

Zika virus emergence in the Americas – A potential threat to Europe?



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Rome 19.04.2016

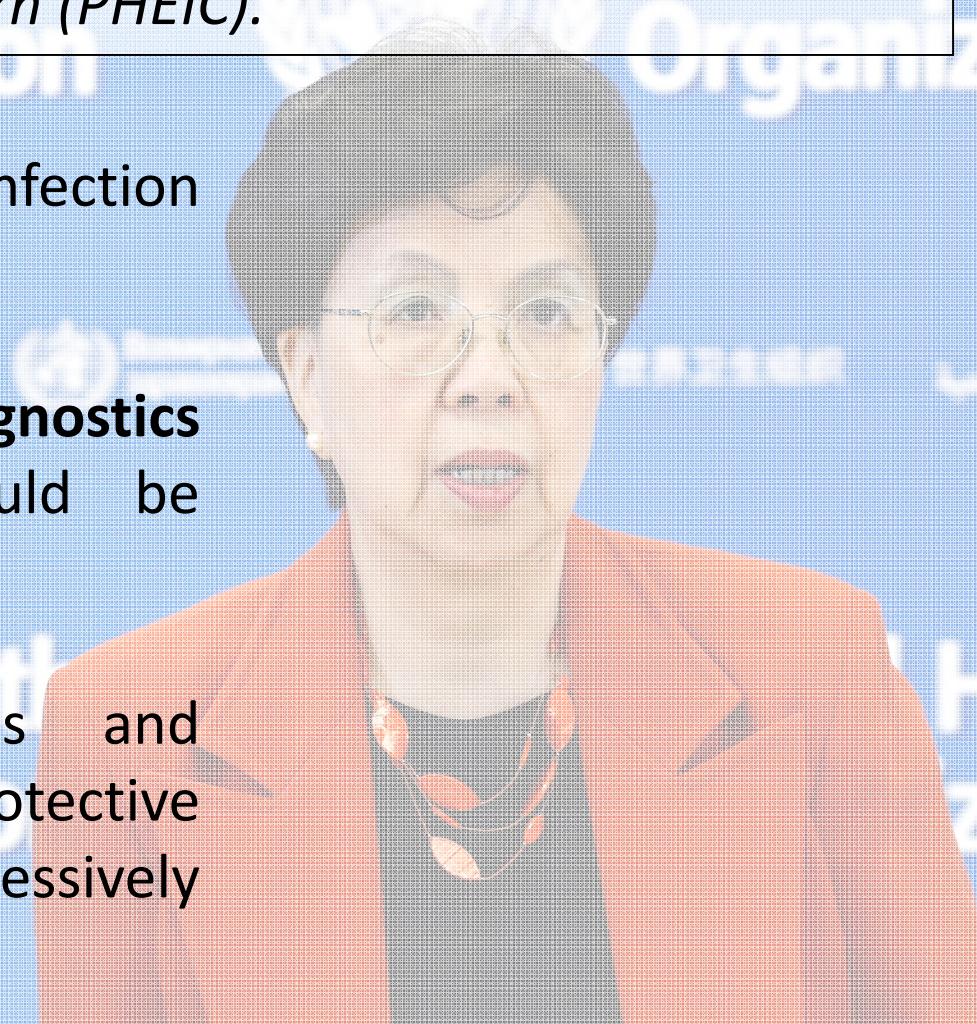
WHO statement, 1 February 2016

*"The Committee advised that the recent **cluster of microcephaly cases and other neurological disorders** reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a Public Health Emergency of International Concern (PHEIC)."*

I. **Surveillance** for Zika virus infection should be enhanced

II. The development of new **diagnostics** for Zika virus infection should be prioritized

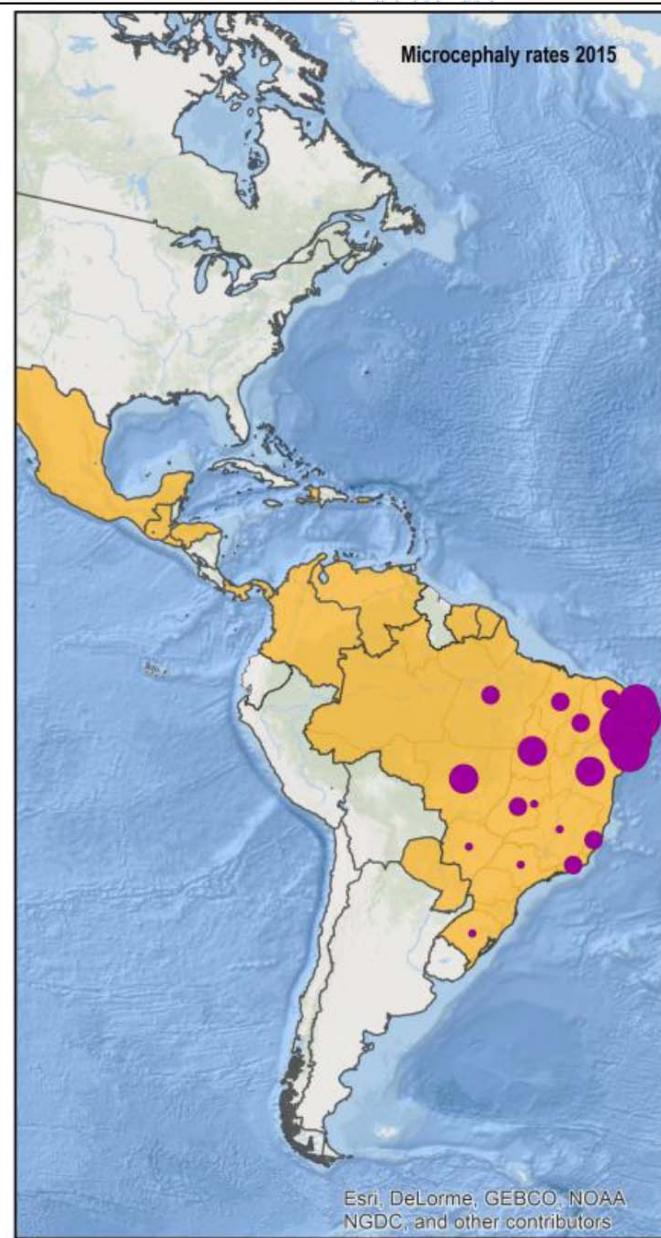
III. **Vector control** measures and appropriate personal protective measures should be aggressively promoted and implemented



Typical



Typical



Updated as of Epidemiological Week 52
(December 27 - January 2, 2015)

Microcephaly rates by state in Brazil
(cases per 1,000 live births)

- 0.1 - 1.0
- 1.1 - 15.0
- 15.1 - 30.0
- 30.1 - 45.0
- 45.1 - 88.6

Countries

Countries with Zika confirmed cases

- EW 52 2015
- Country limits
- Brazil state boundaries

Data Source:

Reported from the IHR National Focal Points
and through the Ministry of Health websites.

Map Production :

PAHO-WHO AD CHAIR ARO

Moderate Microcephaly

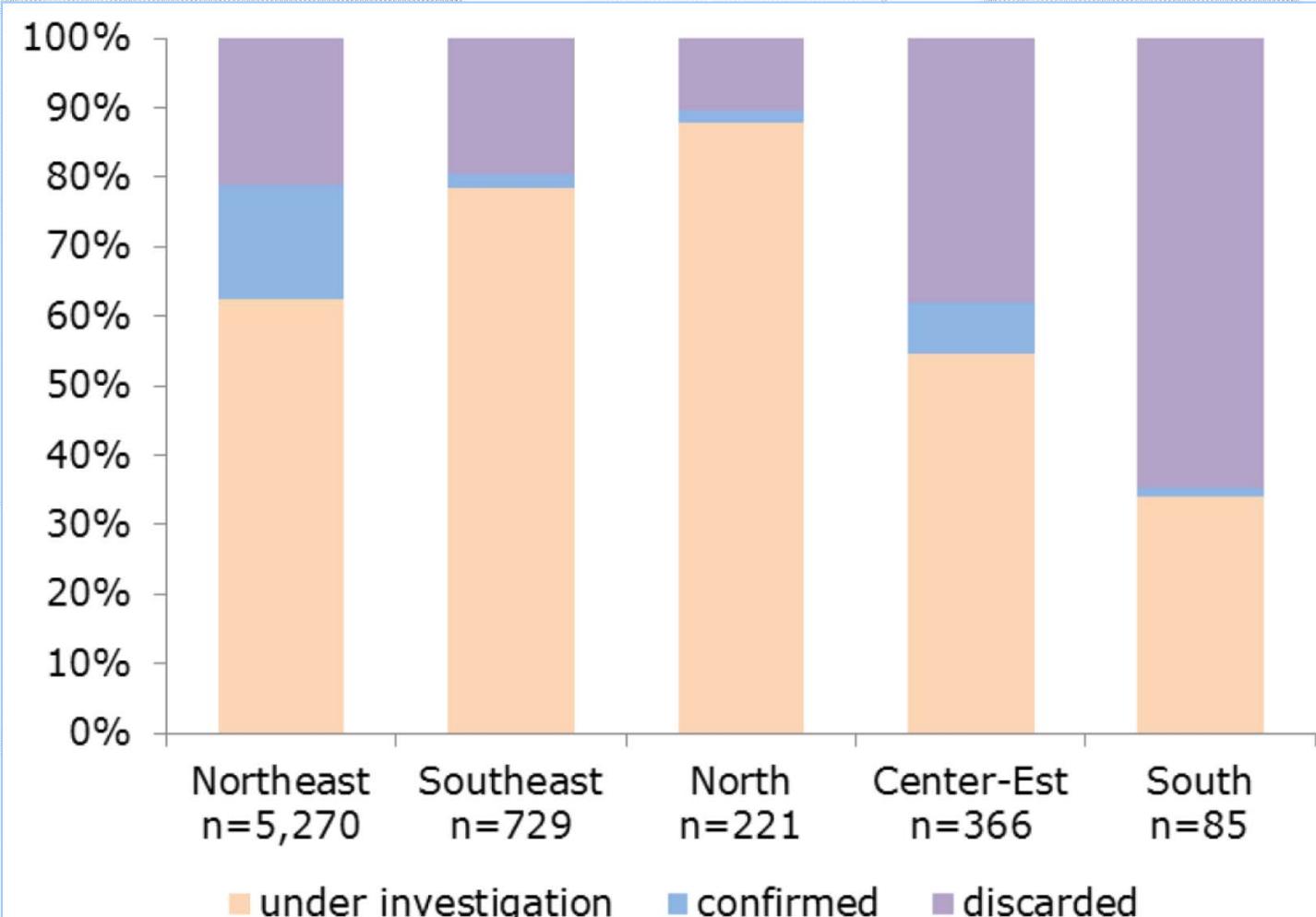
Microcephaly

The number of suspected microcephaly cases in Brazil relied on a screening test that had very low specificity and therefore overestimated the actual number of cases by including mostly normal children with small heads.

	Cutoffs	Specificity*	Sensitivity†	Estimated annual number of suspected cases (thousands)‡	
				Northeast Brazil	Brazil
Brazil's Ministry of Health ⁶ (up to Dec 8, 2015)	≤33 cm for term newborn babies of both sexes; -<2 SD of Fenton reference ⁷ by gestational age and sex for preterm babies	79.3%	92%	158	602
Brazil's Ministry of Health ⁸ (after Dec 8, 2015)	≤32 cm for term newborn babies of both sexes; -<2 SD of Fenton reference by gestational age and sex for preterm babies	93.8%	86%	46	178
Pan American Health Organization ⁹	<3rd percentile (WHO child growth standards ¹⁰) for term newborn babies (<31.6 cm for girls and 32.0 cm for boys) and of the Fenton or InterGrowth reference for preterm babies	96.1%	80%	29	114
Below -2 SD, InterGrowth standards ¹¹	-<2 SD (InterGrowth standards) for gestational age and sex, all newborns	97.8%	85%	18	63
Below -3 SD, InterGrowth standards ¹¹	-<3 SD (InterGrowth standards) for gestational age and sex, all newborns	99.9%	57%	0.8	3

*Based on applying the InterGrowth standards to the distribution of livebirths by gestational age in Brazil. †Preliminary results based on a case series of 31 newborn babies with radiological evidence of brain abnormalities. ‡Calculated on the basis of sensitivity and the gestational age distribution of Brazilian newborn babies.

907 confirmed cases of microcephaly or other nervous system malformation among newborns have been reported in Brazil since 22 October 2015.

