Convegno

Aggiornamenti in tema di medicina dei viaggi e delle migrazioni: 1° Evento

Palazzo Grandi Stazioni, Venezia 30 Maggio

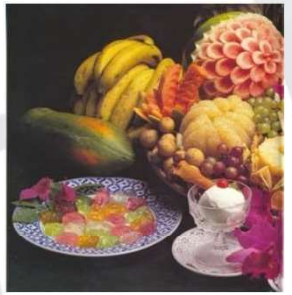
Le problematiche virali emergenti nel mondo: Febbre gialla, Zika virus, Dengue e Chikungunya

Centro Malattie Tropicali
NEGRAR - VERONA - ITALY
Centre for Tropical Diseases
Ospedale Sacro Cuore Don Calabria
FONDAZIONE DON GIOVANNI CALABRIA PER LE MALATTIE TROPICALI

WHO Collaborating Center on strongyloidiasis and other intestinal parasitic infections

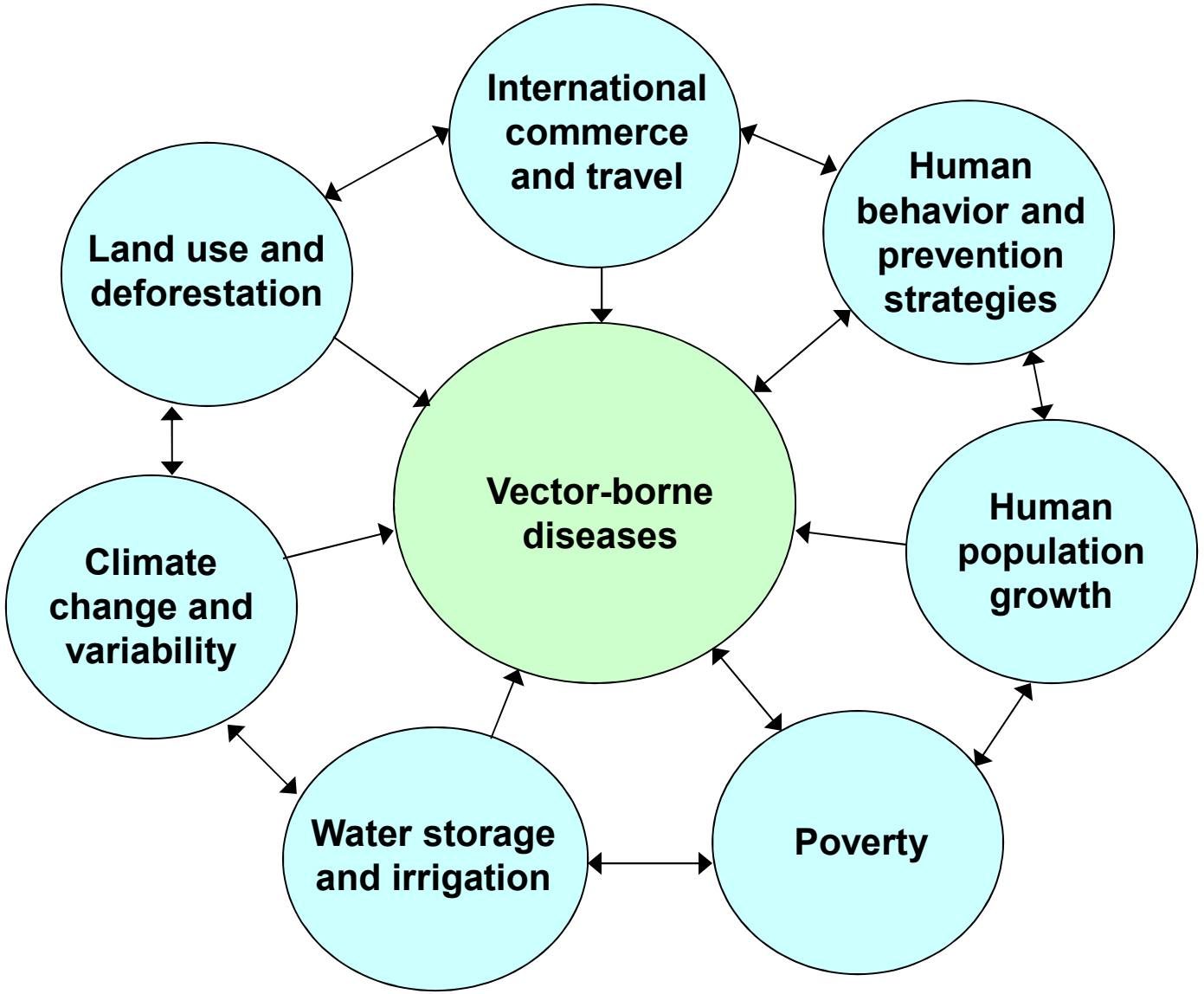
