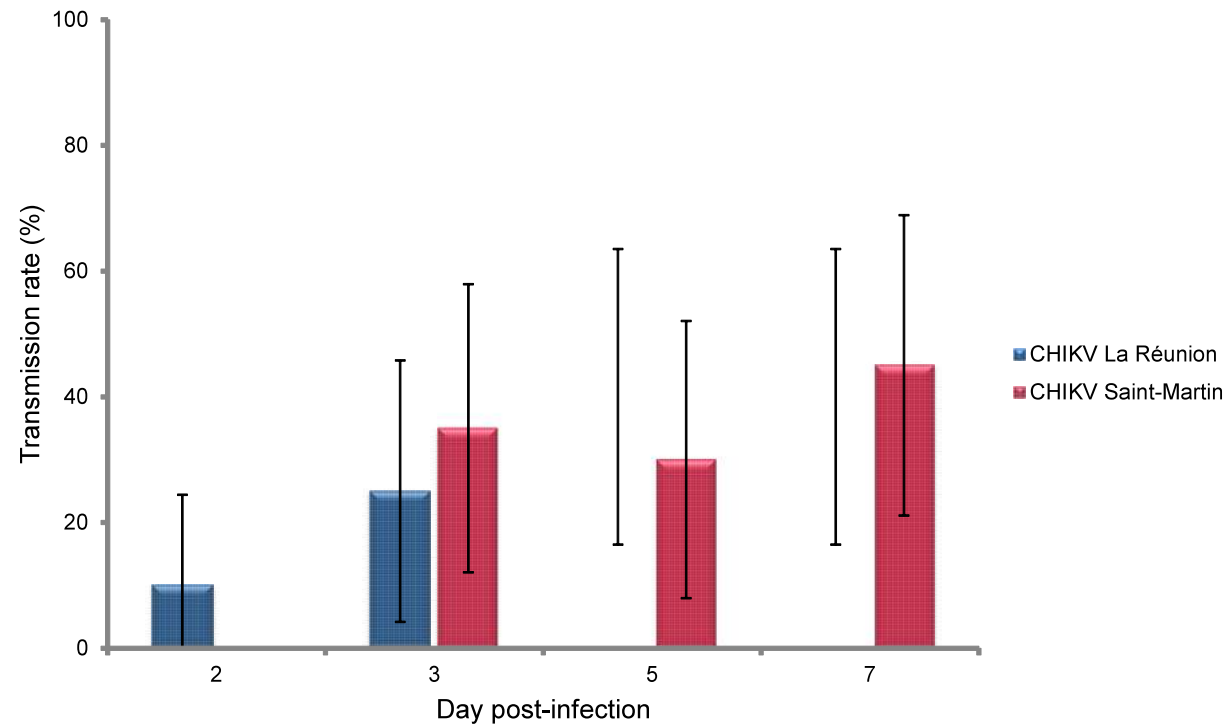
Weaver. *PLoS Negl Trop Dis* (2014)



Leparc-Goffart *et al.* *Lancet* (2014)



Saint-Martin: *Aedes aegypti* more susceptible to the Asian CHIKV genotype?

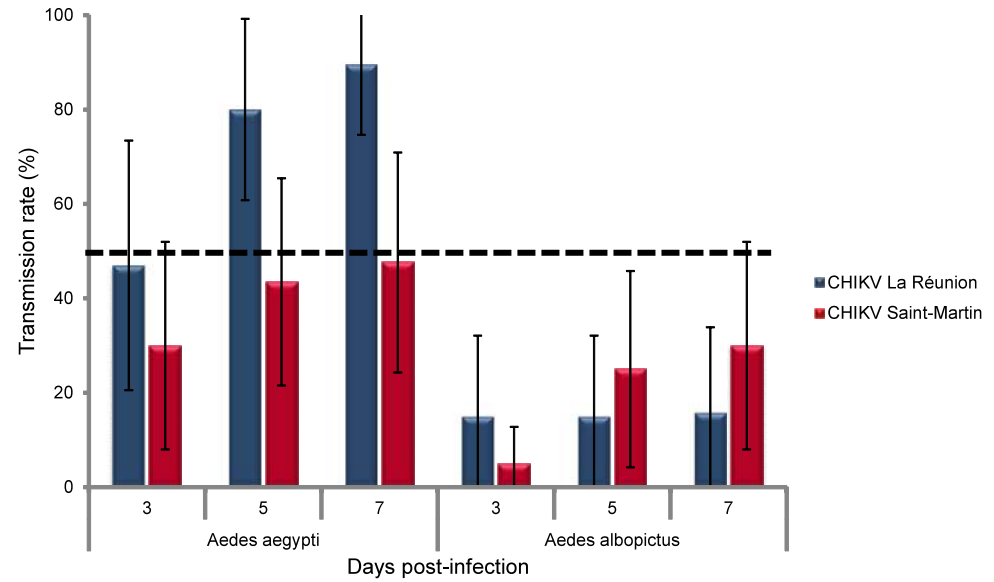


Vega-Rua et al. *PLoS Negl Trop Dis* (2015)

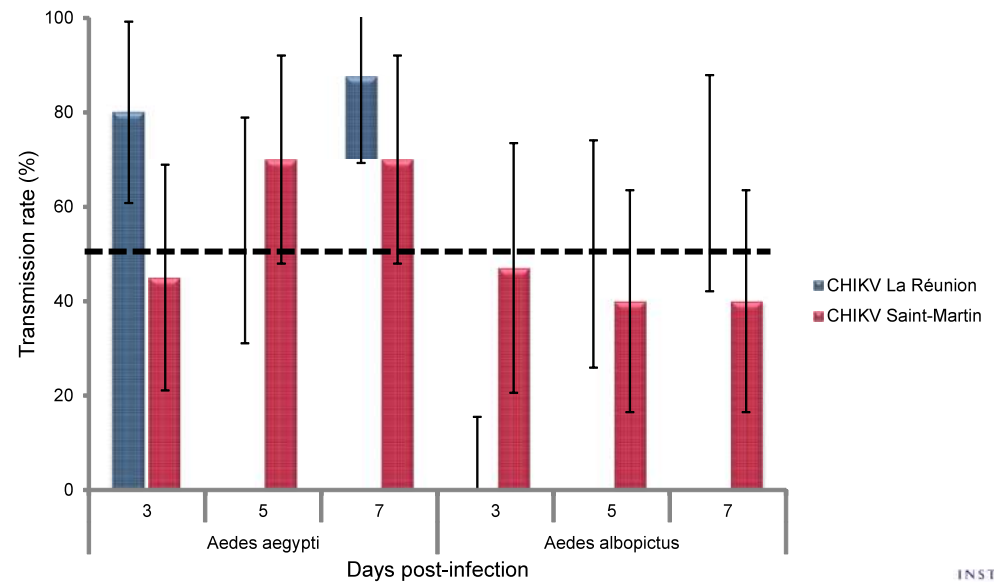
Ae. albopictus?



Florida
(USA)

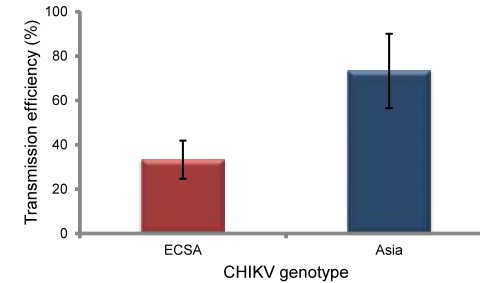
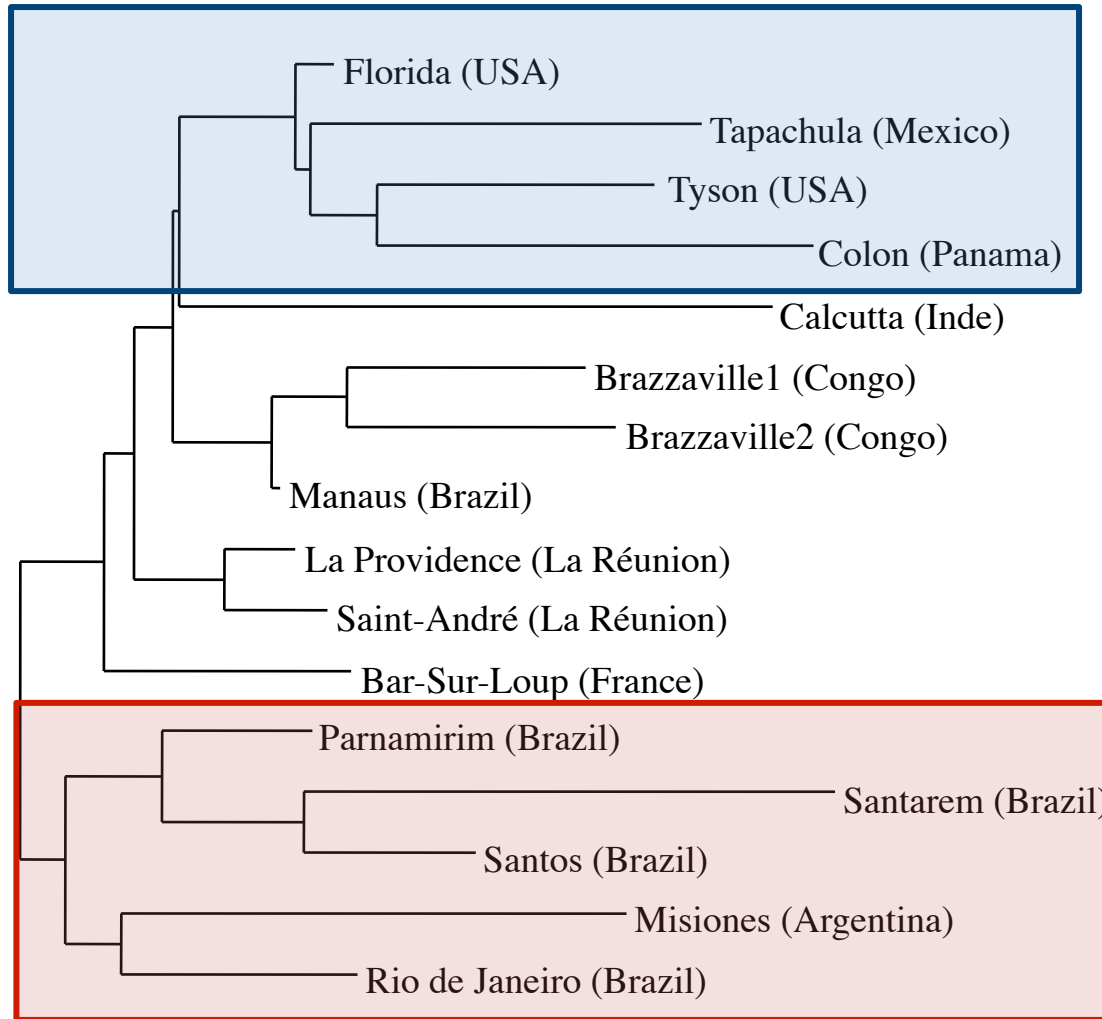