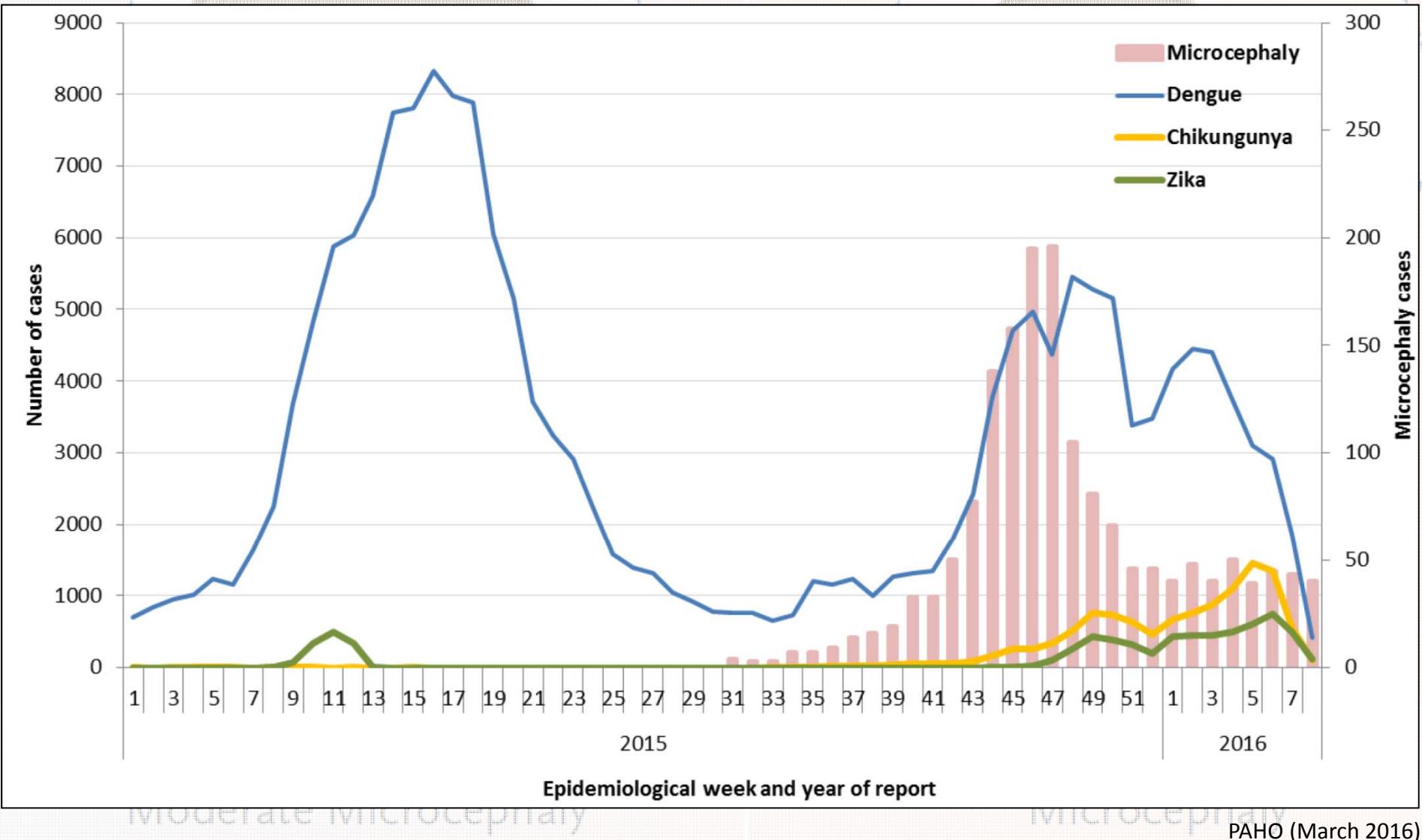


Moderate Microcephaly

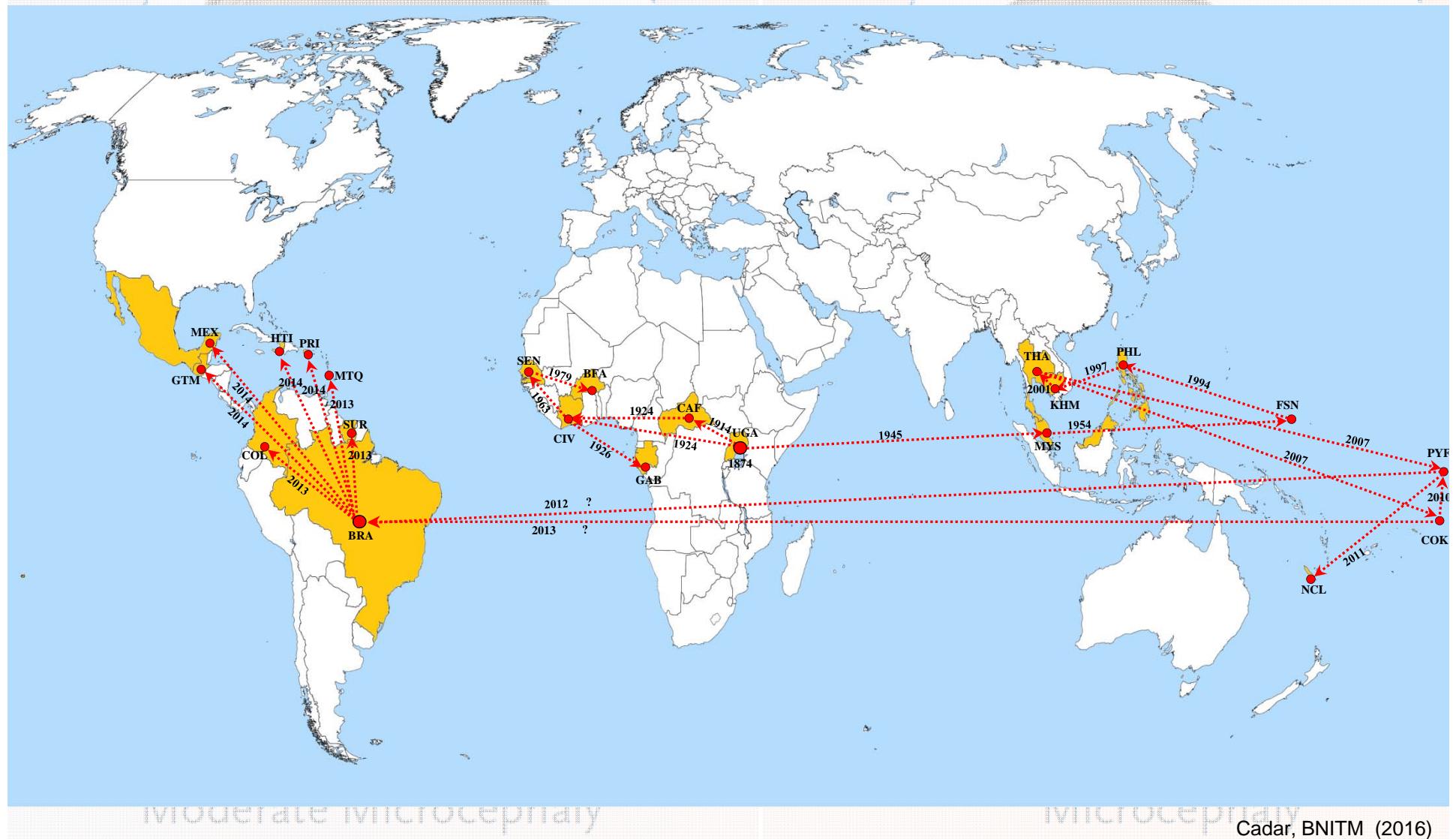
Microcephaly

PAHO (March 2016)

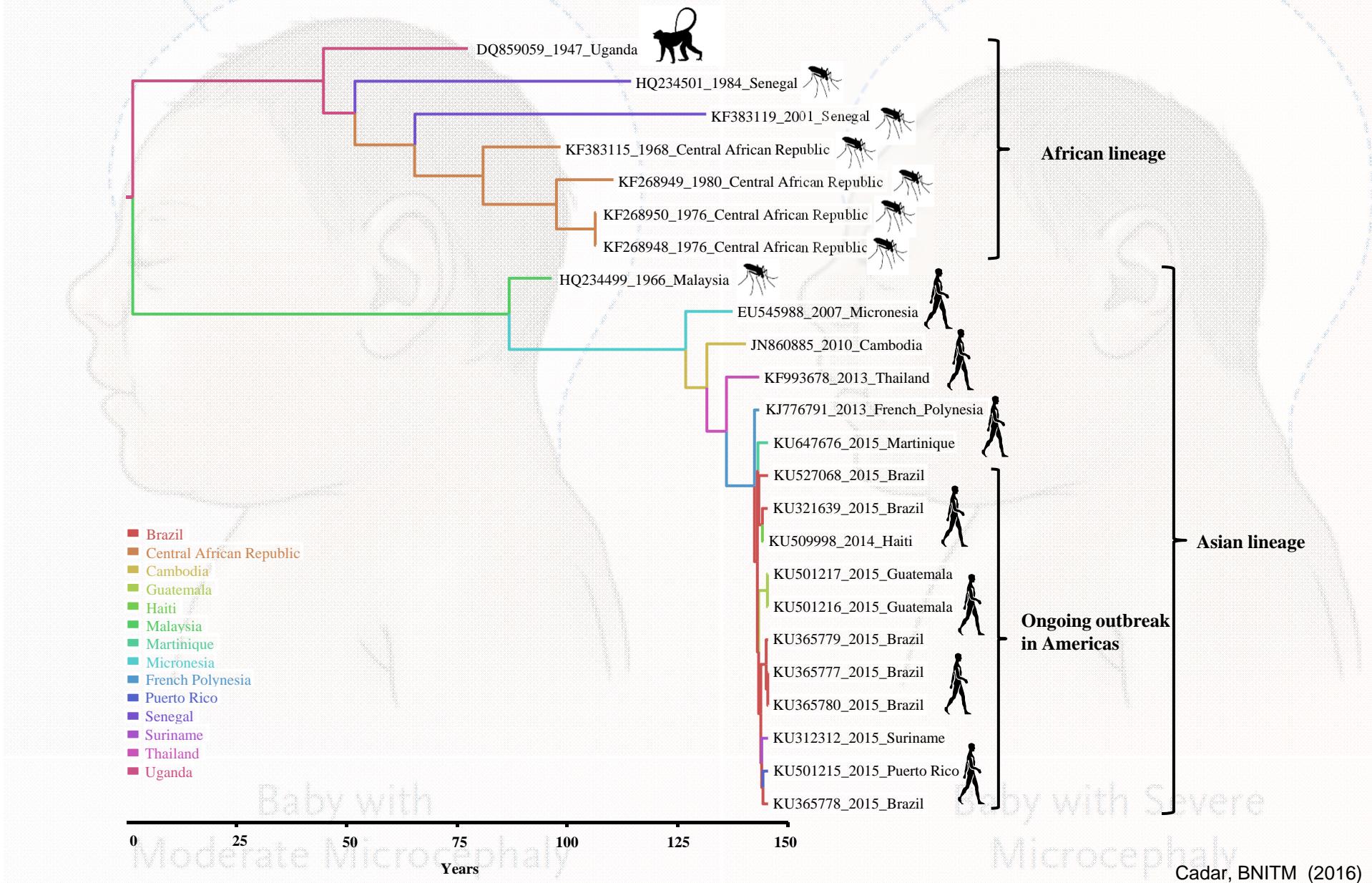
The increases of microcephaly cases in Pernambuco state, Brazil were registered 7-8 months after the first detection of Zika virus cases.



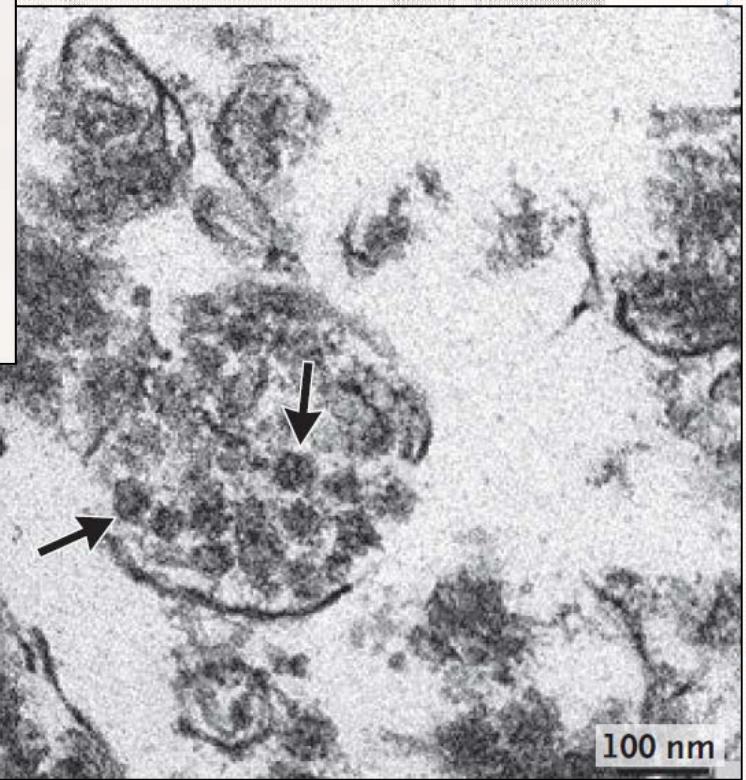
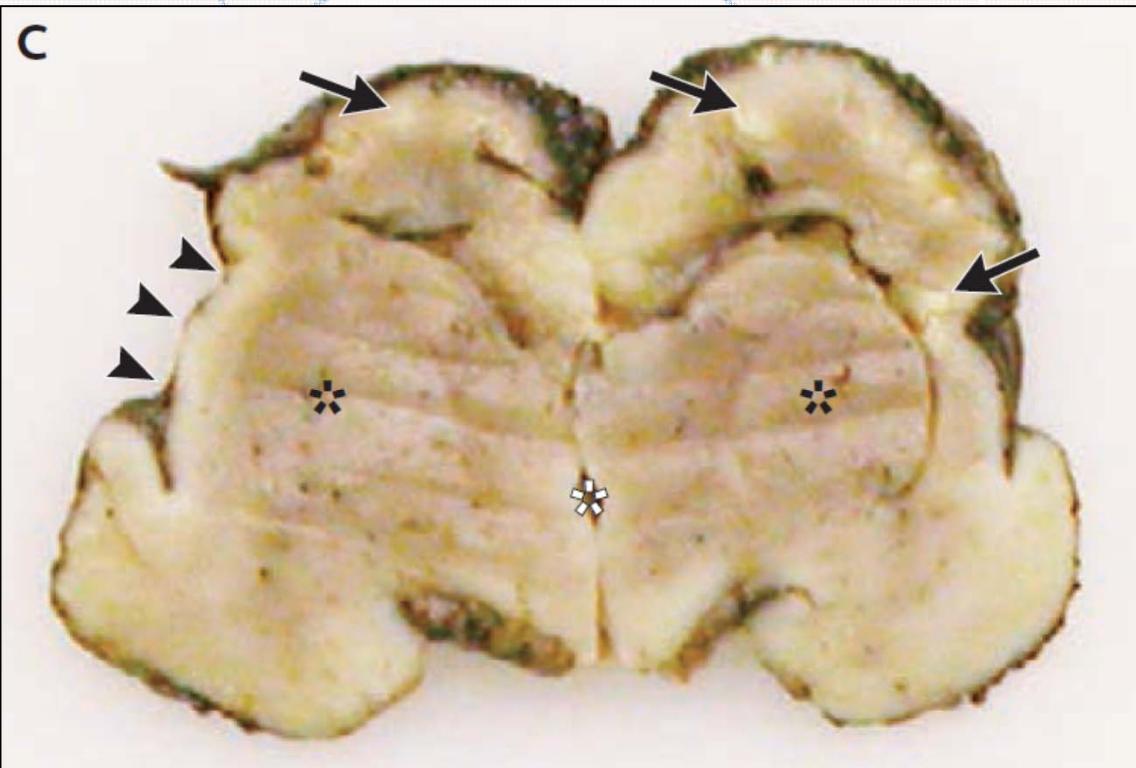
Spatiotemporal spread pattern of Zika virus based on analysis of NS5, envelope, and complete genome sequences demonstrates recent introduction into Brazil.



So far, two genetic lineages are described : the African and the Asian lineage of Zika virus.



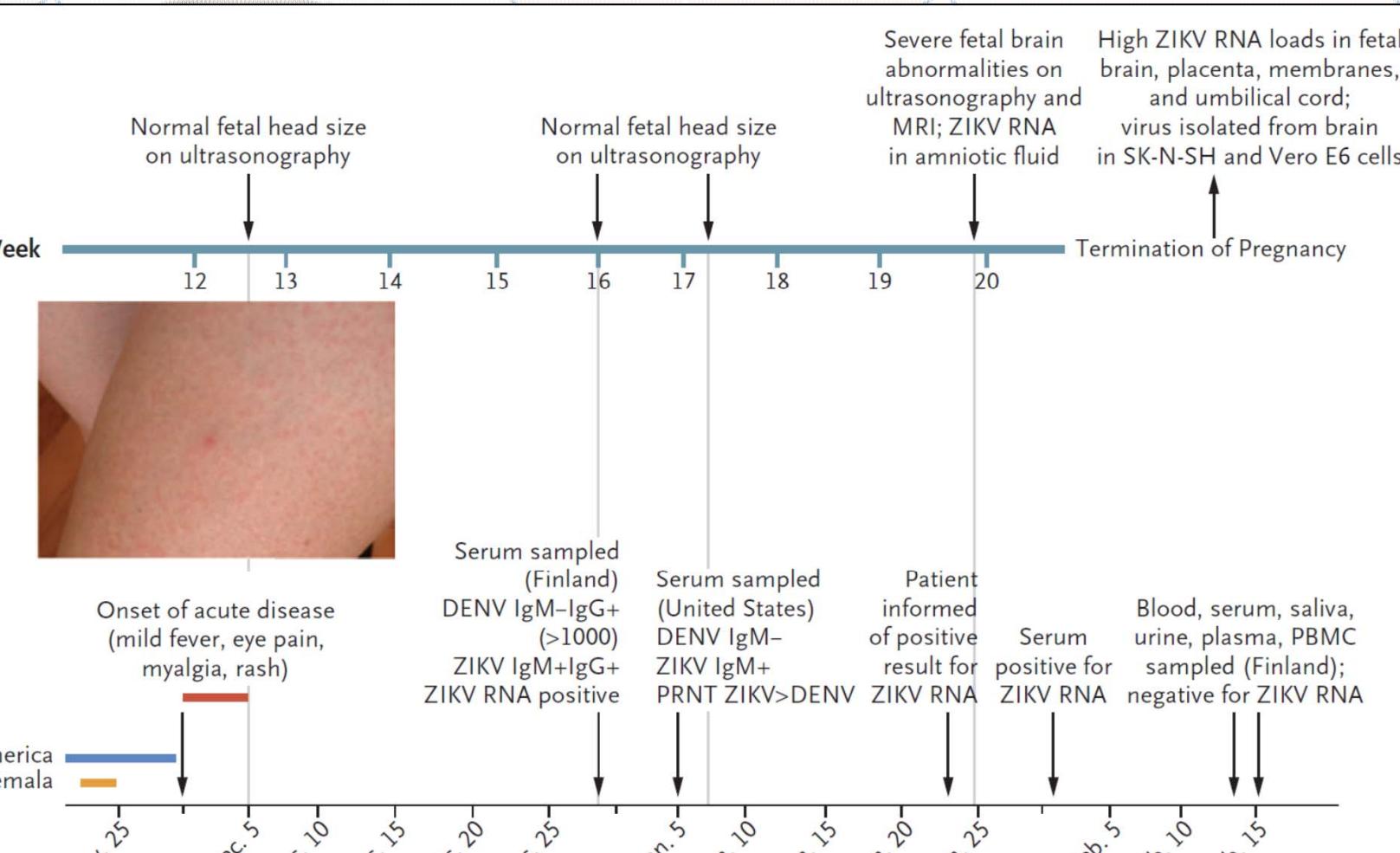
Congenital Zika virus infection and microcephaly