Federico Gobbi

Globalizzazione



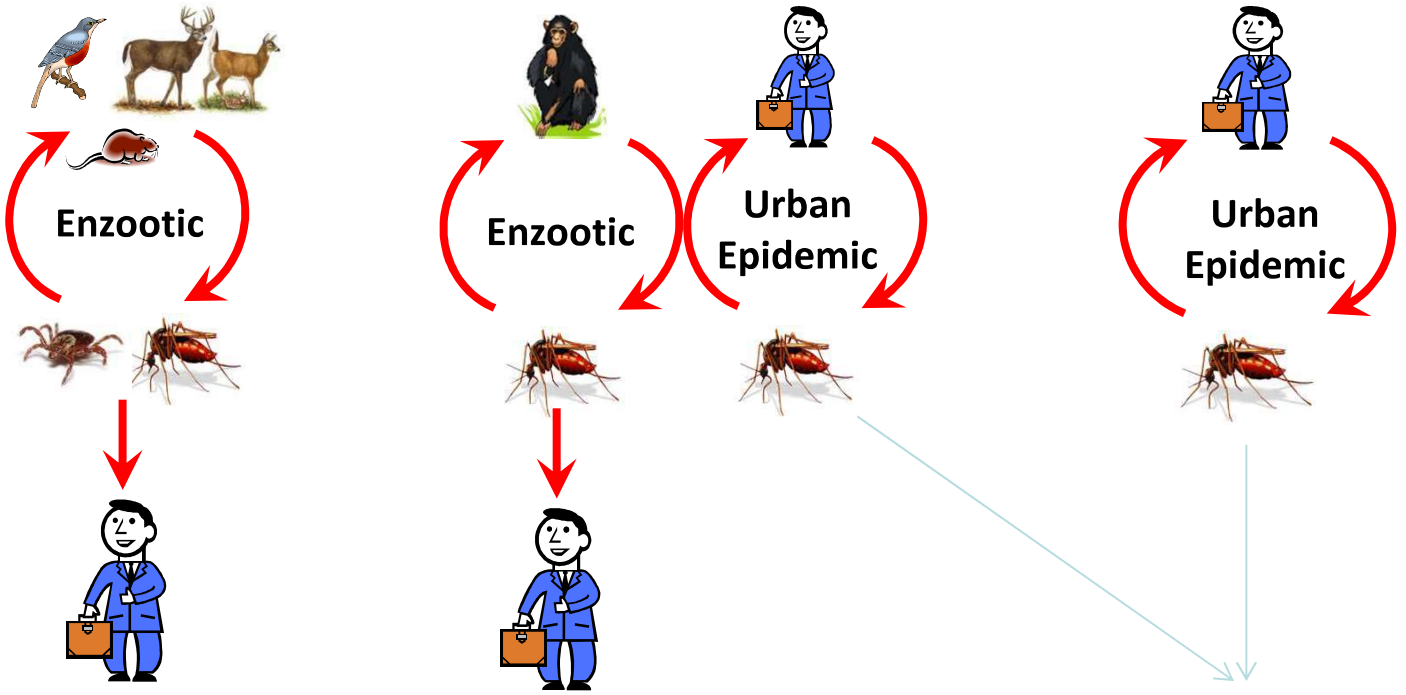
ARBO (**AR**thropod-**BO**rne) - **virus**
(non exhaustive list)

Virus	Family/Genus
Yellow fever virus	Flaviviridae/Flavivirus
Dengue virus	Flaviviridae/Flavivirus
Japanese encephalitis virus	Flaviviridae/Flavivirus
West Nile virus	Flaviviridae/Flavivirus
Tick-borne encephalitis virus	Flaviviridae/Flavivirus
Zika virus	Flaviviridae/Flavivirus
Chikungunya	Togaviridae/Alphavirus
Toscana virus	Buniaviridae/Phlebovirus
Rift Valley virus	Buniaviridae/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