Rio
(Brazil)

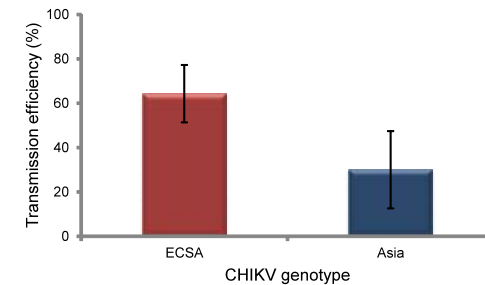


Vega-Rua et al. *PLoS Negl Trop Dis* (2015)

Two clusters of *Ae. albopictus*



North and Central Americas

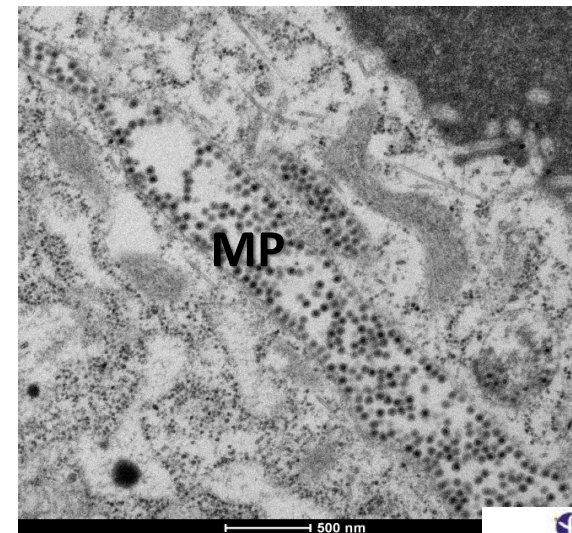
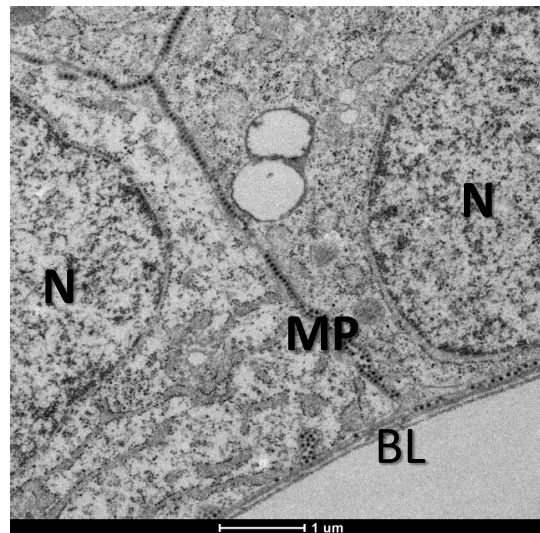
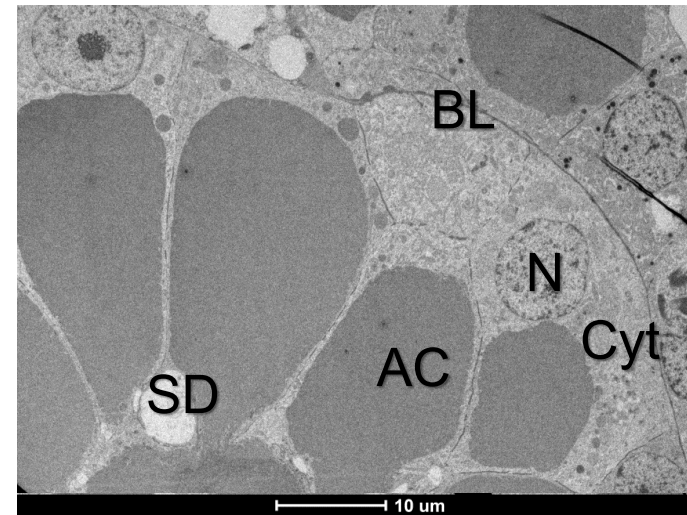
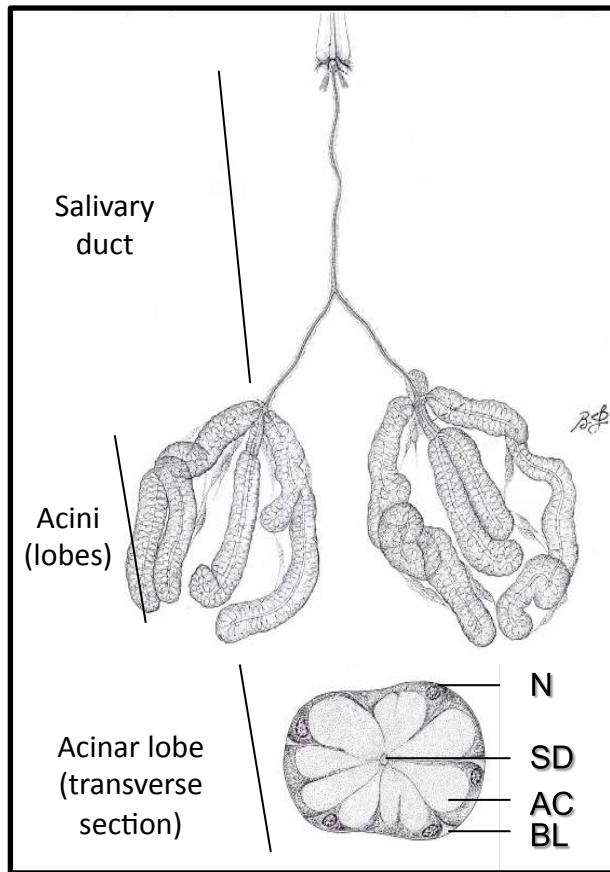


South America

0.02

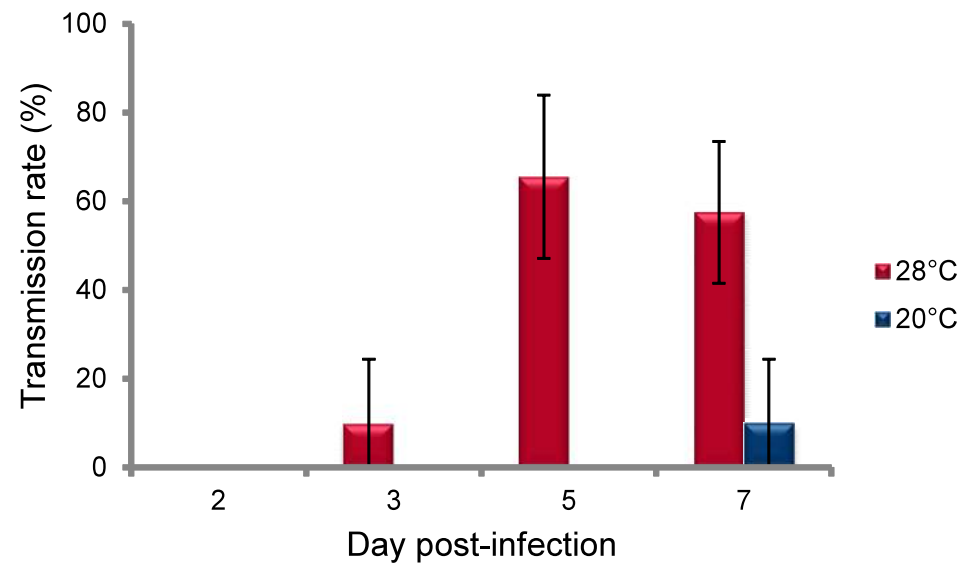
Collaborations: M. Manni, A. Malacrida, G. Gasperi, C. Dauga