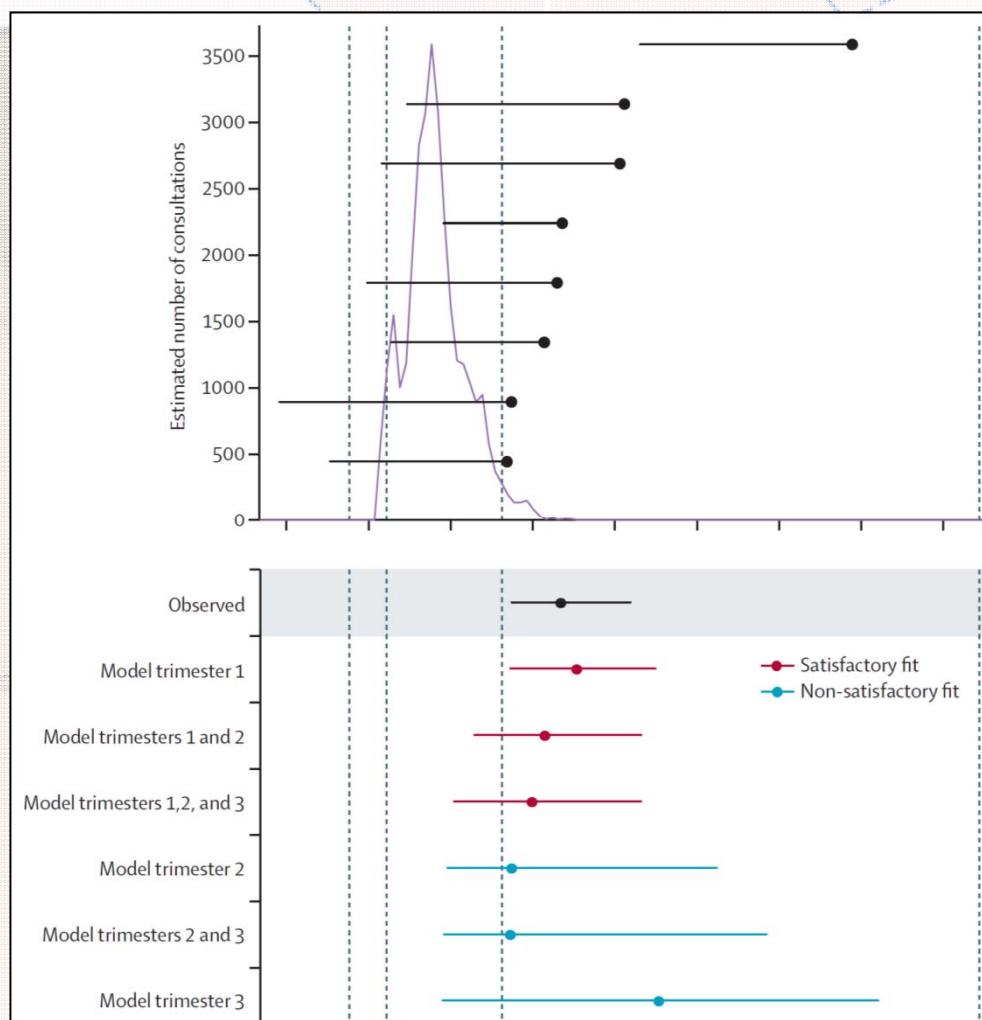
Baby with
Moderate Microcephaly

Microcephaly
Mlakar et al. (2016) NEJM

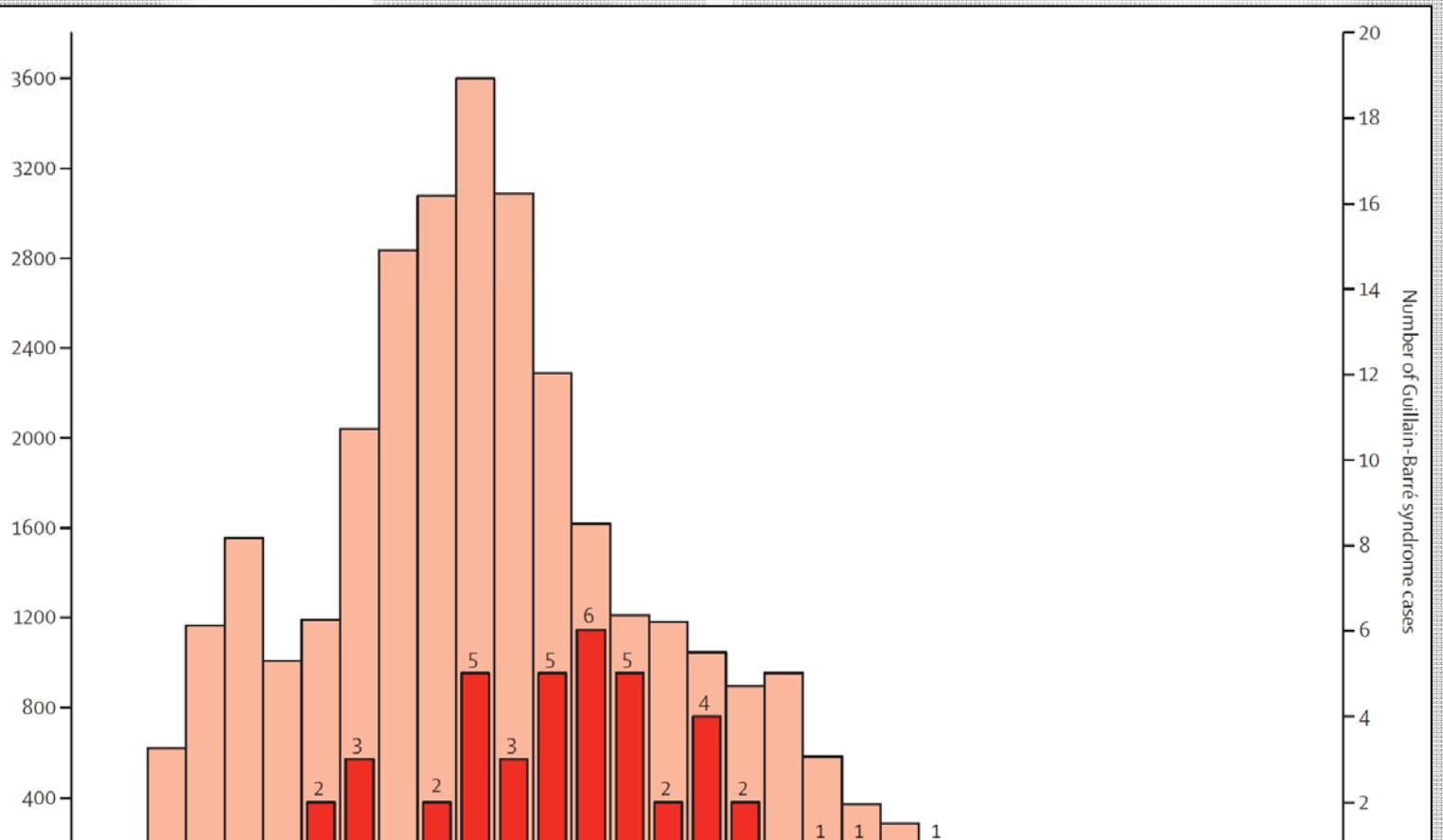
Genital Zika virus infection and fetal brain damage



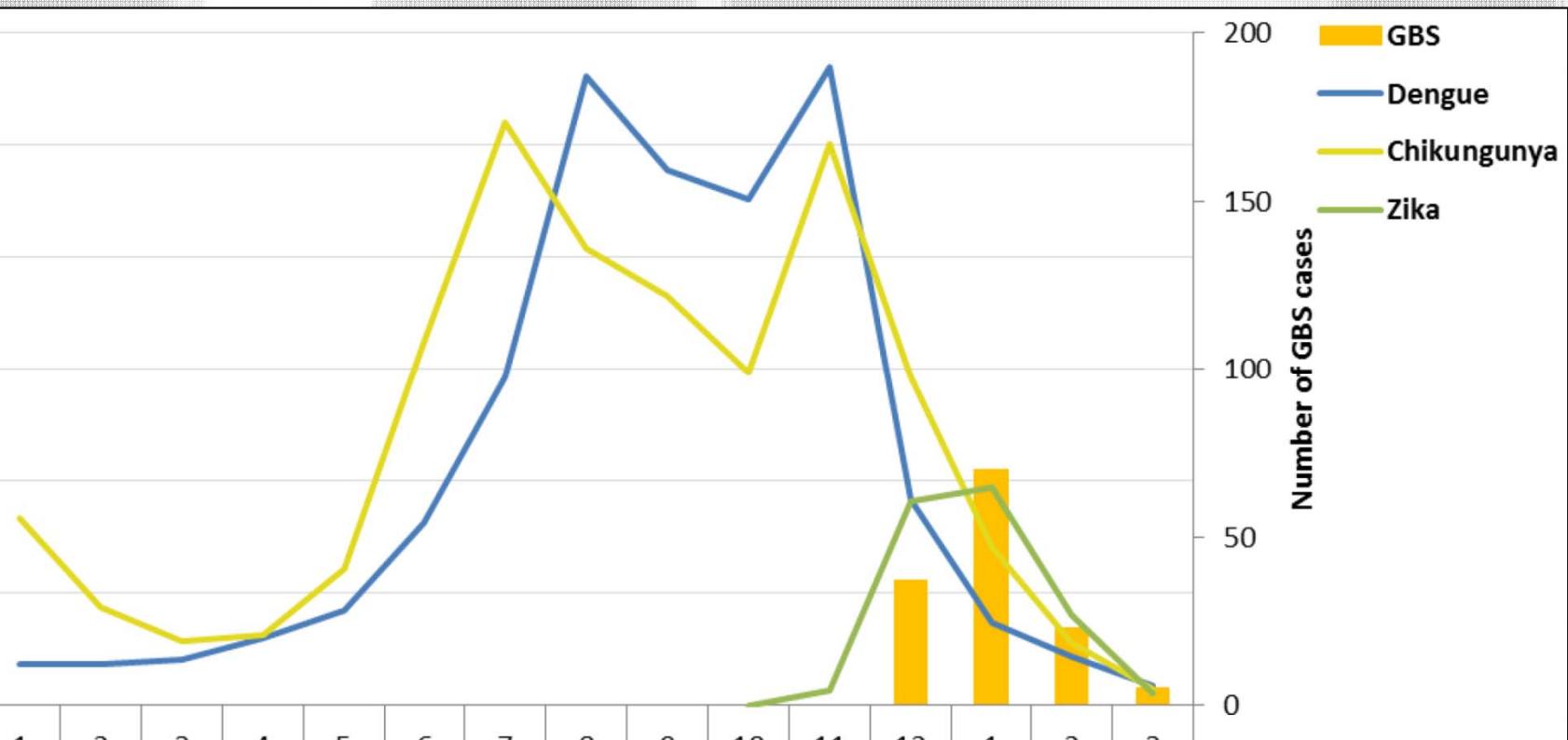
Risk of microcephaly increases to about 1% when mothers are infected with Zika virus during the first trimester of pregnancy.



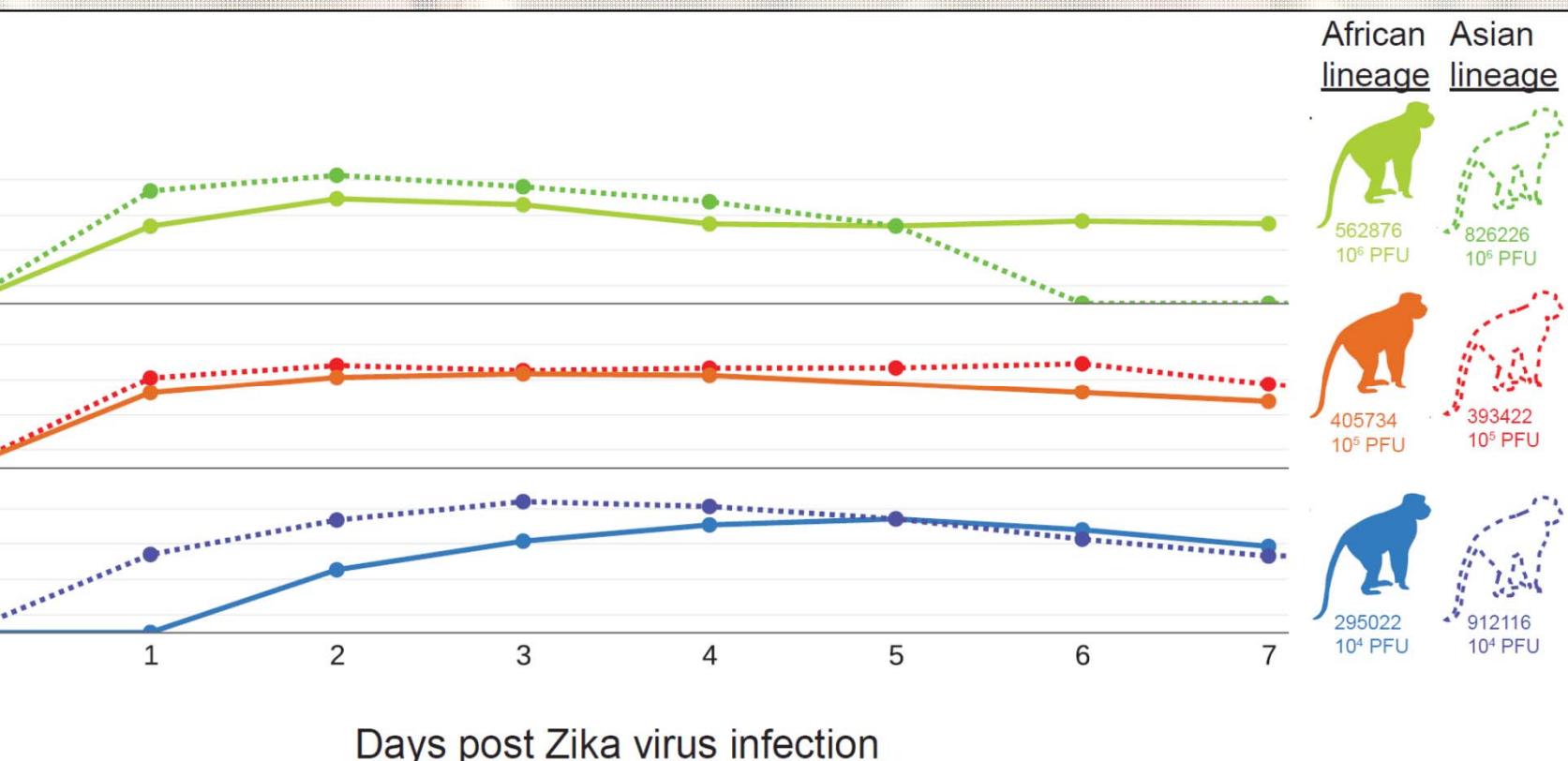
The incidence of Guillain-Barré syndrome cases during the French Polynesian outbreak was estimated to be 0.24 per 1000 Zika virus infections.