ZIKA VIRUS

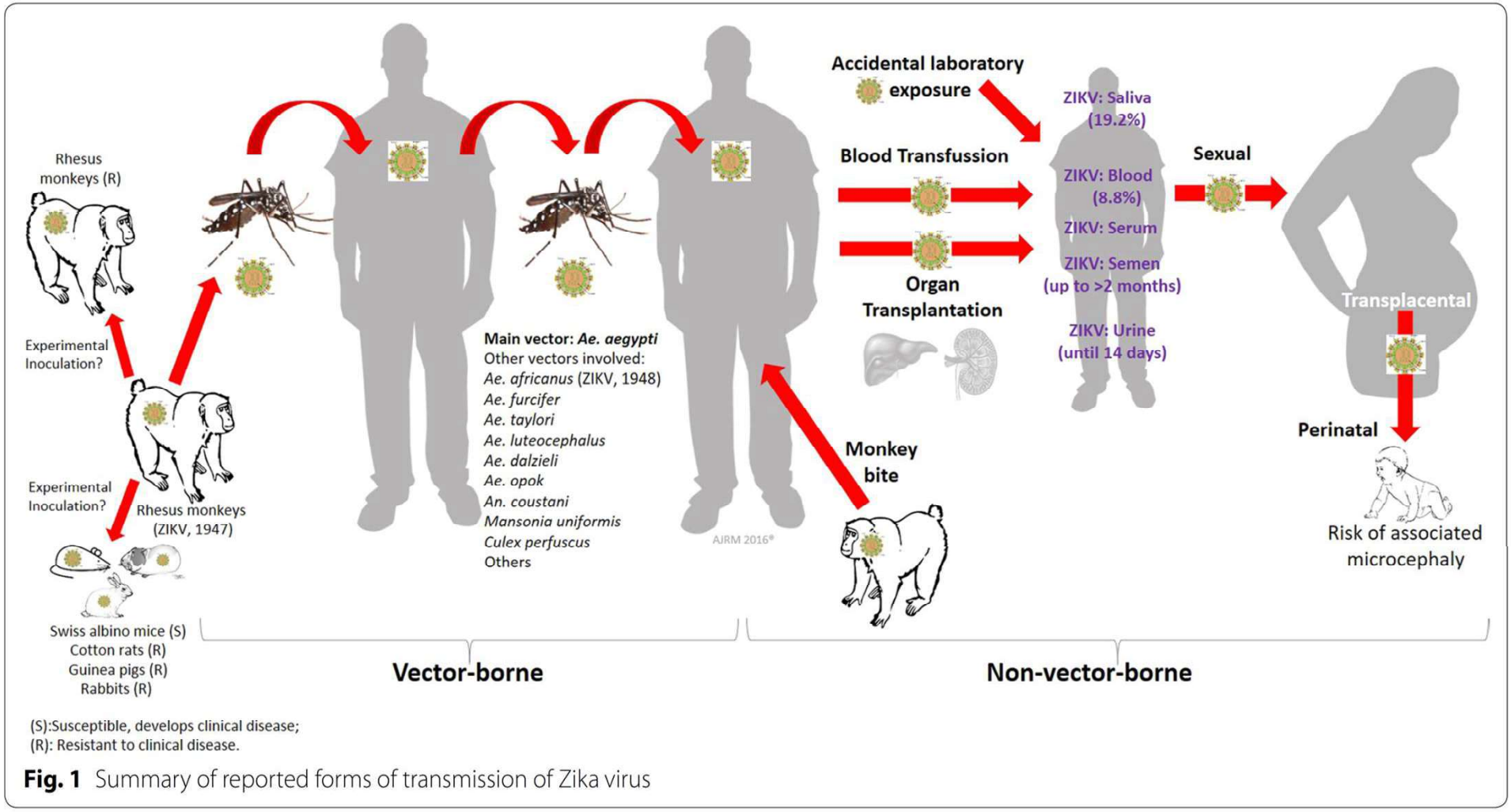


Fig. 1 Summary of reported forms of transmission of Zika virus

Rodriguez-Morales et al., Ann Clin Microb Antimicrobials 2016