Salivary glands of *Ae. albopictus* infected with CHIKV



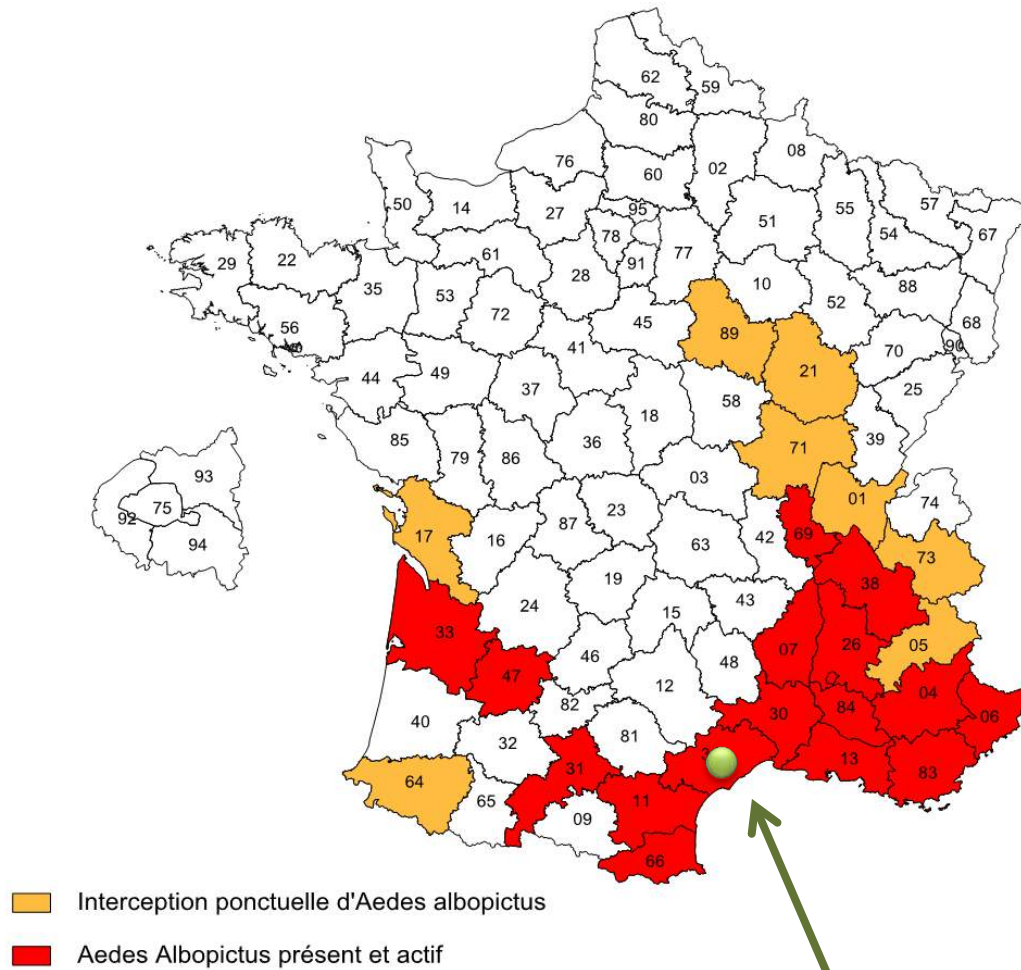
Vega-Rua *et al.* Viruses (2015)

The threat of CHIKV in France



Vega-Rua et al. *PLoS Negl trop Dis* (2015)

CHIKV in France



An ECSA genotype rather than an Asian genotype!

11 CHIK cases in October 2014

INVS (2014)

Zika

Flaviviridae - Flavivirus



Source: ViralZone



Aedes aegypti

Zika forest

Uganda, near Entebbe (1947)



<http://edition.cnn.com/2016/02/02/health/zika-forest-viral-birthplace/>

<http://edition.cnn.com/2016/02/02/health/zika-forest-viral-birthplace/>

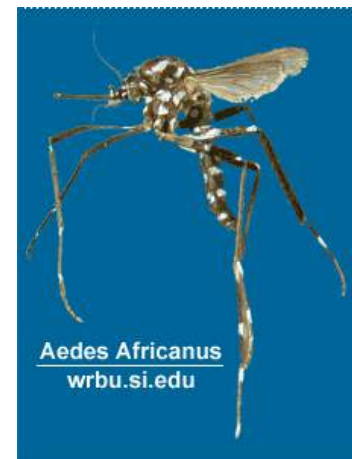
First human cases: 1952 (Uganda, Tanzania)



https://en.wikipedia.org/wiki/Rhesus_macaque

Rhesus monkey (*Macacamulatta*)

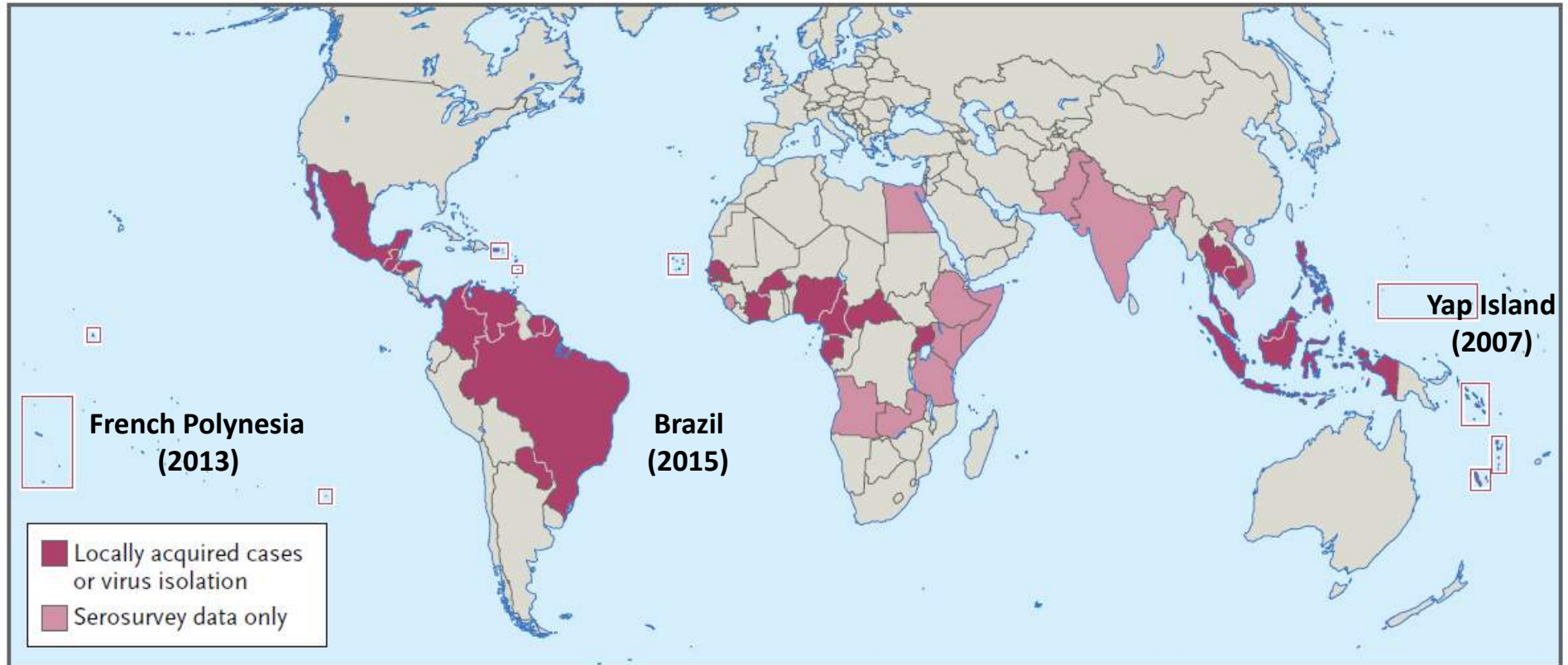
Dick et al. *Trans R Soc Trop Med Hyg* (1952)