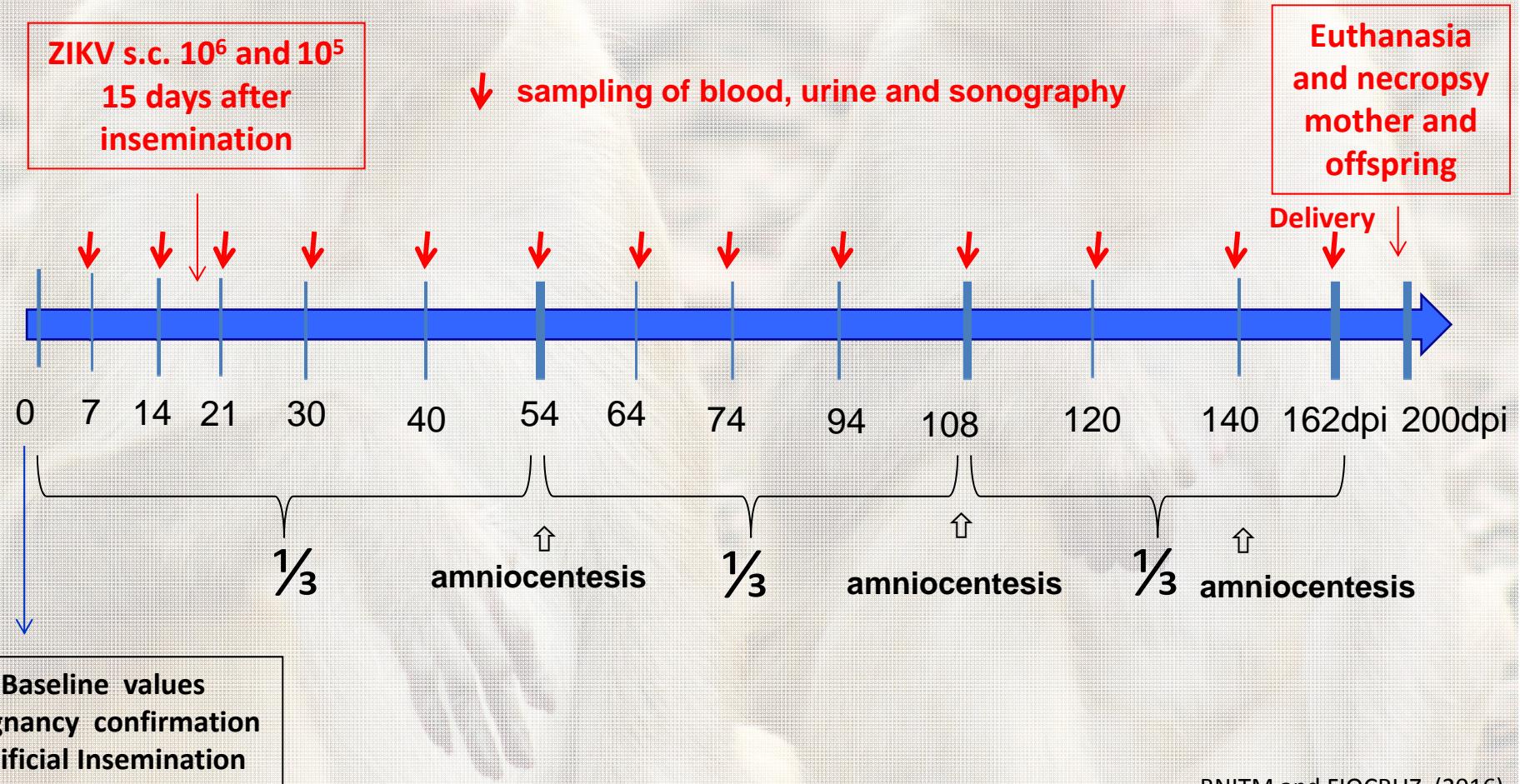
The geographic distribution of GBS cases in El Salvador indicates that there is a spatial and temporal association with Zika virus cases.



HPs, African lineage of Zika virus achieved peak plasma at least one order of magnitude lower those observed in animals infected with the Asian lineage of Zika virus.



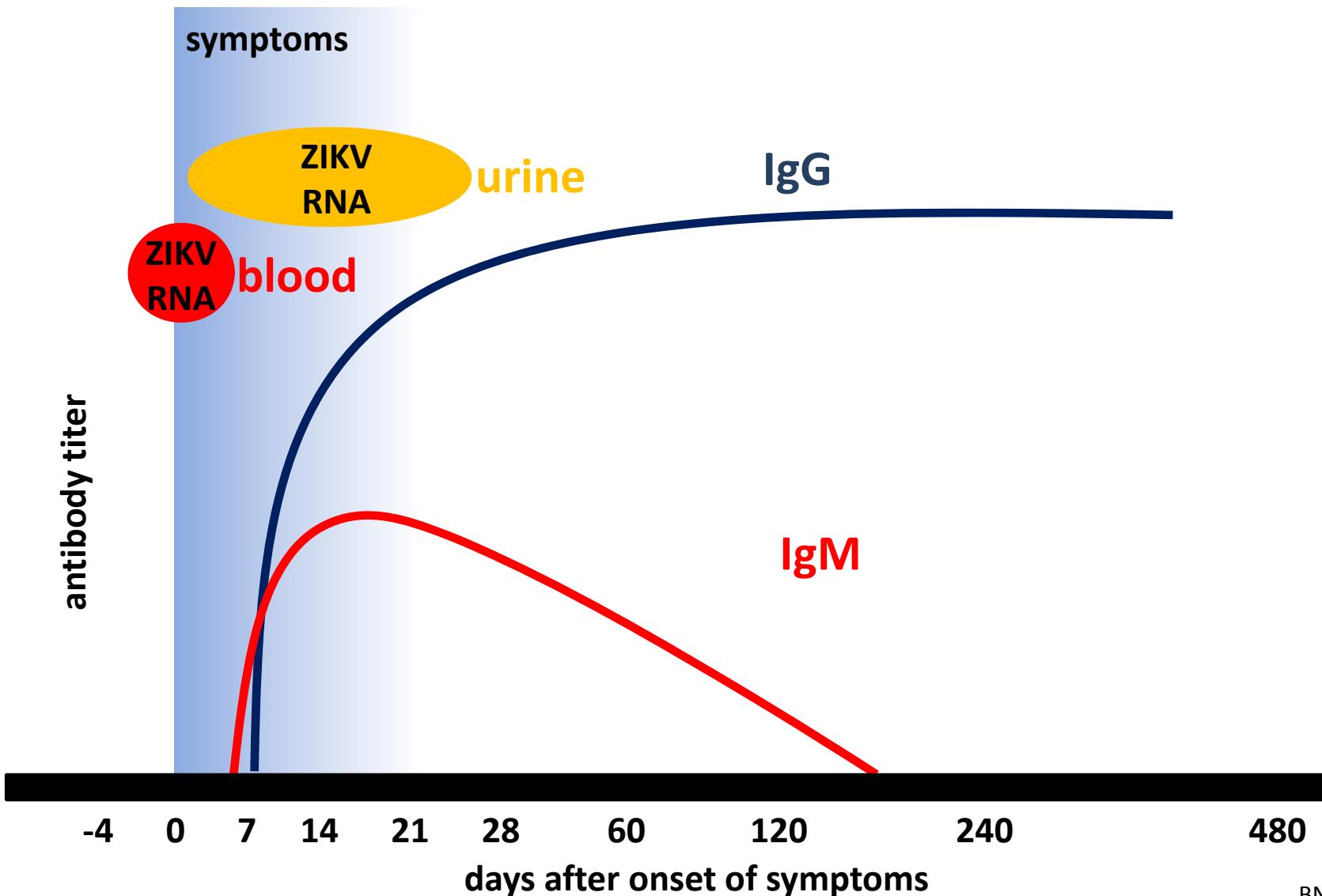
Twenty-two pregnant NHPs with and without pre-existing anti-dengue immunity will be inoculated with low passage Asian and African lineage of Zika virus 15 days after insemination and monitored for birth defects.



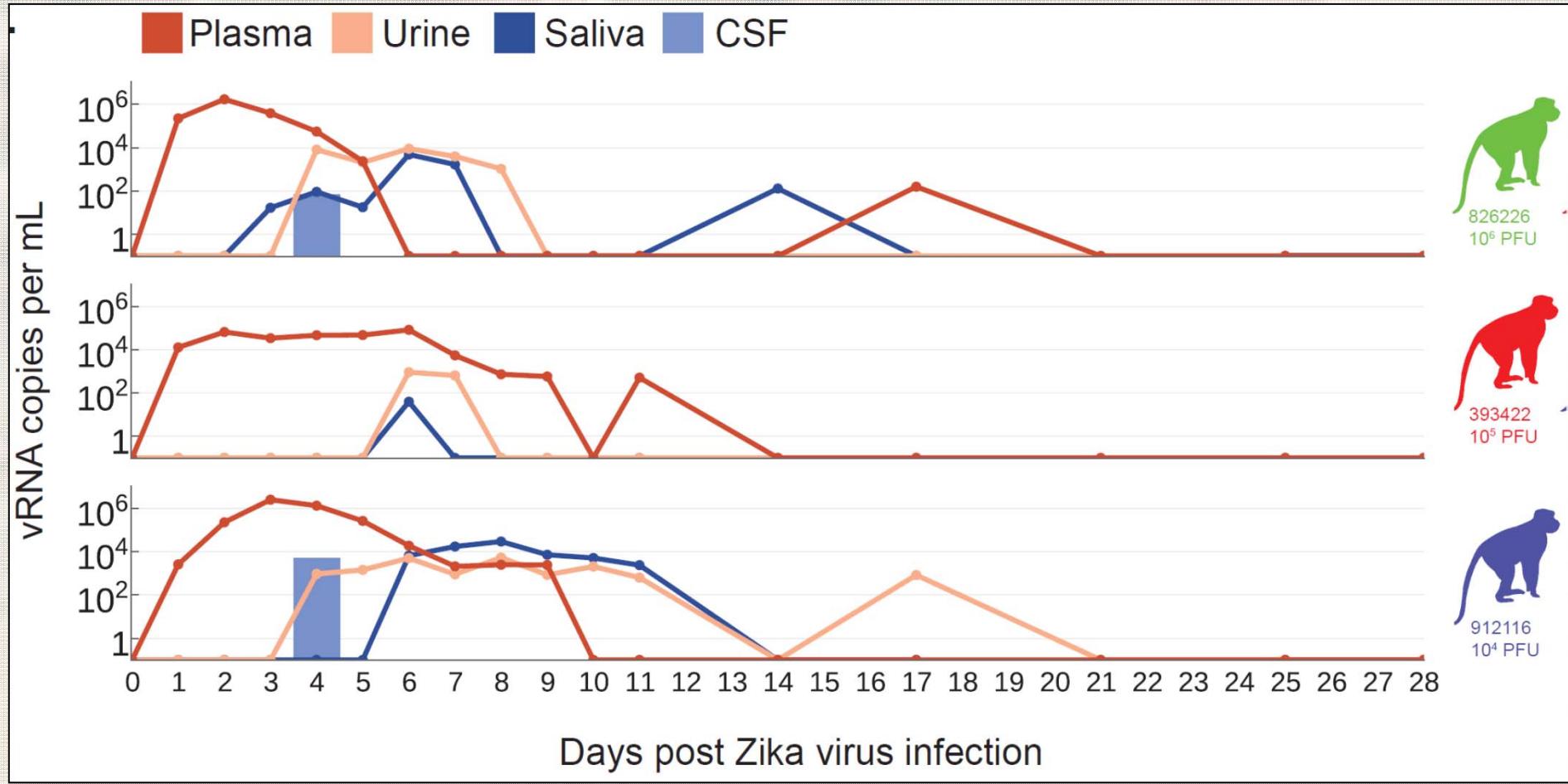
Urgent questions / tasks

- Does the observed association of Zika virus infection with microcephaly and GBS simply reflect an increased incidence of infection or is it the result from a change in virulence or is it caused by co-factors?
- Will Zika virus become endemic and an enzootic transmission cycle develop in the Americas ?

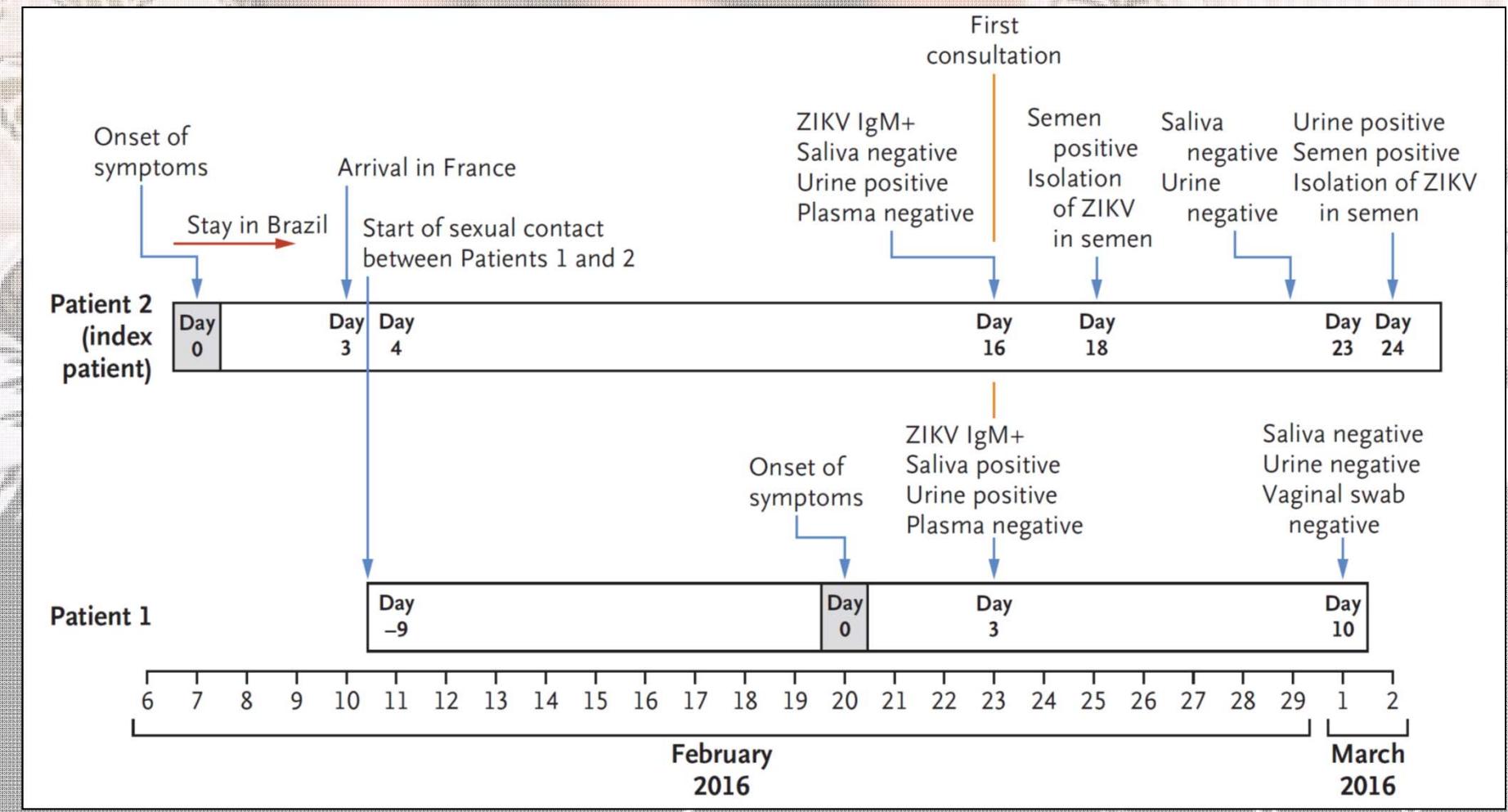
Course of Zika virus diagnostic parameters in flavivirus-naive individuals.