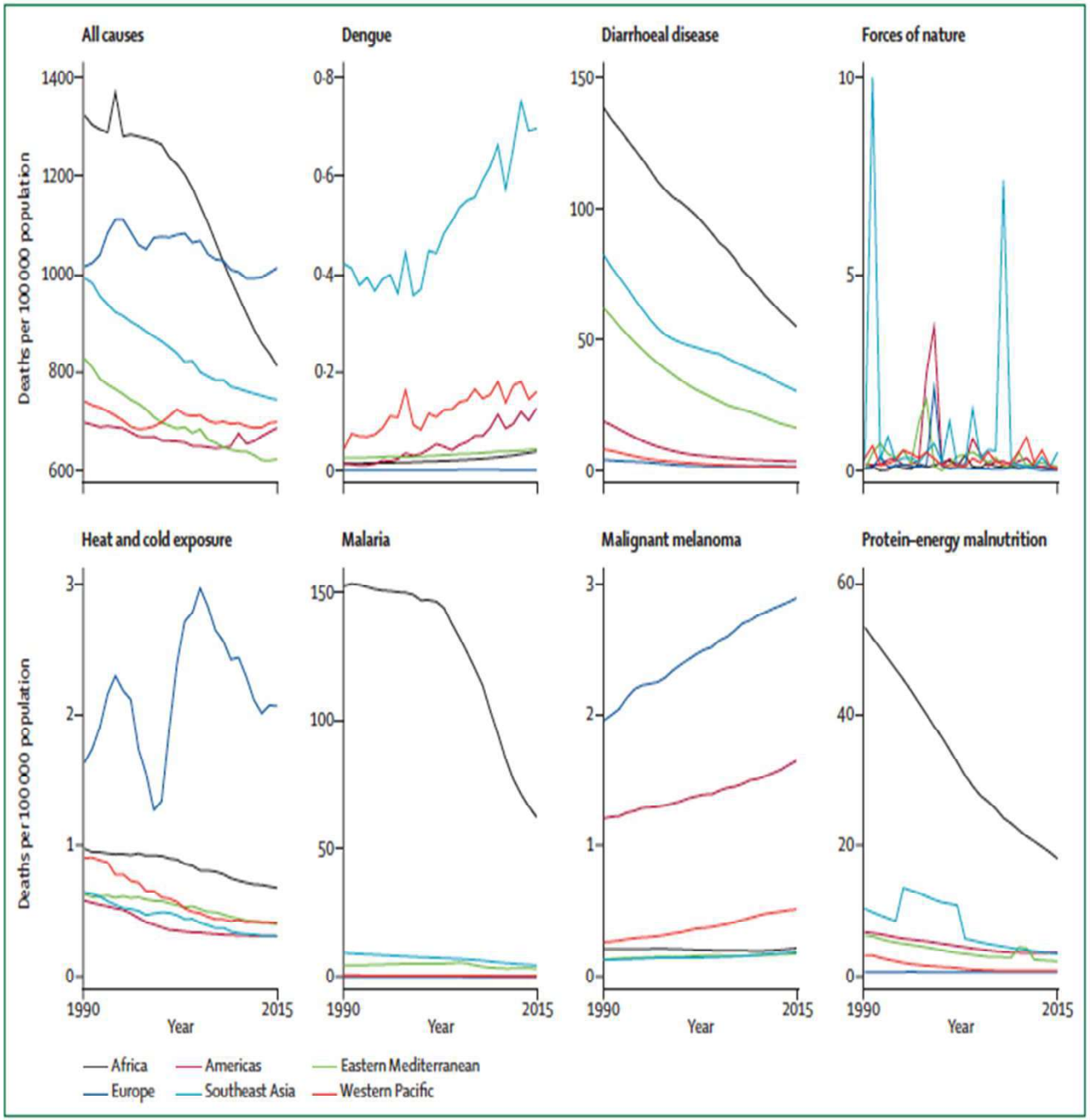


Figure 7: Trends in mortality from selected causes of death, as estimated by the Global Burden of Disease Study 2015, by WHO region