Aedes Africanus
wrbu.si.edu

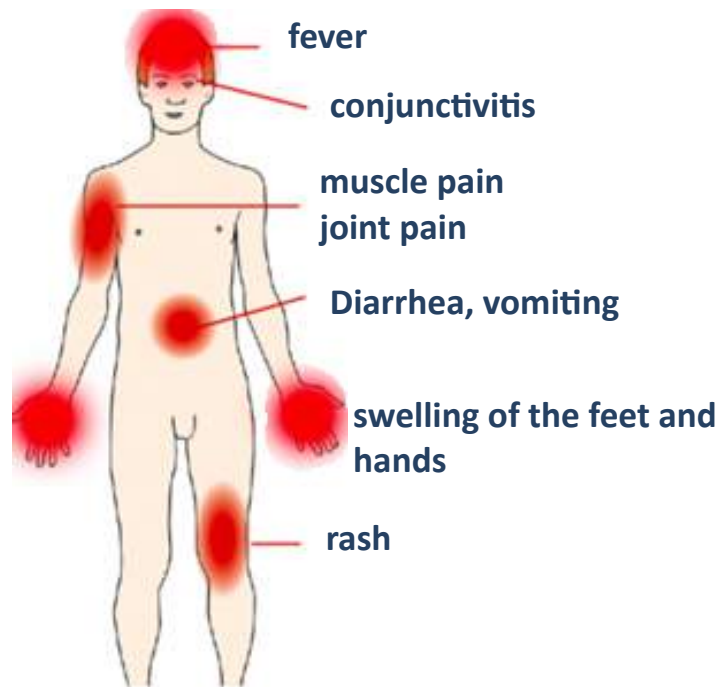
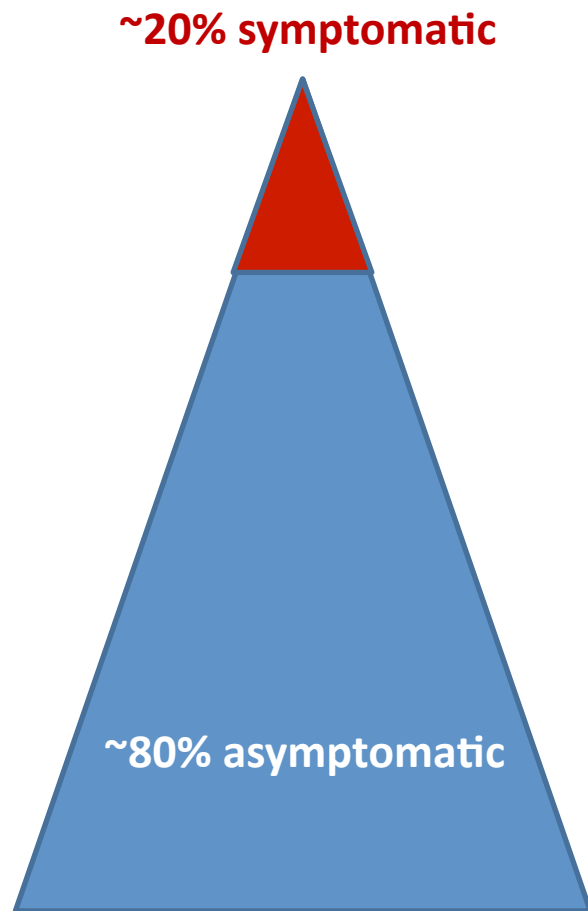
Aedes africanus

Past and Current ZIKV transmission



Fauci & Morens. *New England Journal of Medicine* (2016)

Main symptoms



Kutsuna et al. *Euro Surveill* (2014)



Foy et al. *Emerg Inf Dis* (2011)



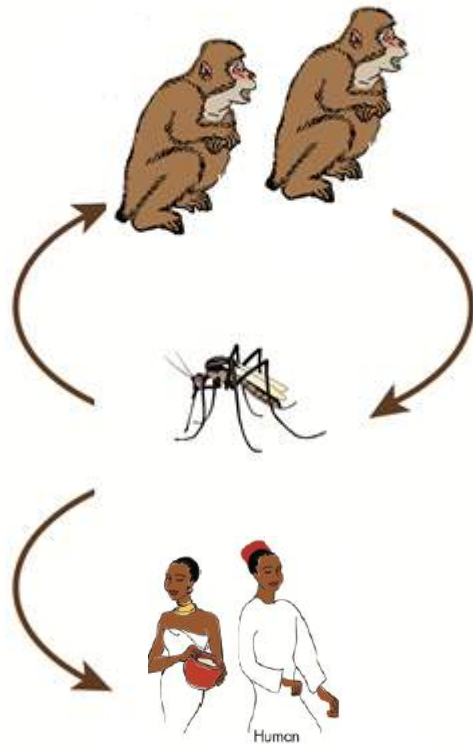
Symptoms appear 3-12 days after the bite of infected mosquito



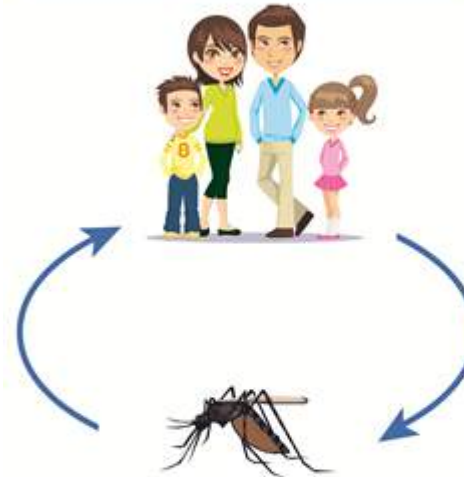
Two transmission cycles



- Ae. dalzieli*
- Ae. fowleri*
- Ae. furcifer*
- Ae. luteocephalus*
- Ae. metallicus*
- Ae. minutus*
- Ae. neoafricanus*
- Ae. tarsalis*
- Ae. vitattus*
- Ae. africanus*
- Ae. flavicollis*
- Ae. furcifer*
- Ae. grahami*
- Ae. opok*
- Ae. taeniarostris*
- Ae. tarsalis*
- Ae. vitattus*
- An. gambiae*
- Mansonia uniformis*
- Eratmapodites*



Sylvatic cycle



Aedes aegypti
Aedes albopictus?

Epidemic cycle

First alert: Yap Island in 2007

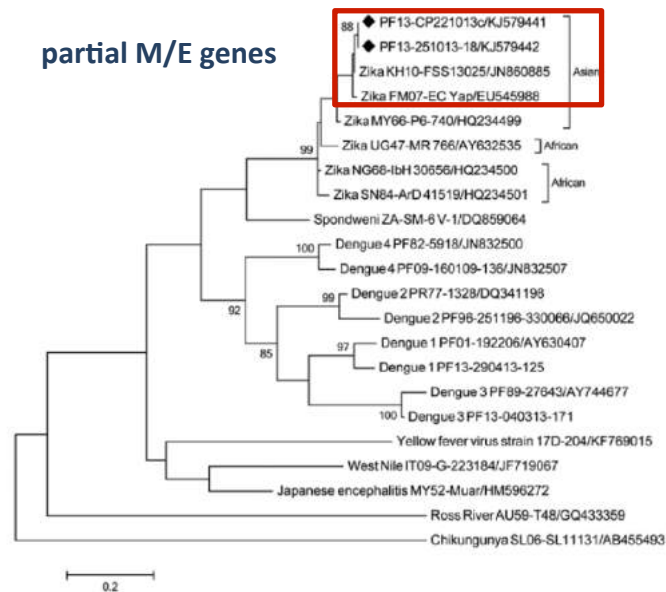


Aedes hensilli is the main vector

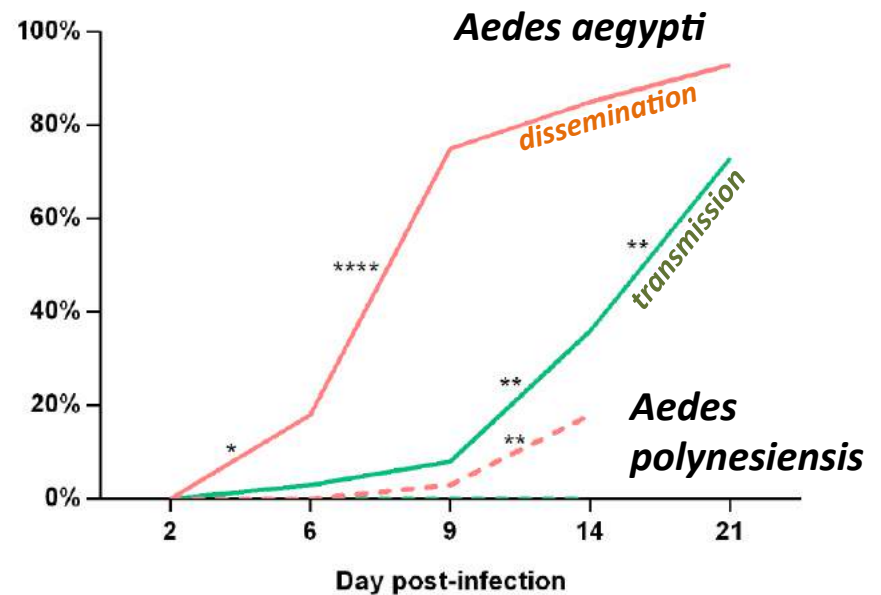
Virus (Strain)	Rep.	Titer (log ₁₀ pfu/mL)	% infection (n)	
			Body	Head
Zika (MR766)	1	4.9	7.1 (14)	0 (1)
	2	5.7	80.0 (20)	12.5 (16)
	3	5.9	86.1 (36)	22.6 (31)
DENV-2 (TR1751)	1	5.3	20.7 (29)	16.7 (6)
DENV-2 (Jam1409)	1	5.5	0 (20)	0
CHIKV (COM 125)	1	5.7	62.5 (32)	80.0(20)

Ledermann et al. *PLoS Negl. Trop. Dis.* (2014)