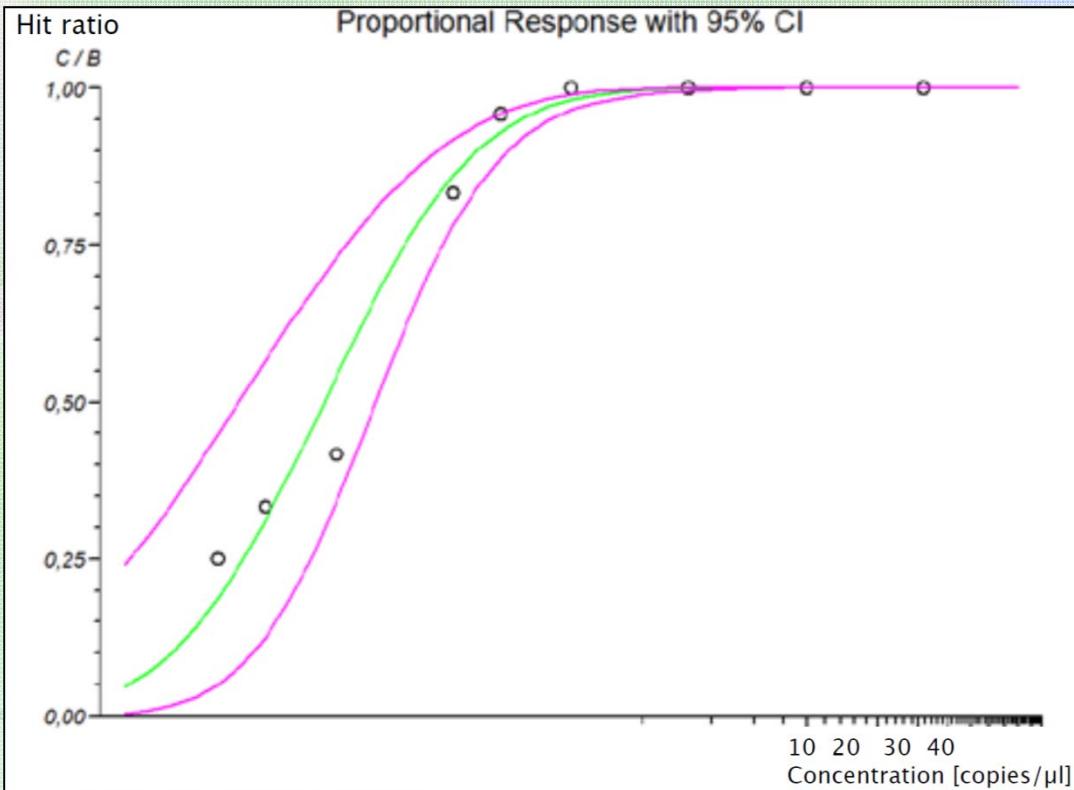
In NHPs, prolonged detection of viral RNA in urine and saliva after clearance from the blood was demonstrated.



There is growing evidence of sexual transmission of Zika virus.



Development and evaluation of specific and sensitive CE-IVD marked real-time PCR test kits for Zika virus detection:

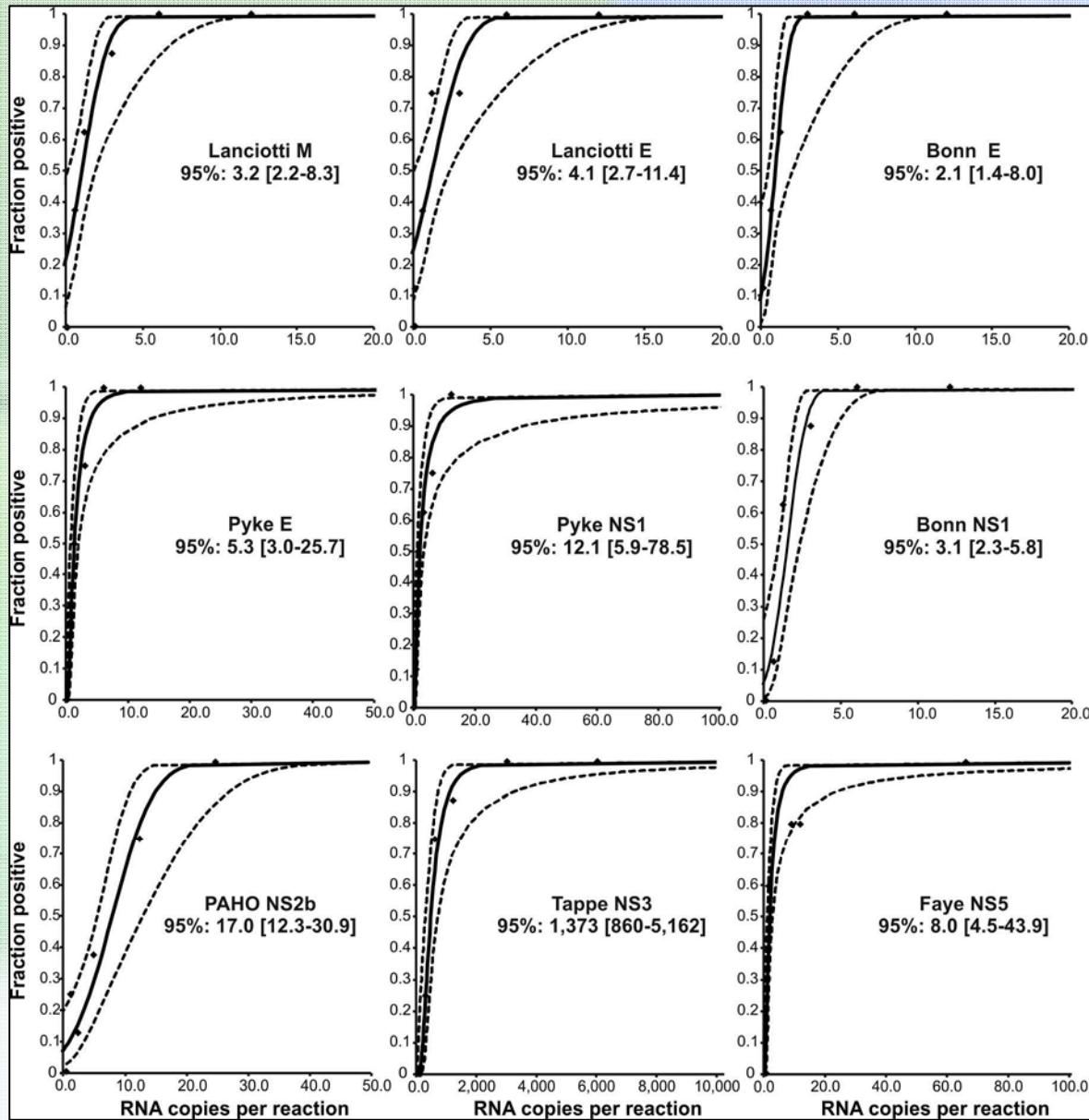


The limit of detection for Zika virus using the RealStar® Zika Virus RT-PCR Kit 1.0 is 0.61 copies/ μ l (95% confidence interval 0.39 to 1.27 copies/ μ l).

Organisms	RealStar® Zika Virus RT-PCR Kit 1.0	
	FAM Channel (Zika virus)	JOE Channel (Internal Control)
Japanese encephalitis virus	Negative	Valid
St. Louis encephalitis virus	Negative	Valid
West Nile virus	Negative	Valid
Yellow fever virus	Negative	Valid
Murray Valley encephalitis virus	Negative	Valid
SEBOV Gulu	Negative	Valid
ZEBOV Mayinga	Negative	Valid
MARV Musoke	Negative	Valid
Dengue virus serotype 1	Negative	Valid
Dengue virus serotype 2	Negative	Valid
Dengue virus serotype 3	Negative	Valid
Dengue virus serotype 4	Negative	Valid

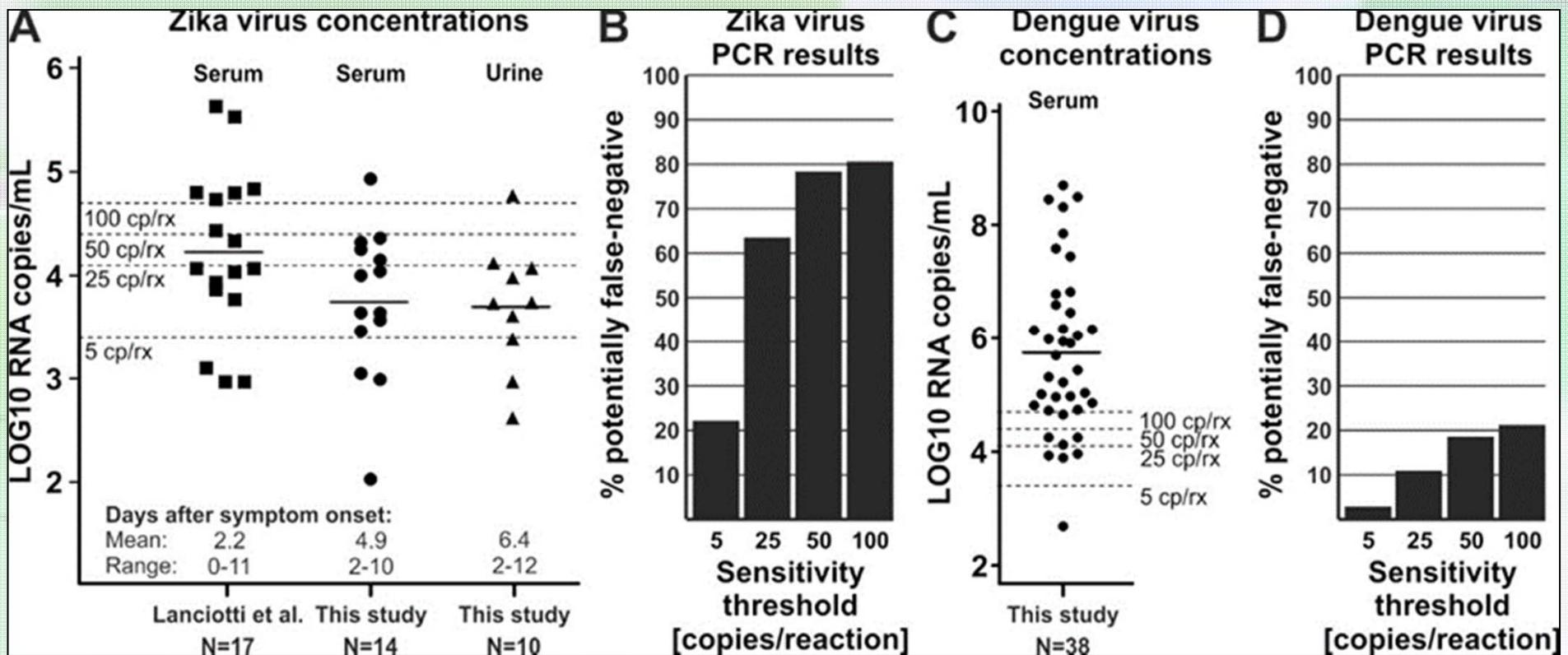
Viruses tested to demonstrate the analytical specificity of the RealStar® Zika Virus RT-PCR Kit 1.0

Most of the in-house assays showed comparably high analytical sensitivity with around 5 copies per reaction.

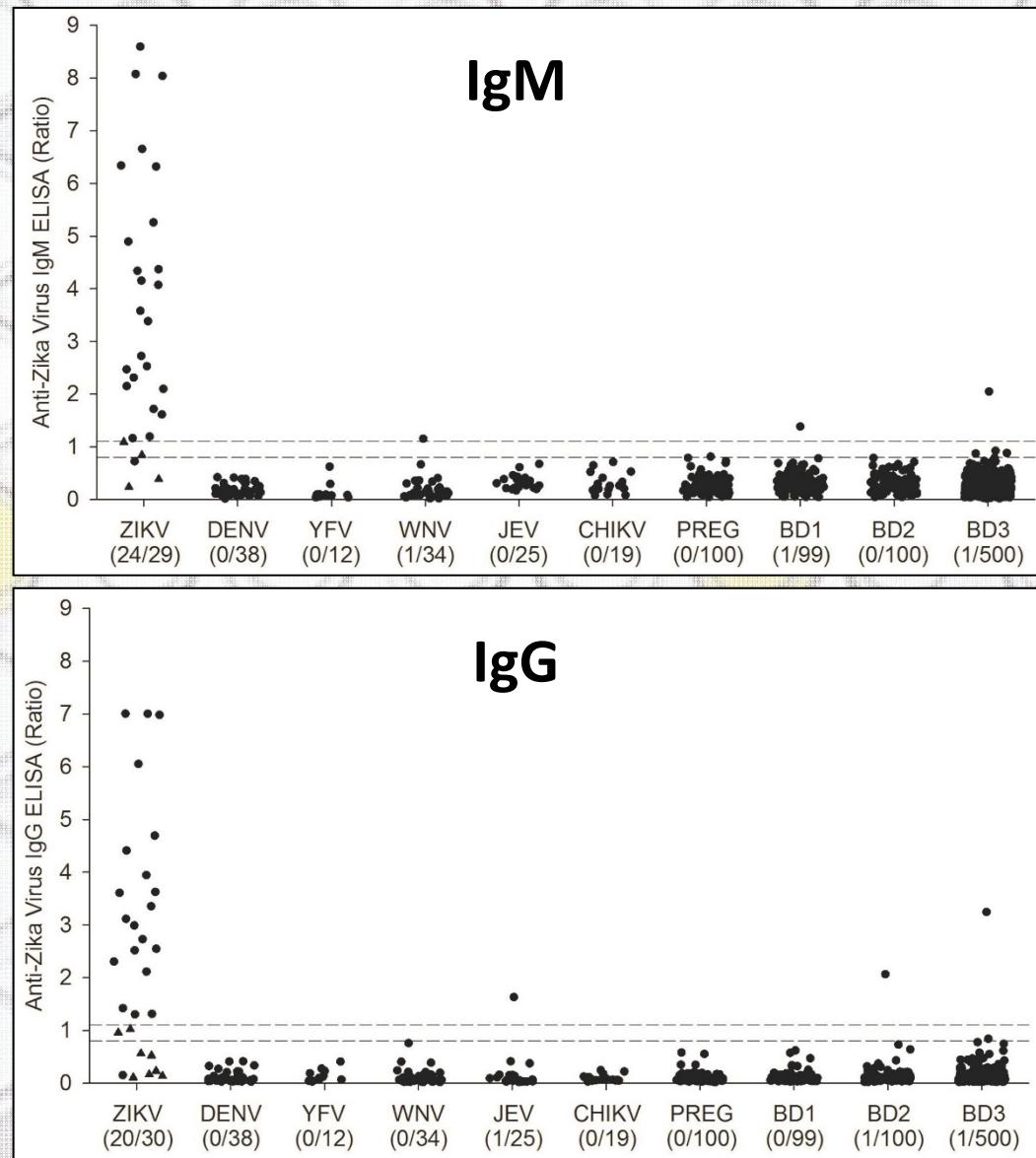


Corman et al. (2016)

We projected the estimated risk of false-negative test results for Zika virus RNA to 20% upon usage of highly sensitive assays with a detection threshold of 5 copies per reaction.