Trends in mortality Global Burden of Disease Study 2015. By WHO regions

Watts et al.
Lancet online
Oct 30, 2017

Extrinsic incubation periods at selected temperatures

Aedes aegypti

Yellow fever virus

10^0 C 37 d

20^0 C 19 d

30^0 C 10 d

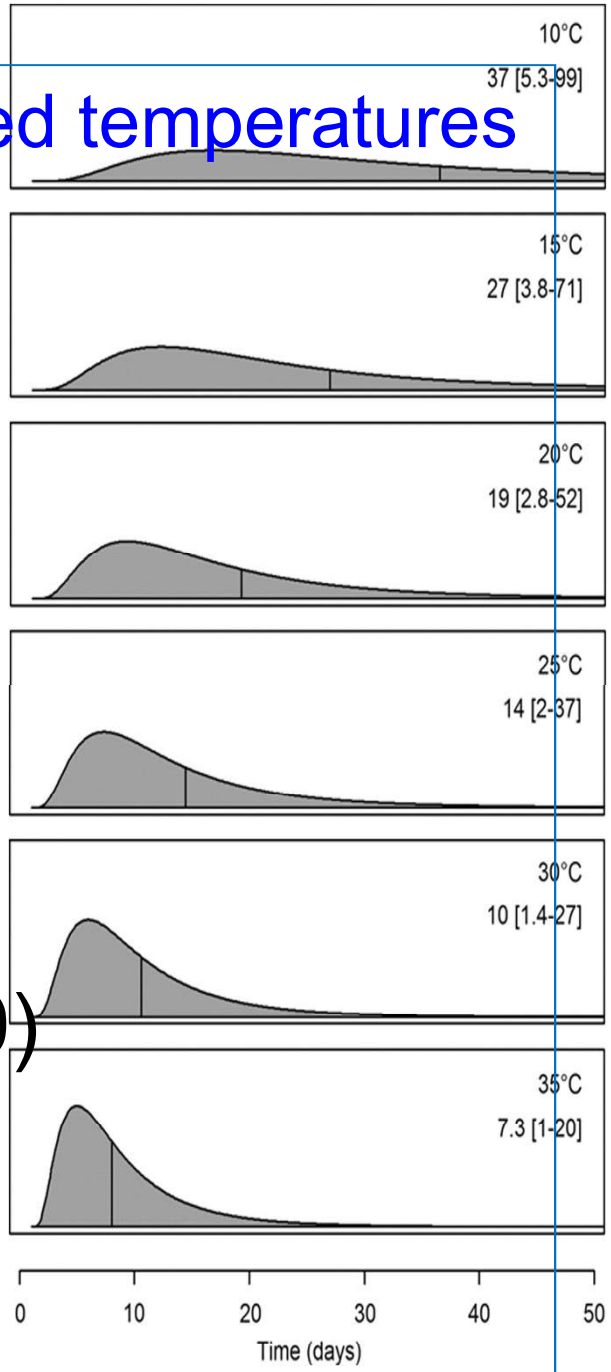
35^0 C 7.3 d (1-20)

Separate study

Dengue virus

30^0 C 12 d

32-35^0 C 7 d



Johansson et al. AJTMH 2010;83(1):183.

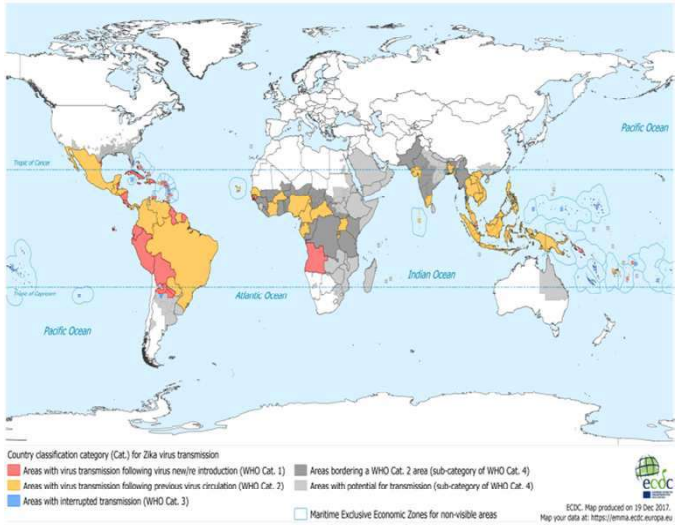
Dengue

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: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Zika virus



Chikungunya

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 and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Adapted from Fields virology
5th ed. Vol. 1. Philadelphia,
Lippincott Williams & Wilkins, 2006:1047
Map Production: International Travel and Health (ITH)
World Health Organization

World Health Organization

Yellow fever

BRAZIL Yellow Fever MAP

2016

Current

Dec 2016-today
>2000 cases/>500 deaths

Table 1. **Frequency of acute symptoms of CHIKV Infection.**[a]