French Polynesia in 2013



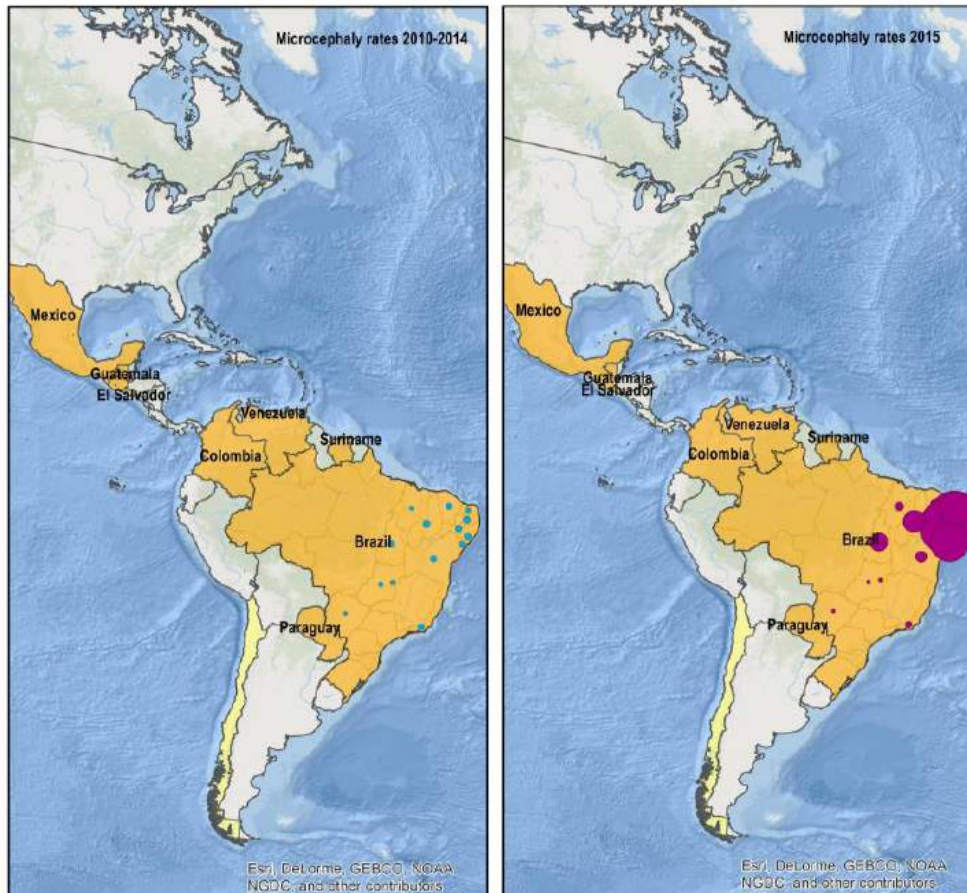
Cao-Lormeau et al. *Emerg Infect Dis* (2014)



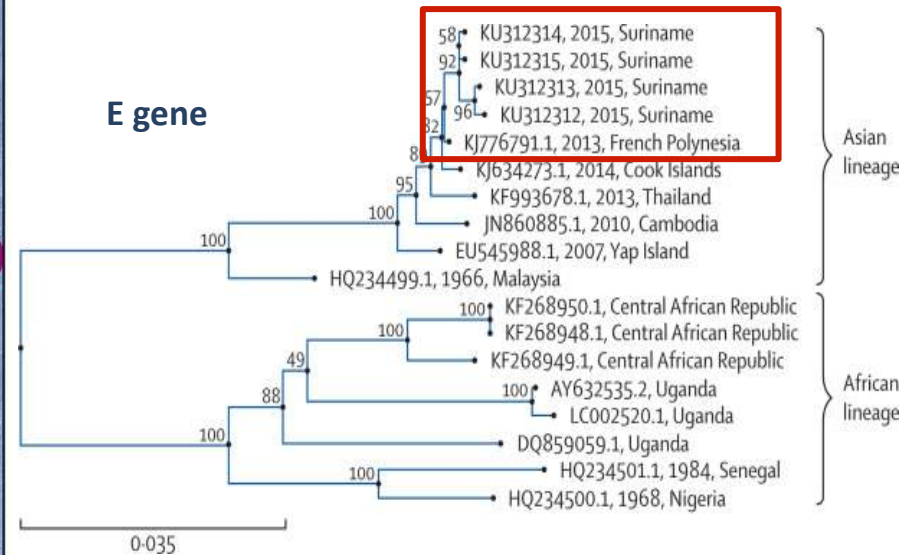
Richard et al. *PLoS Negl Trop Dis* (2014)

28,000 cases, ~11 % of the population (270,000; 67 islands)

May 15 2015: first cases in Brazil



- > 2 million cases
- 50 American countries



ZIKV detected in field mosquitoes

Rio de Janeiro (Brazil)

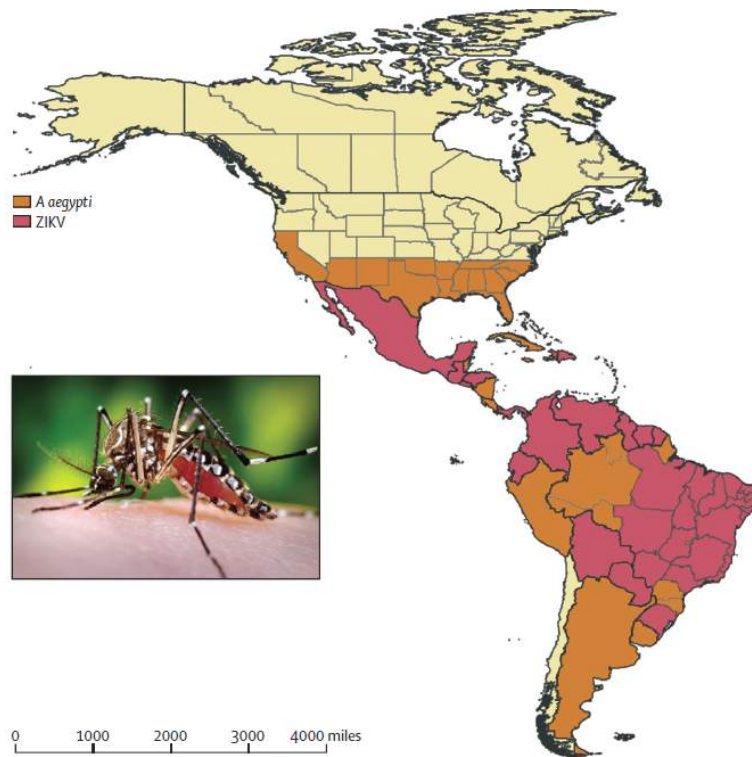
June 2015 – May 2016

1,683 mosquitoes captured (720 ♀ + 963 ♂)

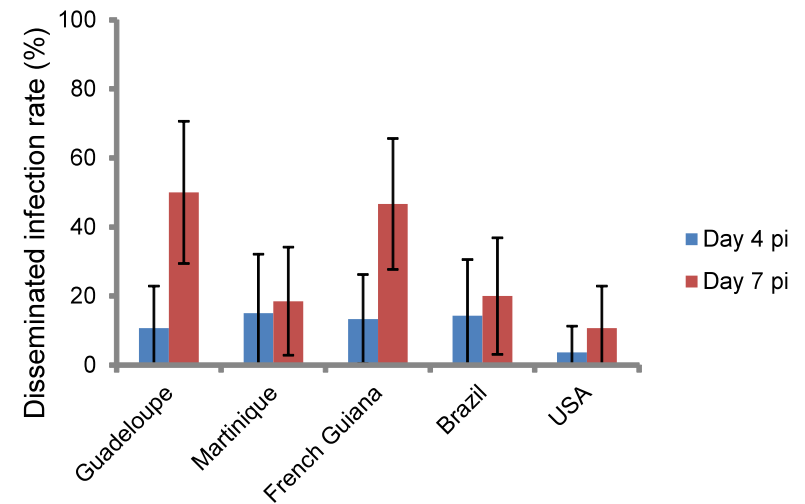
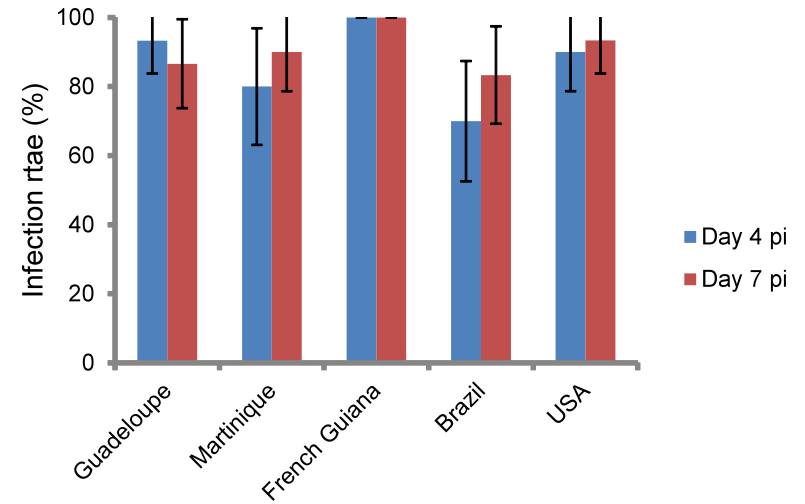
Mosquito species	Number captured	♀ / ♂	ZIKV-infected pools
<i>Aedes aegypti</i>	550	315 ♀	2
		235 ♂	1
<i>Aedes albopictus</i>	26	20 ♀	0
		6 ♂	0
<i>Culex quinquefasciatus</i>	1107	385 ♀	0
		722 ♂	0