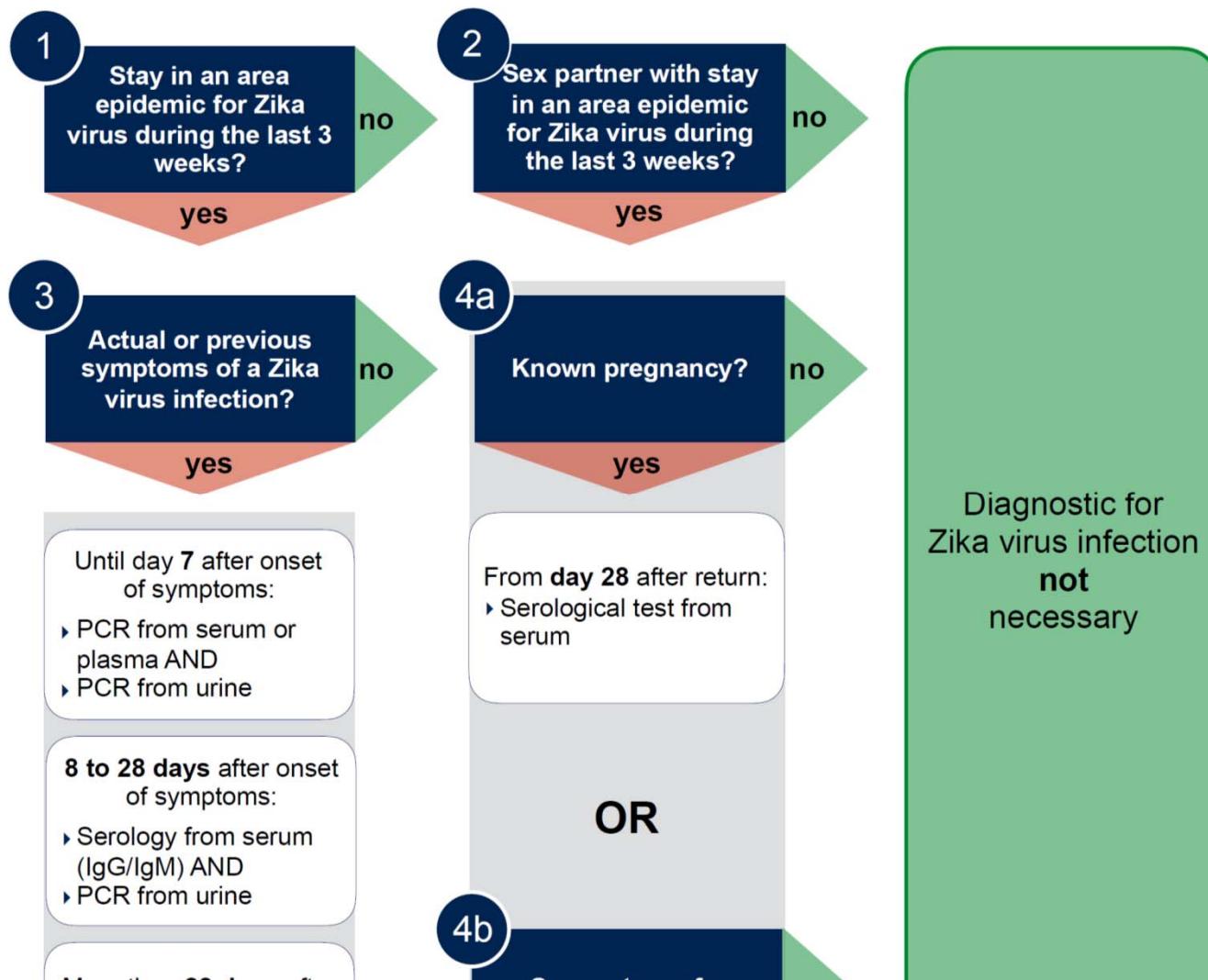
Development and evaluation of specific and sensitive CE-IVD marked Zika virus ELISA:



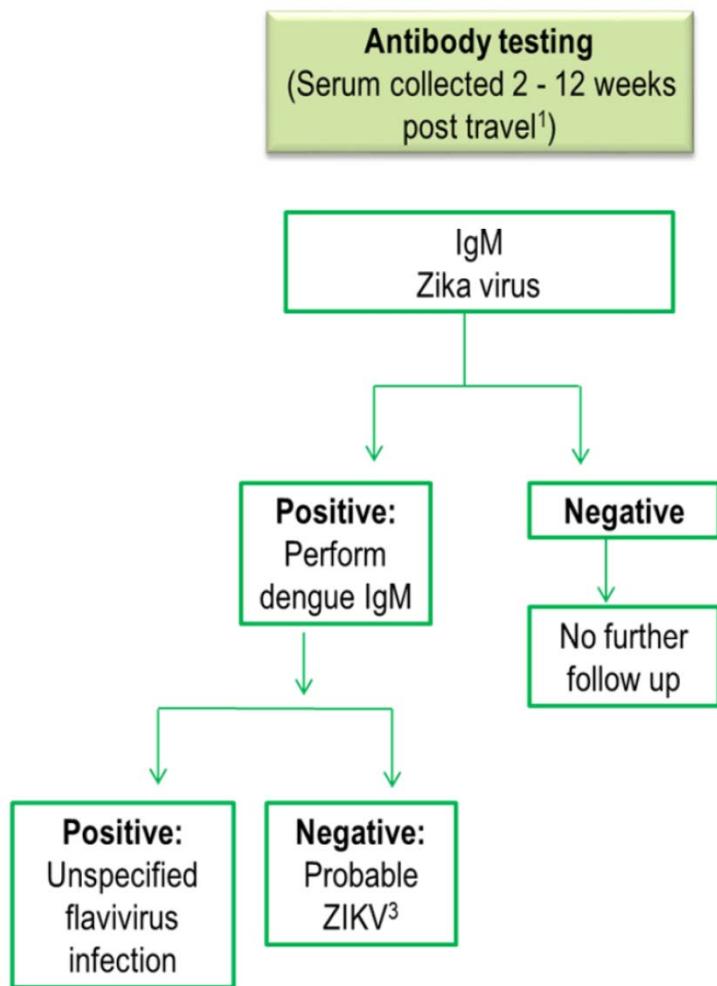
Seroconversion panels confirmed the high sensitivity of the Zika virus ELISA:

Sample	Gender	Age in years	Days after onset of symptoms									
				PCR		EUROIMMUN ELISA						
				Material	Results	IgG (Ratio)	IgG	IgM (Ratio)	IgM	Results		
						pos: > 1,1	Results	pos: > 1,1	Results			
						bl: 0,8-1,0		bl: 0,8-1,0				
patient 1	f	27	3	Serum	pos.							
			17			2,2	pos.	4,8	pos.			
			56			3,0	pos.	0,8	bl.			
patient 2			7			1,3	pos.	4,0	pos.			
			25			2,2	pos.	1,1	pos.			
patient 3	m	45	3	Urine	pos.							
			4			0,1	neg.	0,2	neg.			
			11			0,8	bl.	1,7	pos.			
			26			2,1	pos.	1,6	pos.			
patient 4	m	4	3	Urine	pos.	0,1	neg.	0,4	neg.			
patient 5	f	28	11	Urine	pos.	2,6	pos.	7,5	pos.			
			22			4,8	pos.	5,6	pos.			

Zika virus diagnostic algorithm in Germany



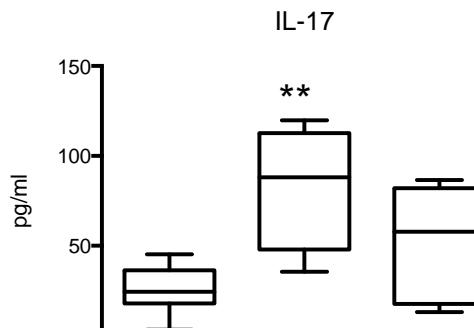
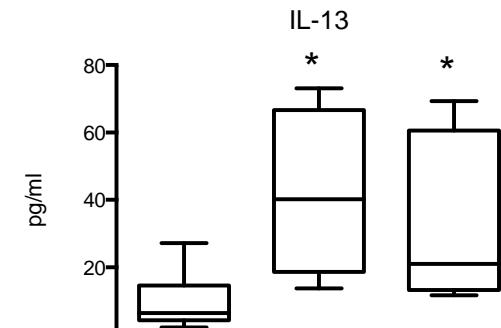
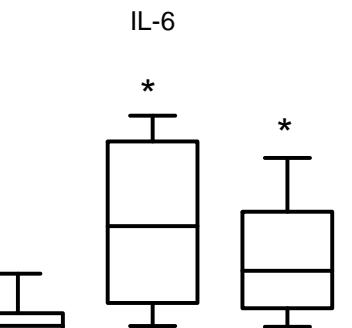
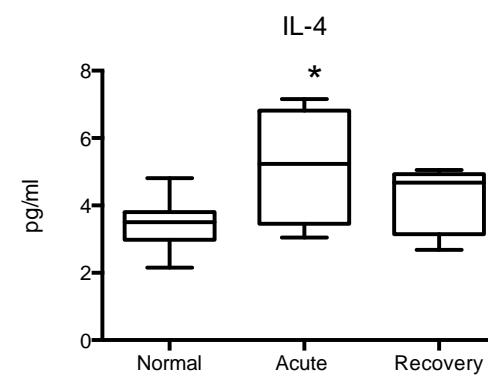
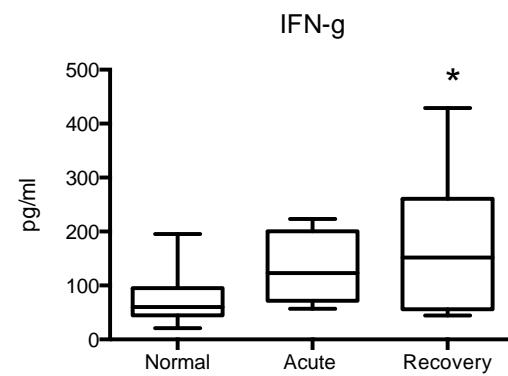
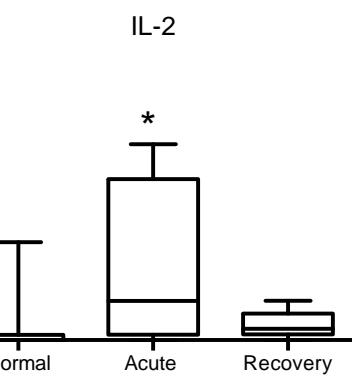
virus diagnostic algorithm of the CDC



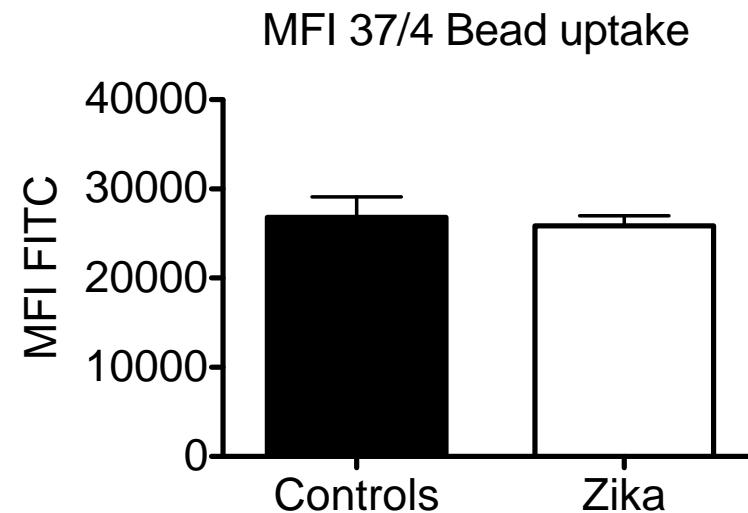
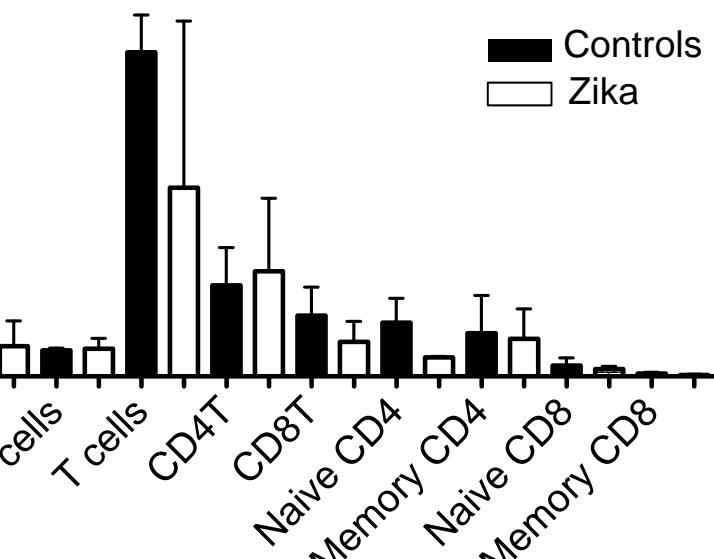
and laboratory findings of imported Zika virus infections diagnosed at the WHO CC until the beginning of the epidemics in the Americas.

	year	clinical findings	Zika virus diagnostics	reference
	November 2013	52-year-old woman, fever, polyarthralgia, rash	IgG+, IgM+, VNT+, RT-PCR-	Tappe et al. (2013) Eurosveillance
	December 2013	31-year-old woman, fever, polyarthralgia, myalgia, rash, Lymphopenia, neutropenia	IgG+, IgM+, RT-PCR+	Wæhre et al. (2014) Emerg Infect Dis
	January 2014	31 Jahre, weiblich, fever, polyarthralgia, rash, conjunctivitis, lymphadenopathy, Zahnfleischblutungen	IgG+, IgM+, qRT-PCR+	Zammarchi et al. (2015) J Clin Virol
	January 2014	33-year-old man, fever, polyarthralgia, rash, conjunctivitis, lymphadenopathy, leukopenia, thrombozytopenia	IgG+, IgM+, RT-PCR-	Zammarchi et al. (2015) J Clin Virol
	August 2014	45-year-old woman, fever, polyarthralgia, rash, conjunctivitis,	IgG+, IgM+, VNT+, PCR-	Tappe et al. (2015) Emerg Infect Dis

Functional T cell activation was seen during the acute phase of virus disease (ZVD) characterized by respective cytokine levels, followed by a decrease in the convalescent phase of ZVD.



covery from ZIKV infection is associated with restoration of normal numbers of immune cells in the periphery as well as with normal function of antigen-presenting cells.

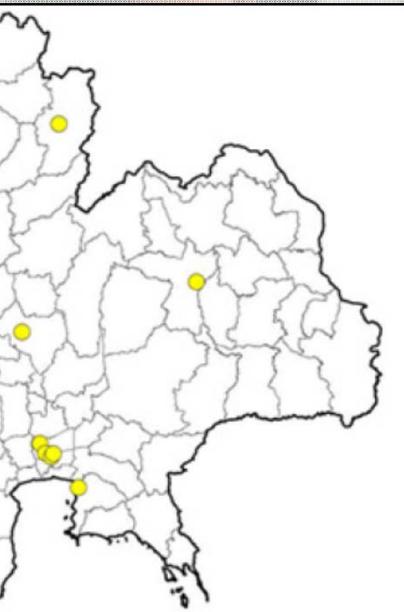


Urgent questions / tasks

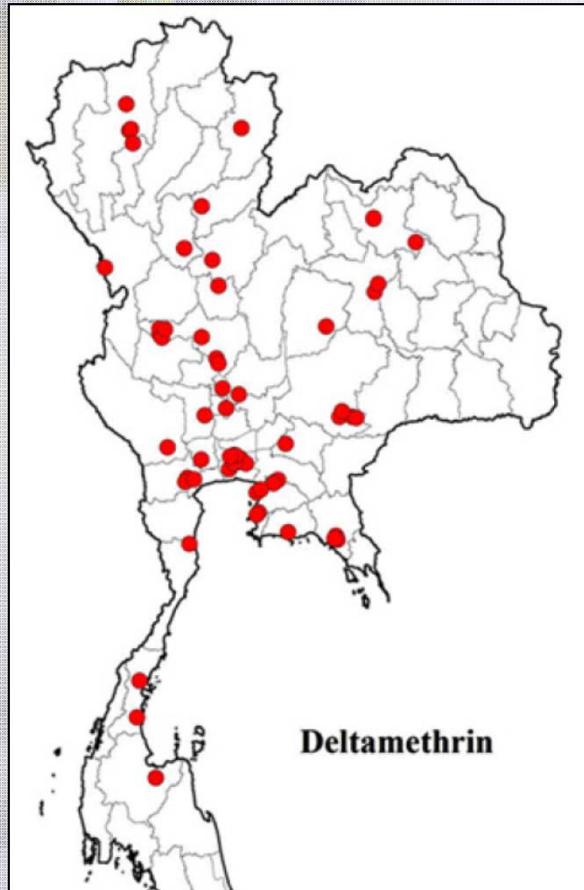
Simple point-of-care diagnostics (Ag, Ab or RNA)
will be needed.