Symptom or sign	Frequency range (% of symptomatic patients)
Fever	76–100
Polyarthralgias	71–100
Headache	17–74
Myalgias	46–72
Back pain	34–50
Nausea	50–69
Vomiting	4–59
Rash	28–77
Polyarthritis	12–32
Conjunctivitis	3–56

Majority (72-97%) of infected persons are symptomatic

Dengue and **Zika**

80% of infected persons are

asymptomatic **!!!!**

Yellow fever

Yellow fever Clinical characteristics

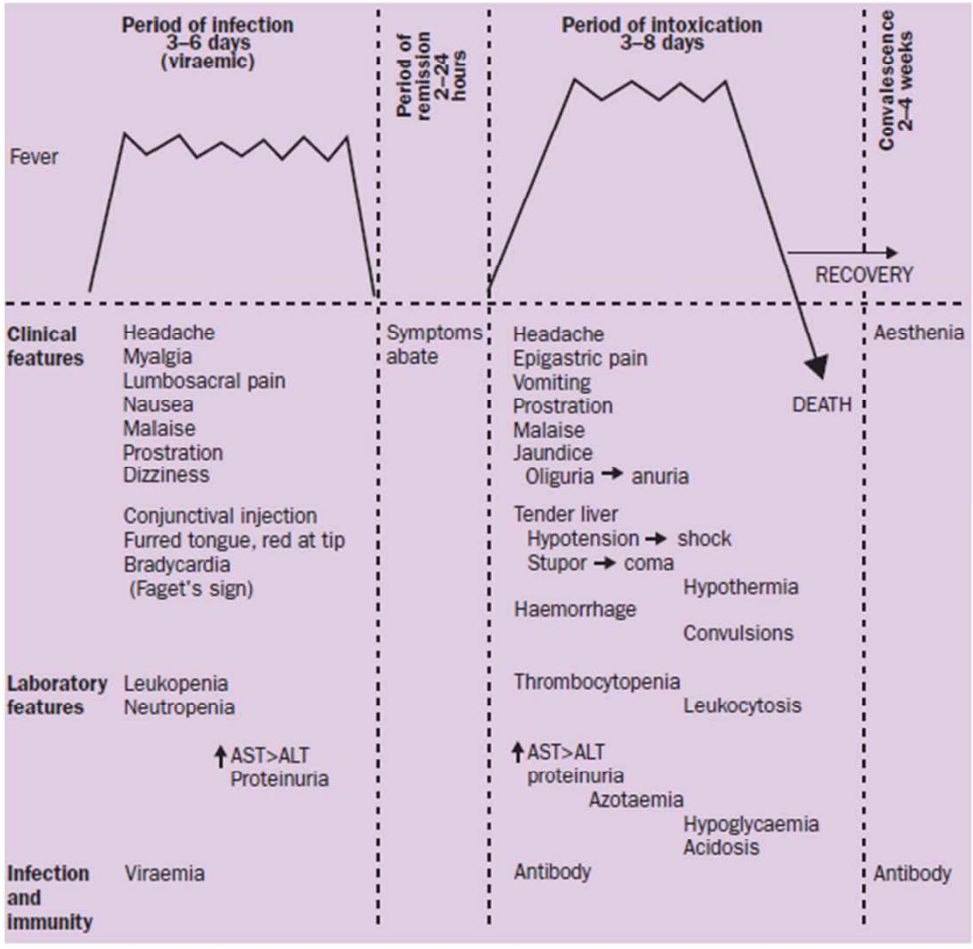


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