Ferreira-de-Brito et al. *Mem Inst Oswaldo Cruz* (2016)

Aedes aegypti and ZIKV

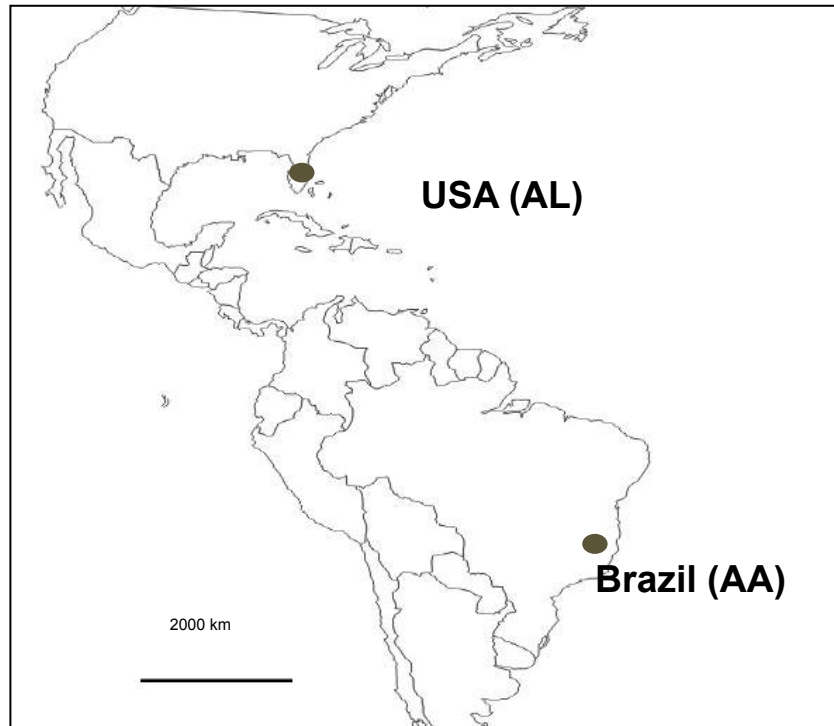


Yakob & Walker. *Lancet Glob Health* (2016)

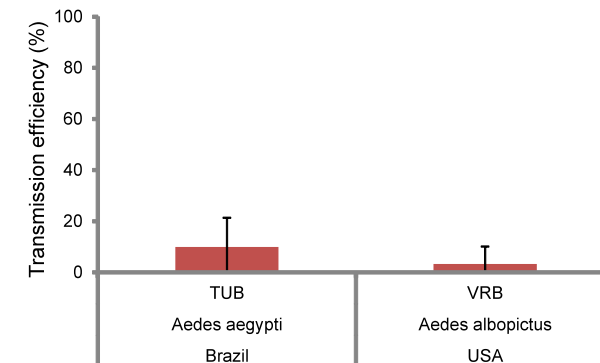
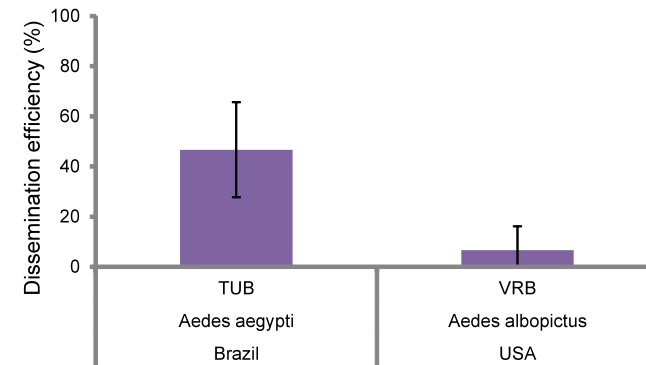
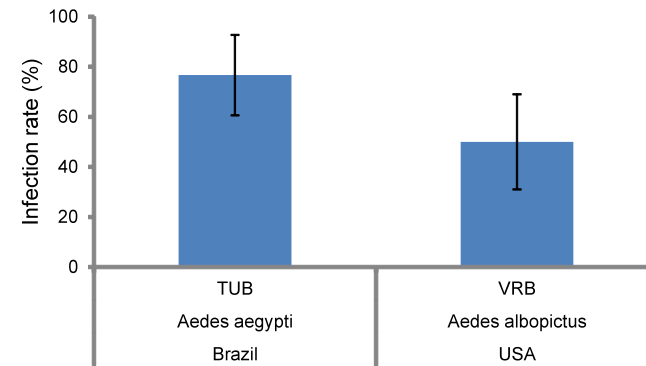


Chouin-Carneiro et al. *PLoS Negl Trop Dis* (2016)

Aedes aegypti and *Aedes albopictus*



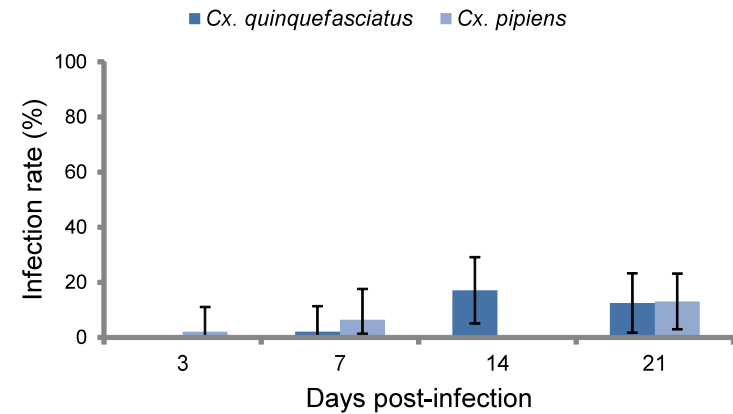
Chouin-Carneiro et al. *PLoS Negl Trop Dis* (2016)