Harmonization of VNTs (reference ZIKV strains?,
PRNT50 or PRNT90, FRNTs, endpoint titration?)

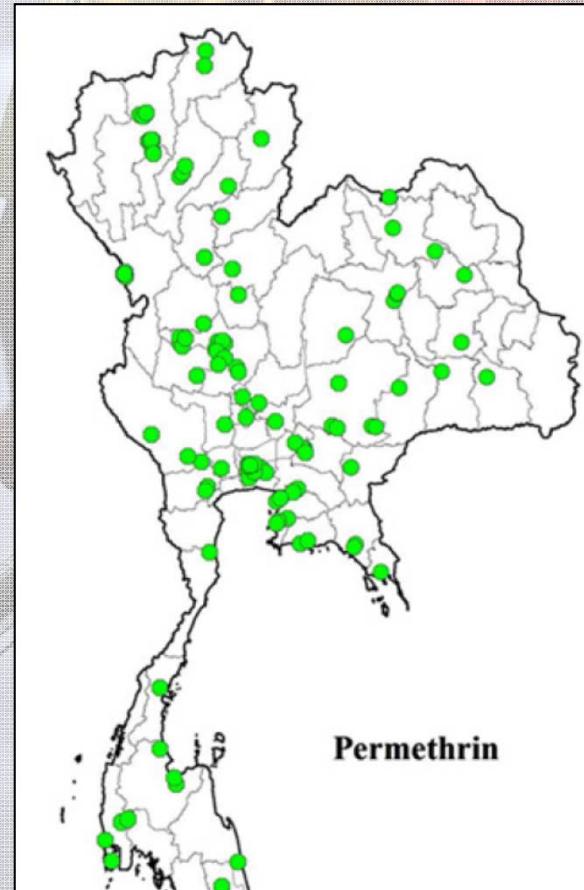
Aedes aegypti populations with widespread resistance to insecticides



DDT

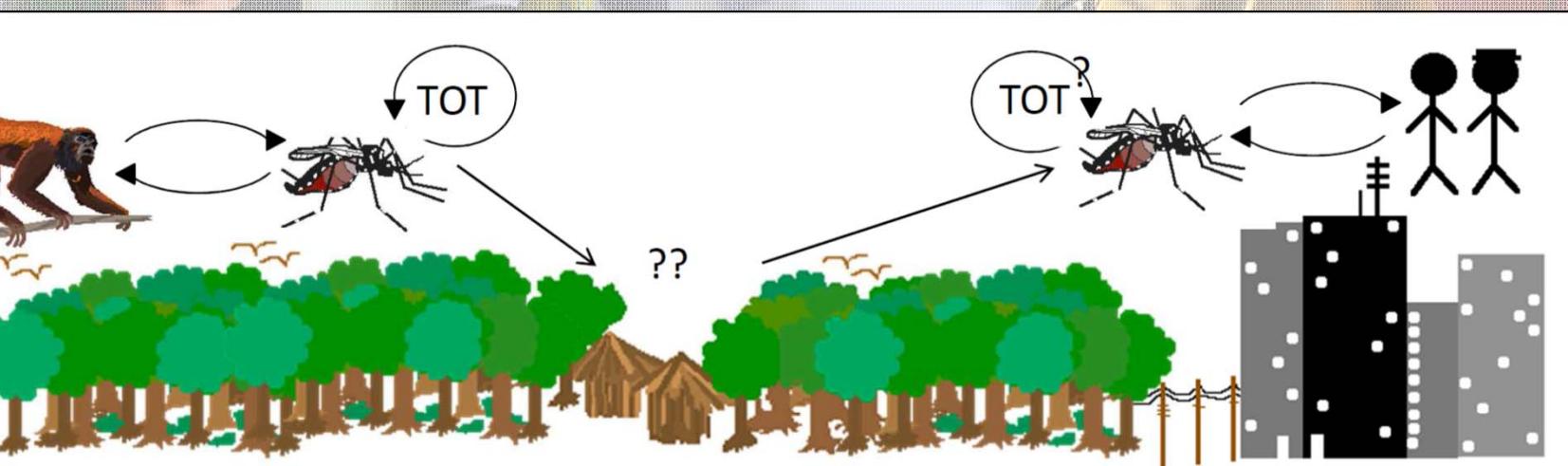


Deltamethrin



Permethrin

More than 19 mosquito species were found to be infected with Zika virus



Sylvatic

Aedes vexans (Africa)*
Aedes vexans (Africa)
Aedes vexans (Africa)*
Aedes vexans (Africa)*
Aedes vexans (Africa)

Ae. metallicus (Africa)
Ae. opok (Africa)
Ae. taylori (Africa)*
Ae. unilineatus (Africa)
Megarhinus (Africa)

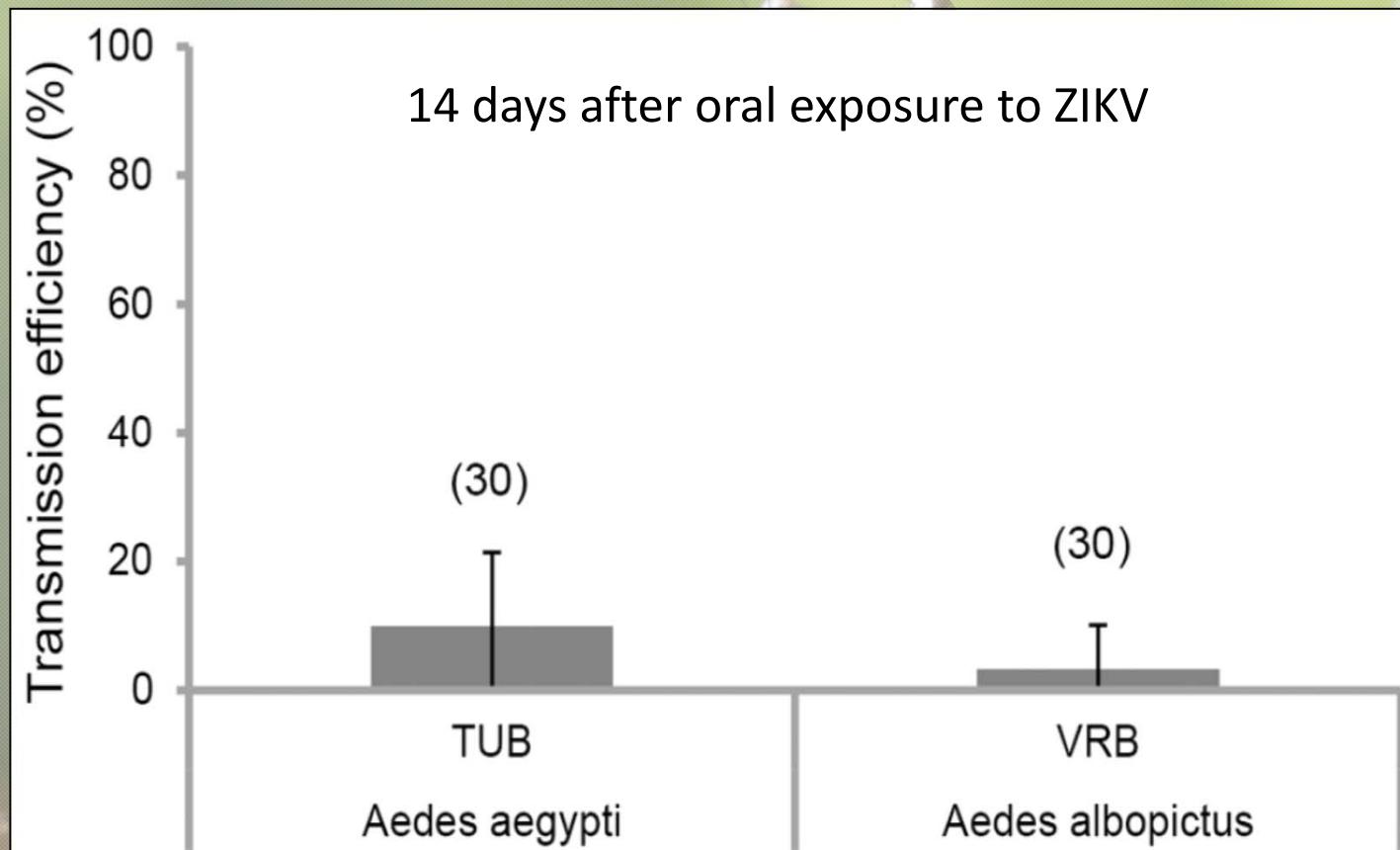
Zone of emergence

Ae. vittatus (Africa)

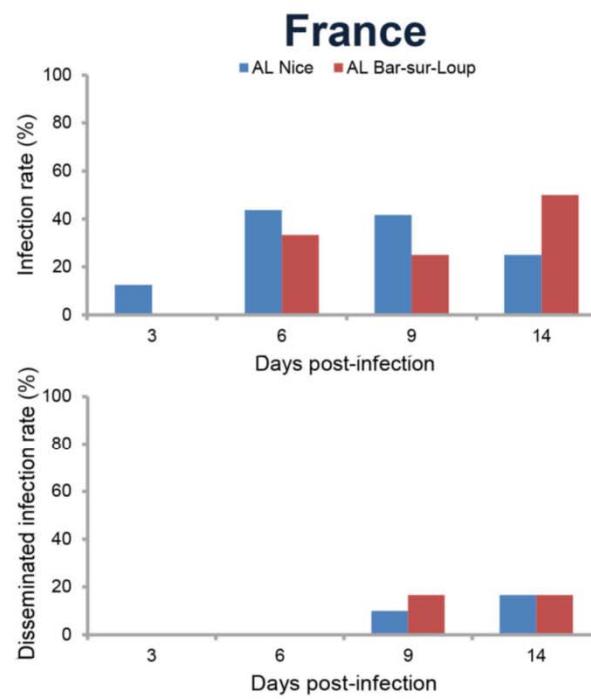
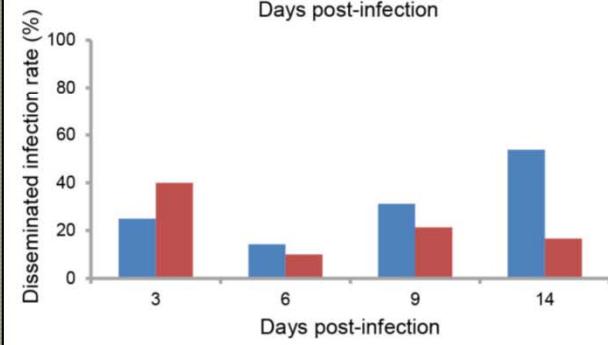
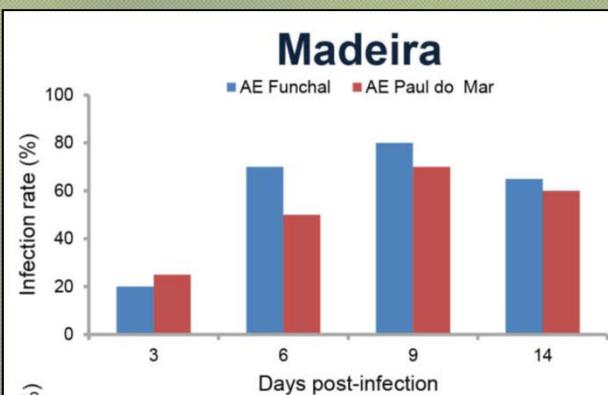
Urban

Ae. aegypti *aegypti* (global)
Ae. albopictus (global?)
Ae. polynesiensis (Polynesia)
Ae. hensilii (Polynesia)

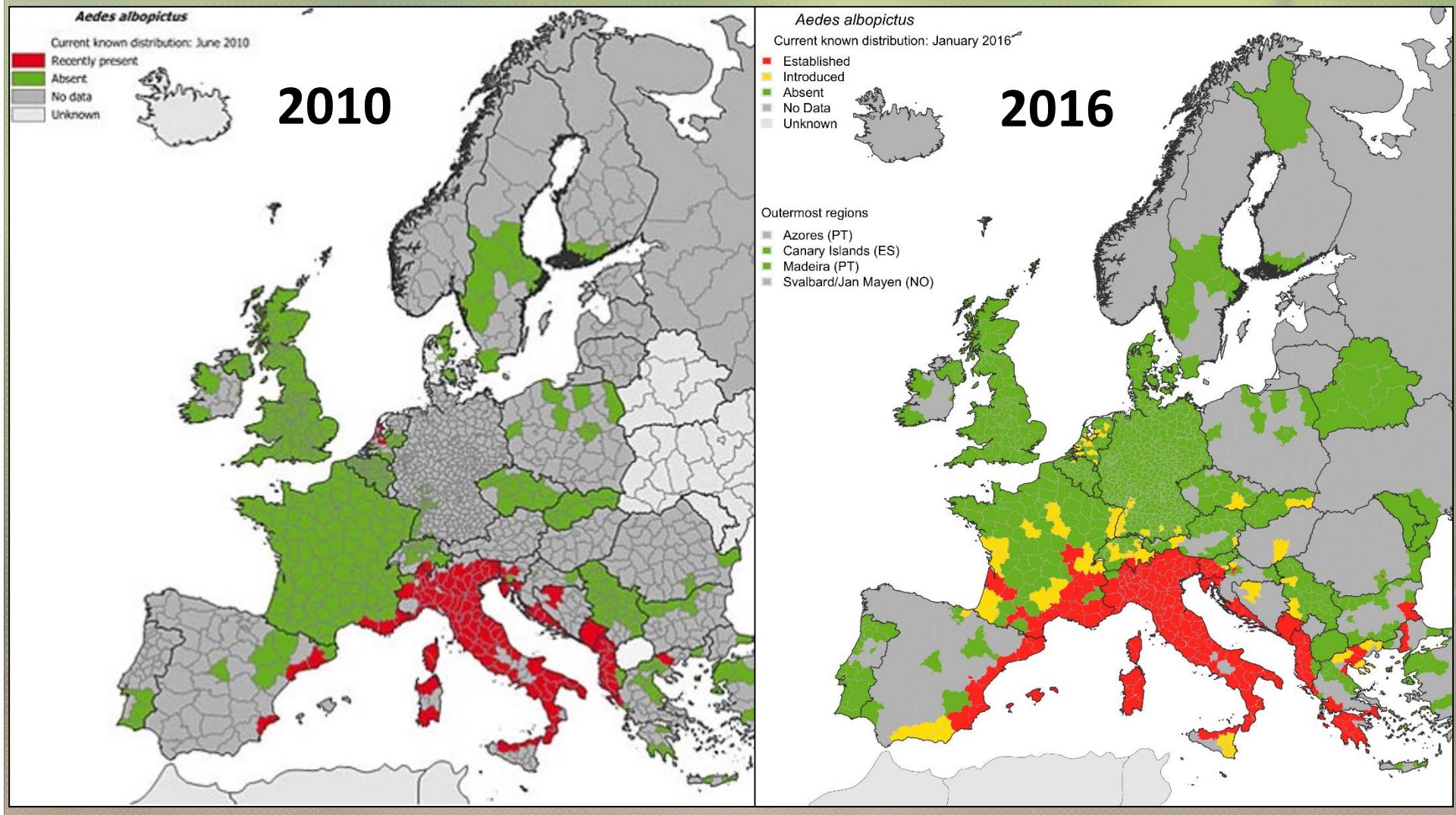
Important intraspecies differences for the vector competence of *Aedes aegypti* and *Aedes albopictus*