Monath, Lancet Infectious Diseases 2001; 1: 11–20

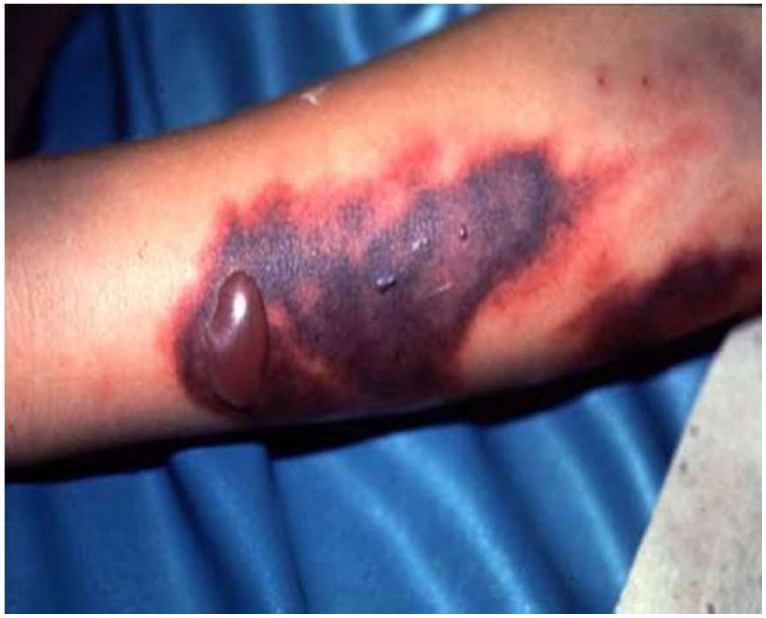
Differential diagnosis

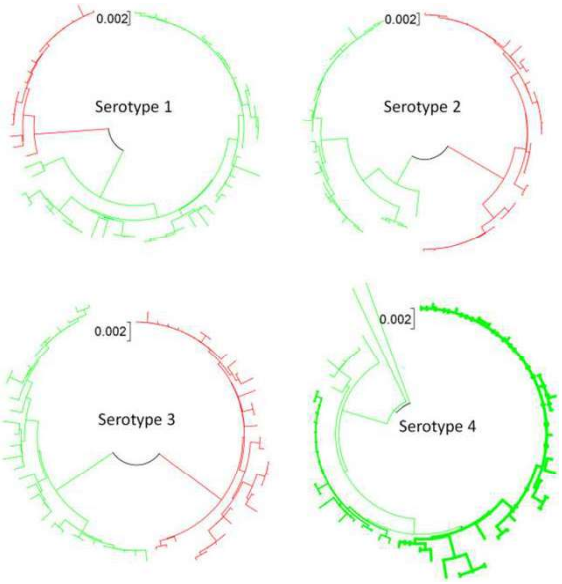
Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

CDC. Zika virus-What clinician should know? http://emergency.cdc.gov/coca/ppt/2016/01_26_16_zika.pdf

DENGUE: Hemorrhagic manifestations

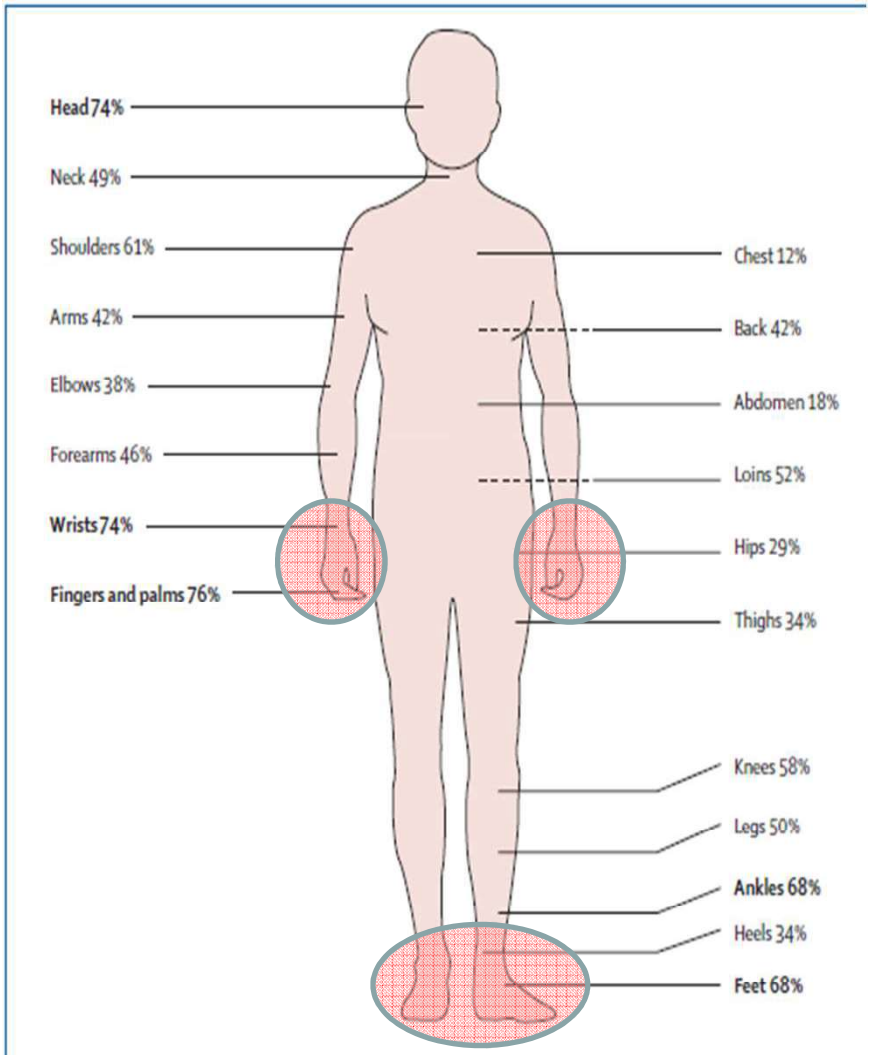
Attack rate of DHF/DSS in persons with prior dengue infection who become infected with new serotipe: **4.2%**