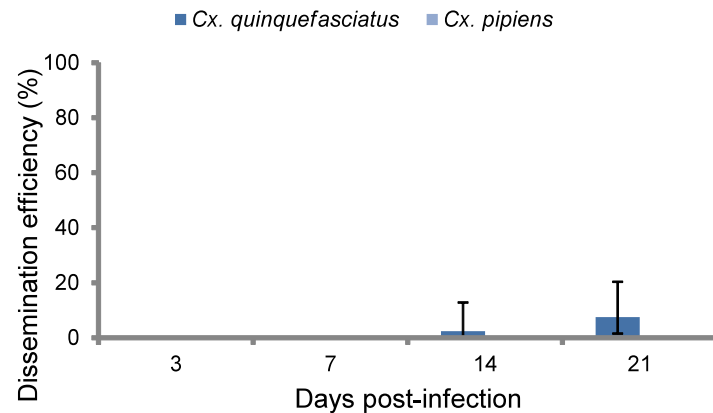
Cx. pipiens complex and ZIKV



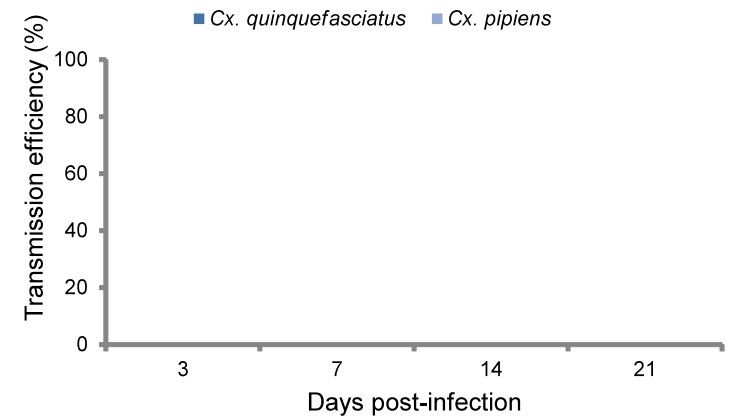
Infection



Dissemination



Transmission



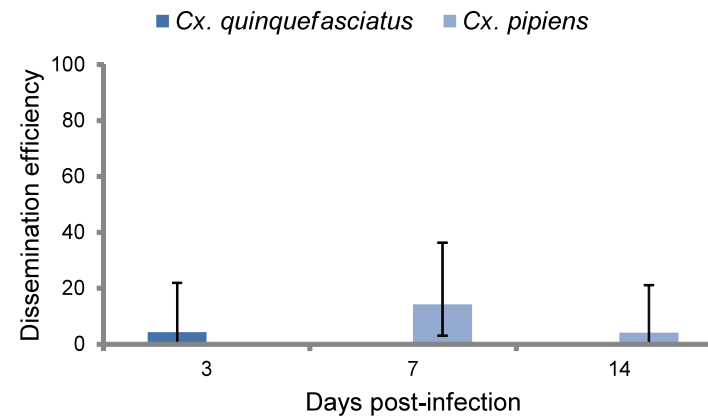
No transmission by *Culex spp.*

Intra-thoracic inoculation

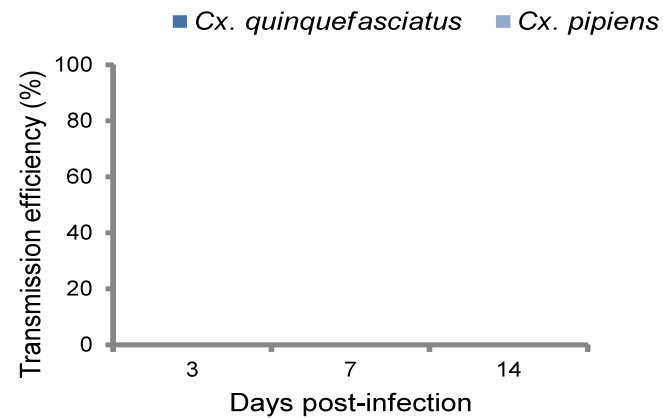


~2500 viral particles

Head



Saliva



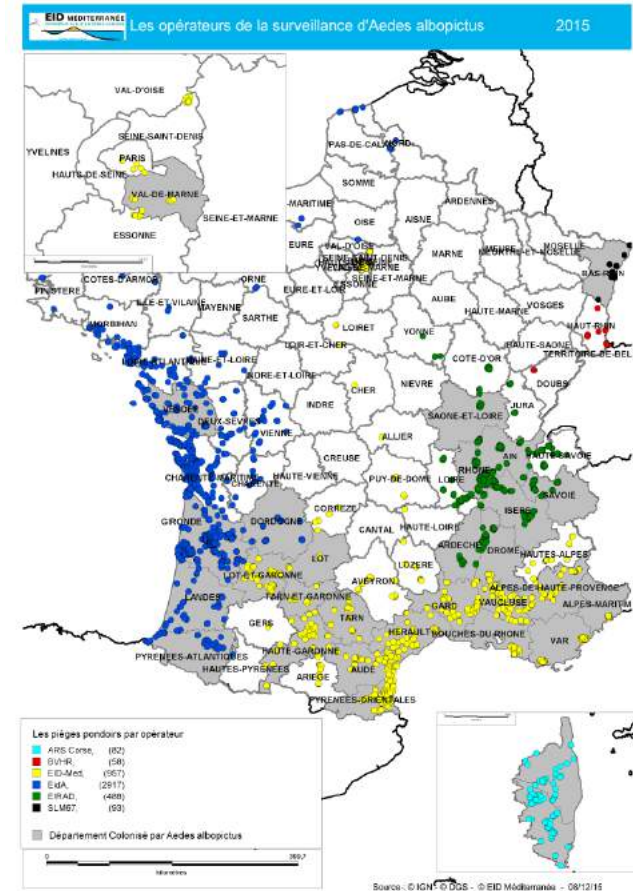
Aedes albopictus in Europe

20 countries

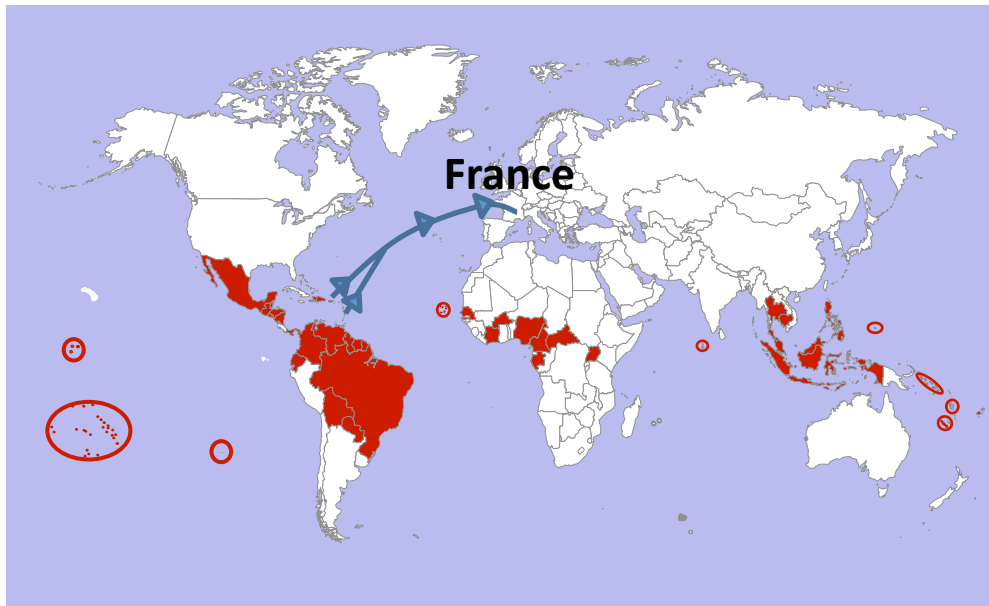


Medlock et al. VBZD (2012)

30 departments



Risk for Europe (1)

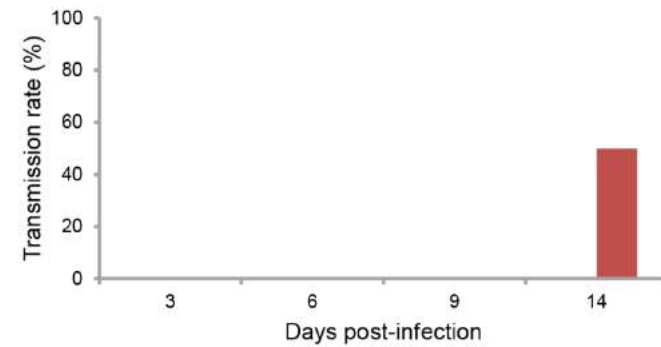
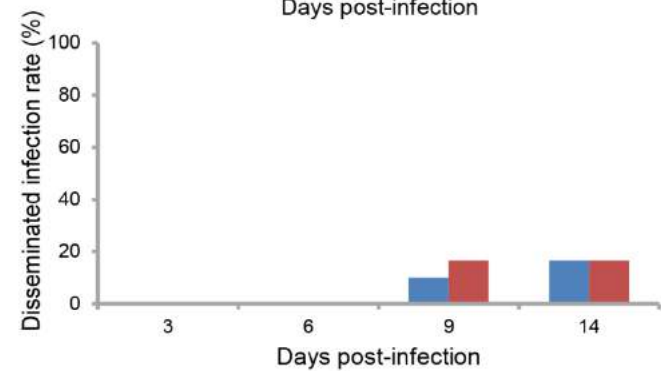
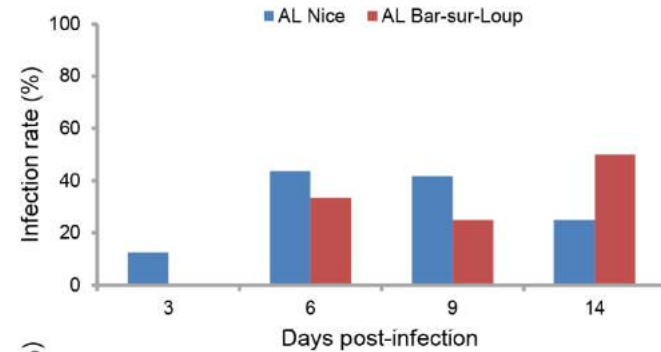