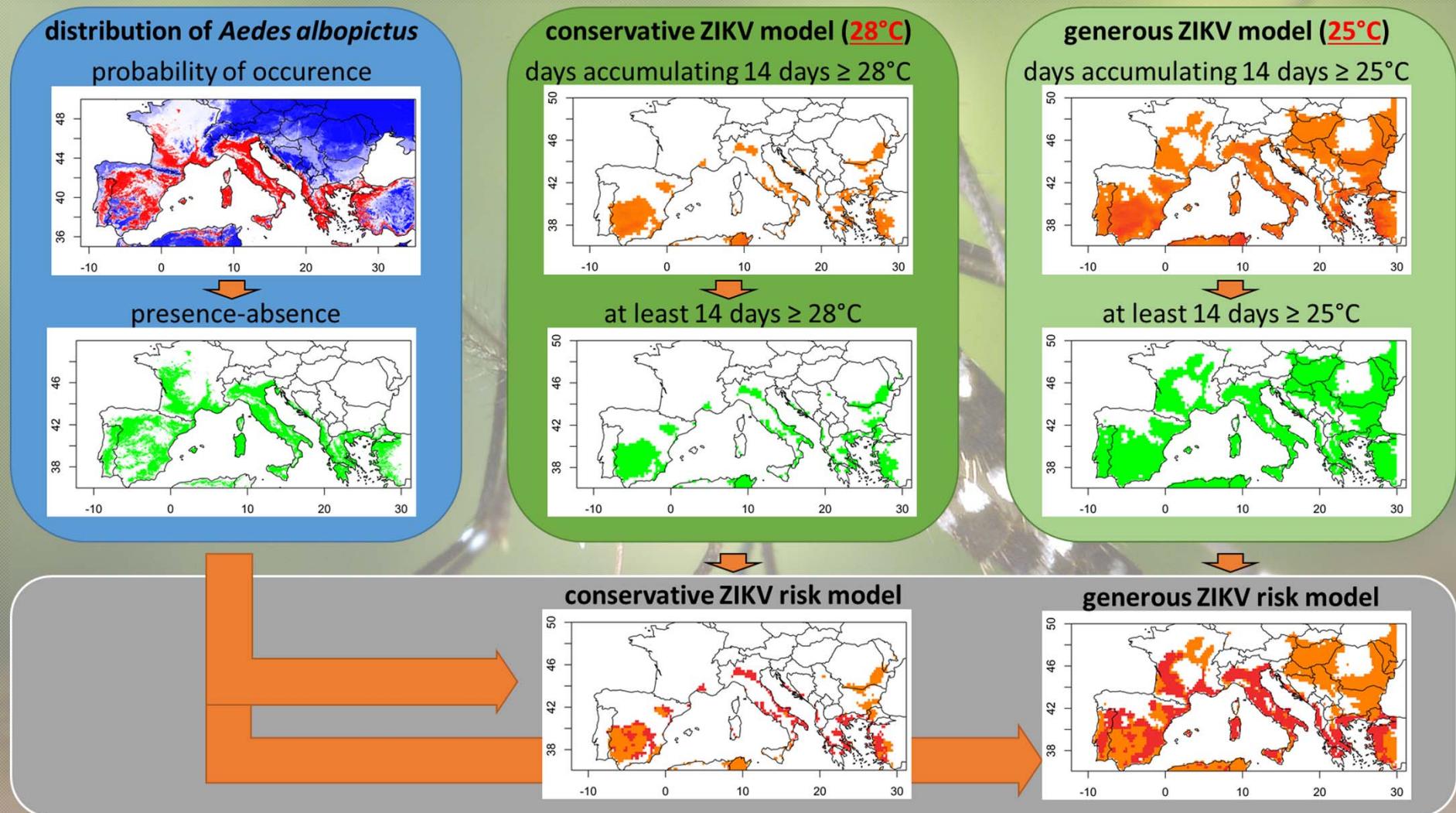
European *Aedes aegypti* and *Aedes albopictus* populations are competent vectors for Zika virus.



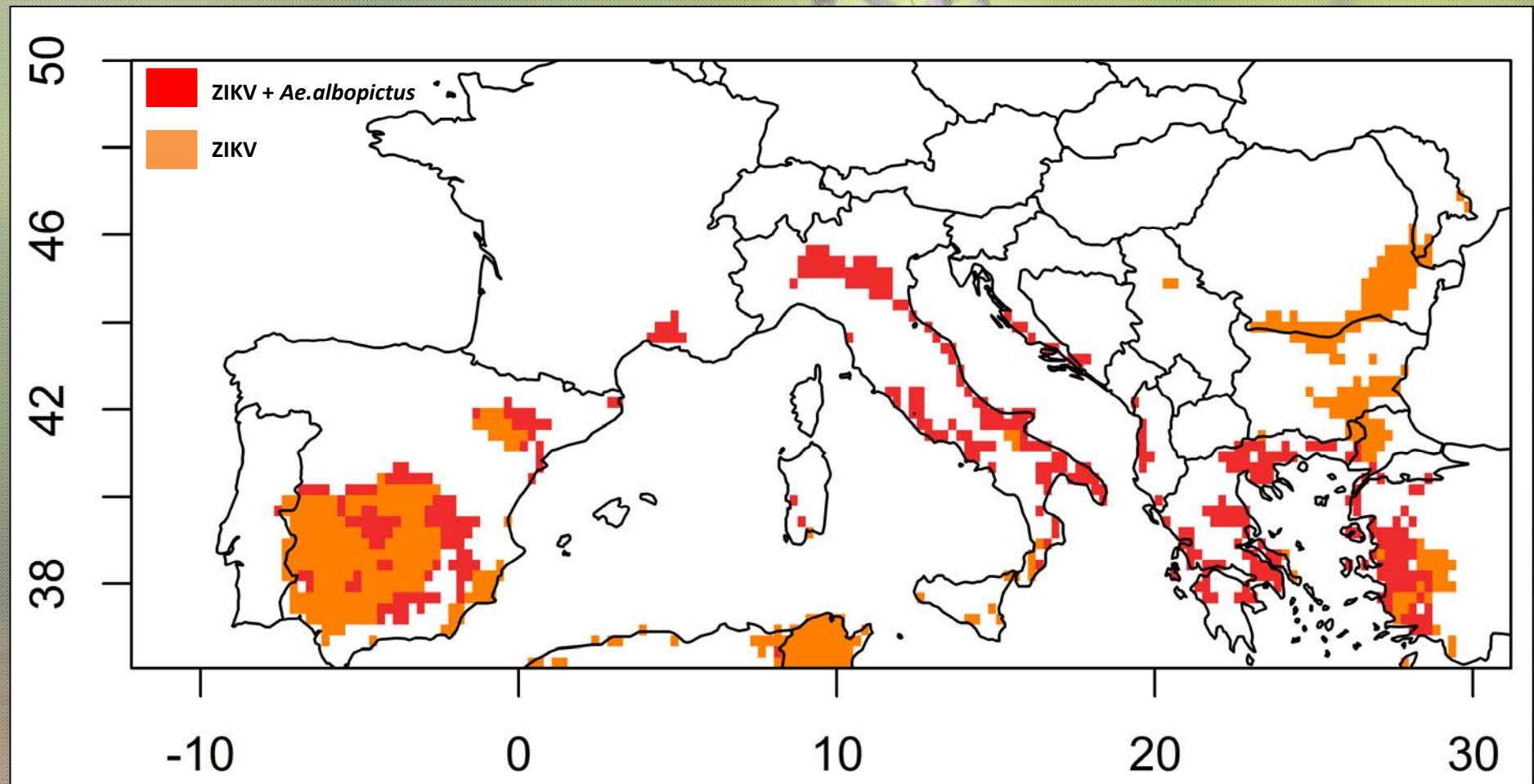
Aedes albopictus is an invasive mosquito species in Europe:



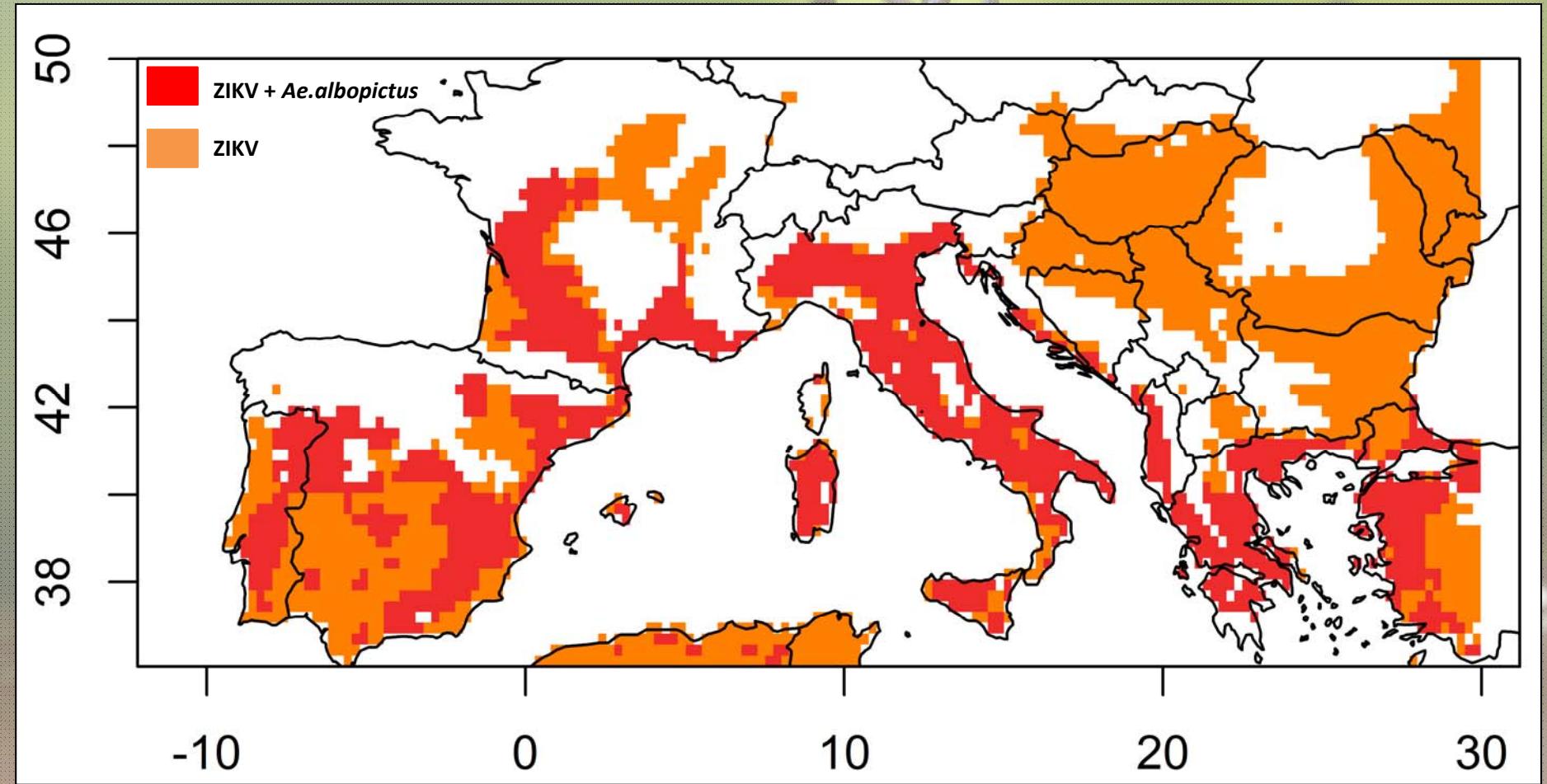
Modeling of suitable areas for Zika virus in Europe



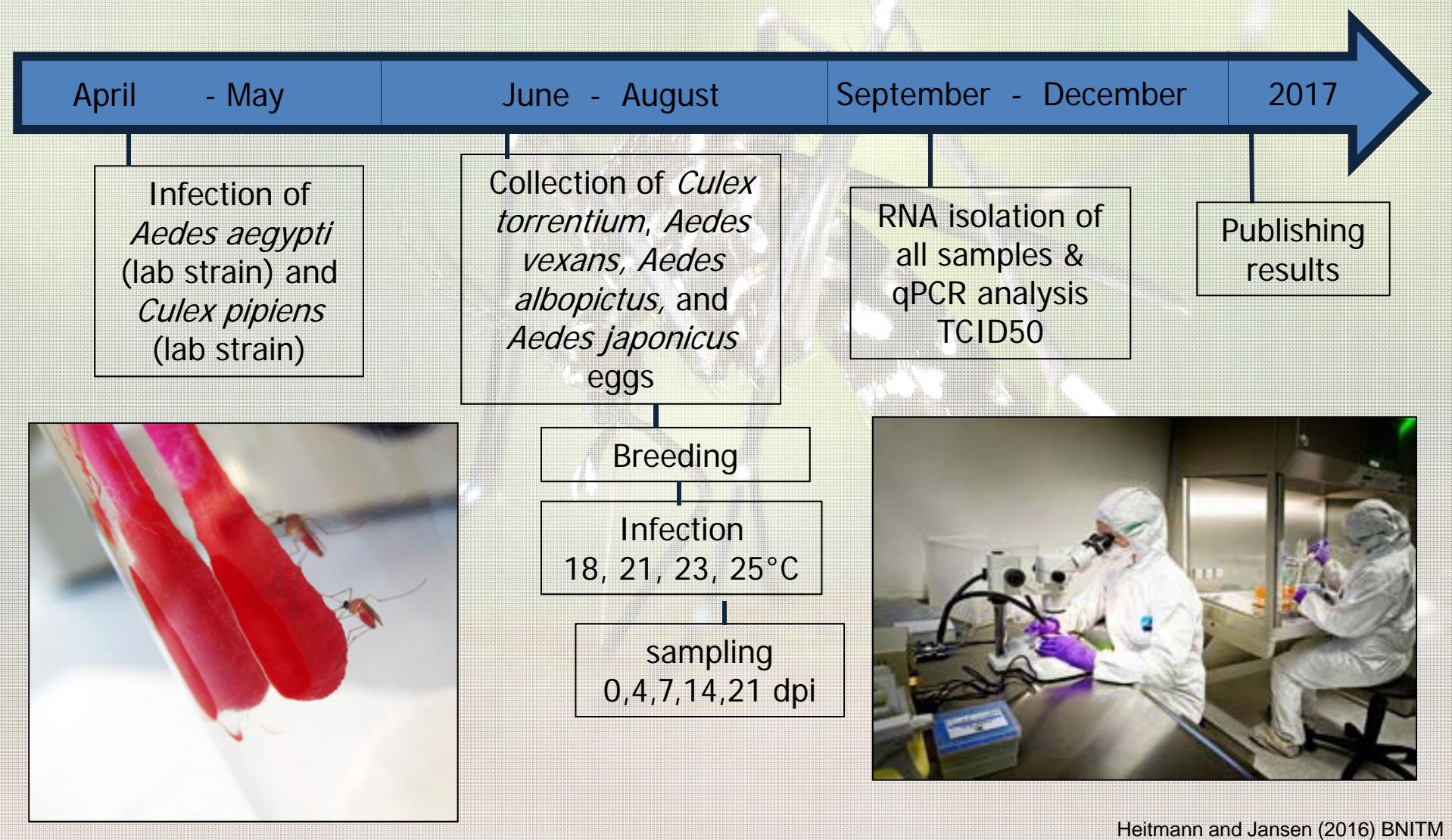
The conservative model (28°C), demonstrates that costal areas of France, Italy, Greece, and Turkey are suitable for Zika virus.



The generous model (25°C), demonstrates that most parts of the Mediterranean countries are suitable for Zika virus.



Indigenous and invasive mosquito species from Germany will be infected with low passage Asian and African lineage of Zika virus and tested for virus replication and transmission.



Returning viremic travellers may ignite autochthonous infections in European countries. Therefore, it will be important to enhance vigilance towards the early detection of imported cases of ZIKV infection in Europe, in order to reduce the risk of autochthonous transmission.

„Mit der Meldepflicht für Arboviren sorgen wir außerdem dafür, dass etwa eine Zika-Infektion bei Reiserückkehrern in Deutschland besser überwacht werden kann. Damit gewinnen die Gesundheitsämter vor Ort wertvolle Zeit zum schnellen Handeln.“



Hermann Gröhe - Minister of Health, Germany

Urgent questions / tasks

Targeted and sustainable vector control measures

Is Zika virus able to infect and be transmitted by other mosquito genera (e.g. *Culex*, *Mansonia*, *Anopheles*) ?