French Overseas departments

Guadeloupe

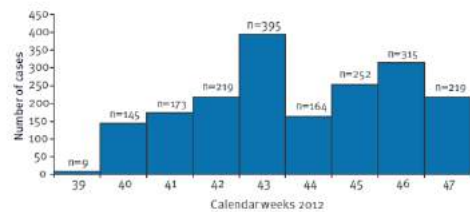
Martinique

French Guiana



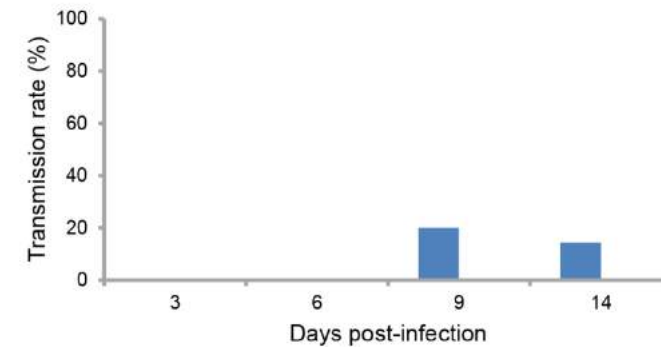
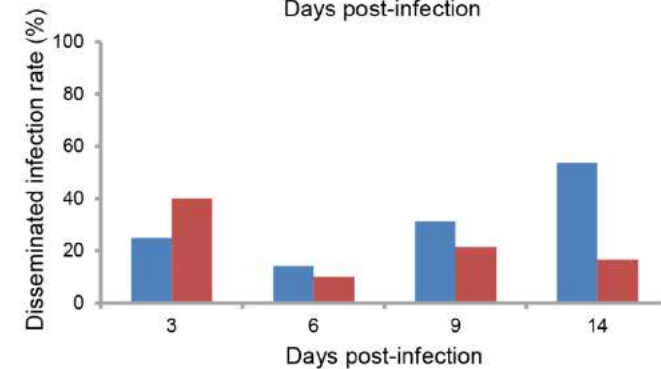
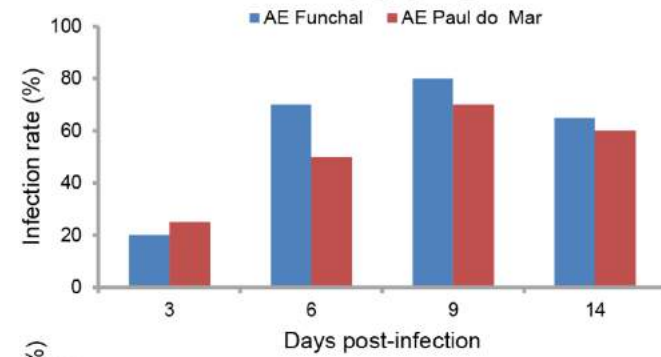
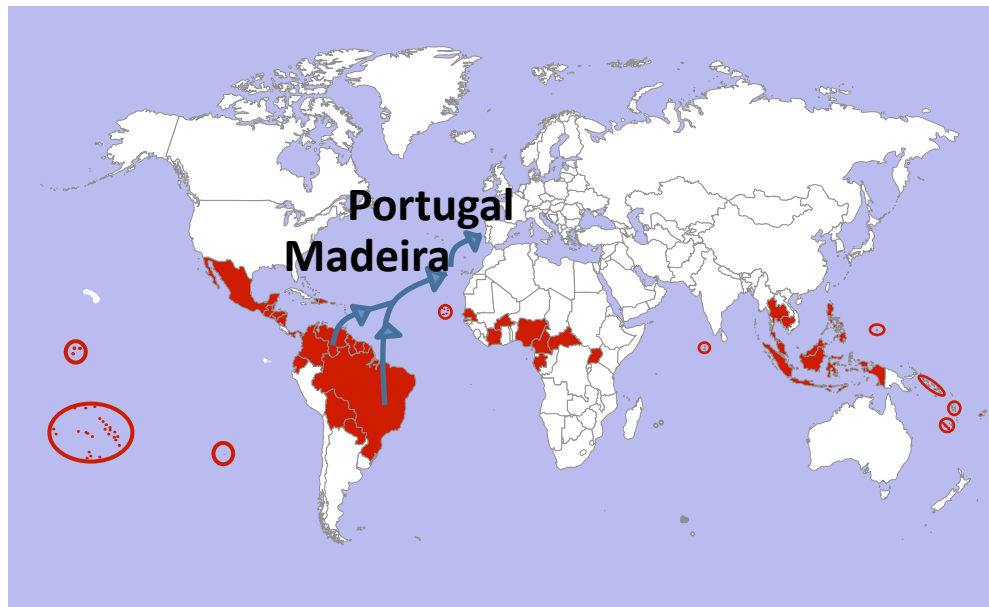
Risk for Europe (2)

Aedes aegypti introduced in Madeira in 2005



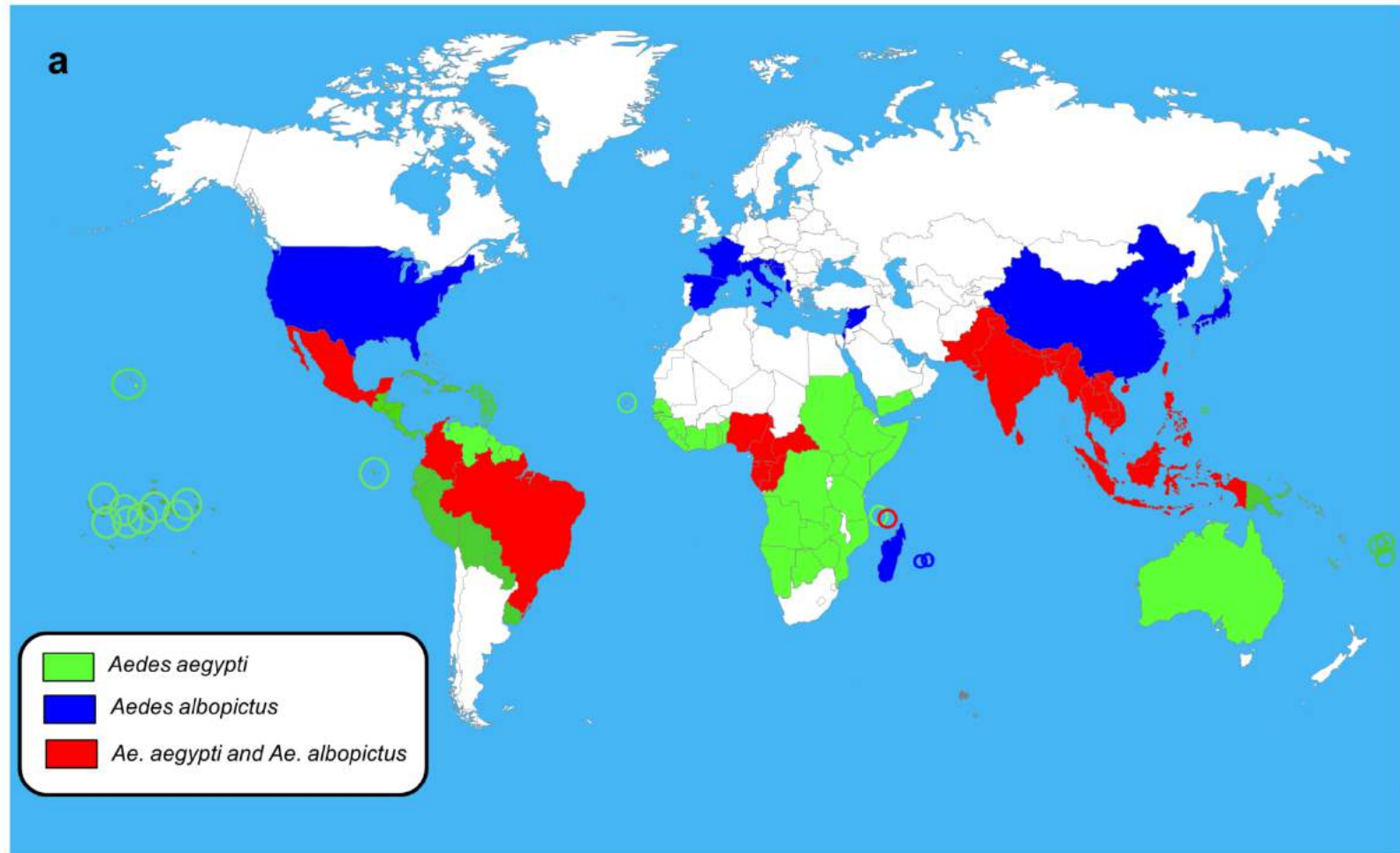
2012:
1891 DENV-1 cases

Sousa et al. *Euro Surveill* (2012)



Jupille et al. *PLoS Negl Trop Dis* (2016)

Same vectors



Zouache and Failloux. *Curr Opin Insect Sci* (2015)

Co-infections

New Caledonia (2014)

Co-circulation of DENV-1, DENV-3, ZIKV

→ 2 co-infected people

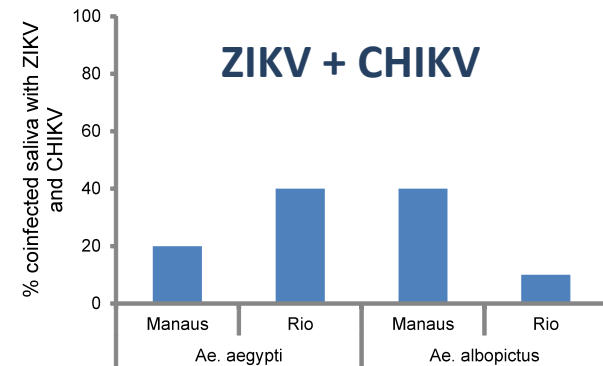
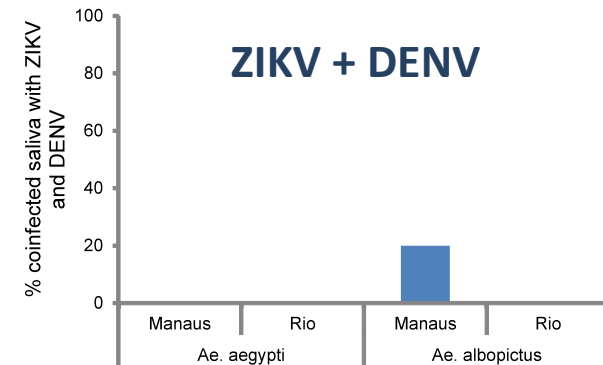
Dupont Rouzeyrol et al. *Emerg Inf Dis* (2015)

Colombia (2015)

Co-circulation of DENV, CHIKV and ZIKV





→ 1 patient infected with 3 viruses

Villamil-Gómez *J Infect Public Health* (2015)



Chouin-Carneiro et al. (unpublished Data)

The future of VBD

	Volume	Number	
Type			Duration
Conditions			Distance

Arboviruses and Insect Vectors

Department of Virology



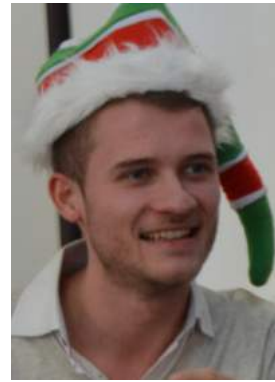
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