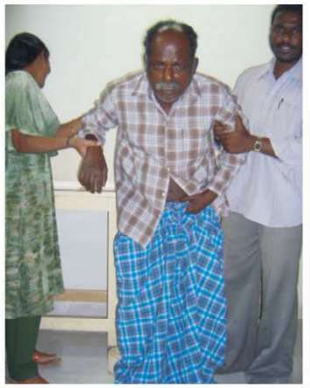




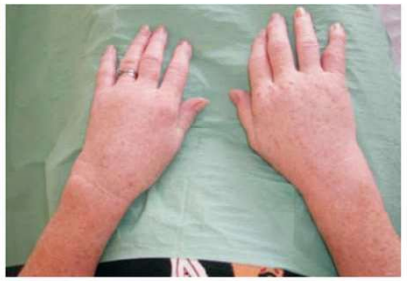
Guzman MG, Kouri G, Valdes L, et al.
Epidemiologic studies on dengue in Santiago de Cuba.
1997. Am J Epidemiol 2000; 152:793-799.

Frequency of pain by location during acute stage of CHIKV infection

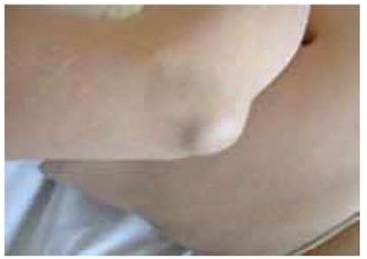




Chikungunya, that which bends up
Source: Dr RVSN Sarma.



Arthropathy: wrists and small joints



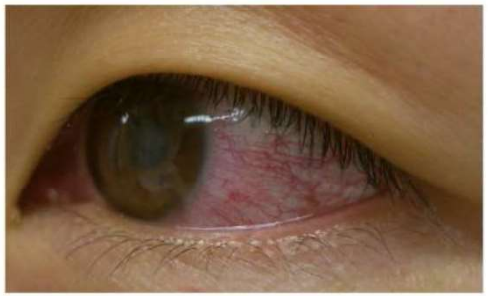
M. Elbow hygroma

N. Swollen and stiff hands in a 55-year-old man who was infected 5 years earlier

Queyriaux B, Lancet 2008

Zika virus

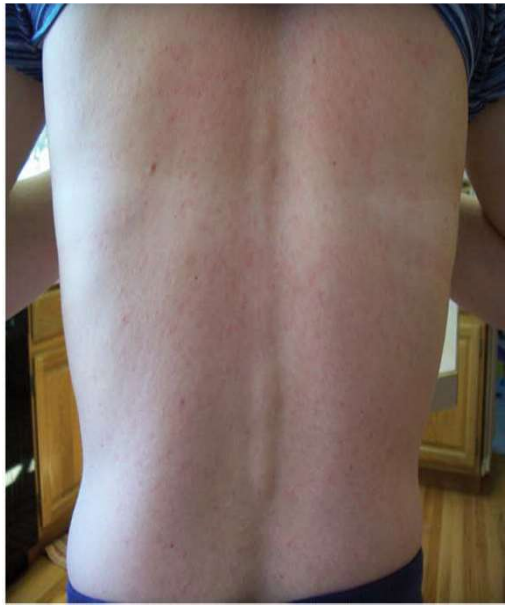
Conjunctivitis in a case of imported Zika virus infection from French Polynesia, Japan, January 2014

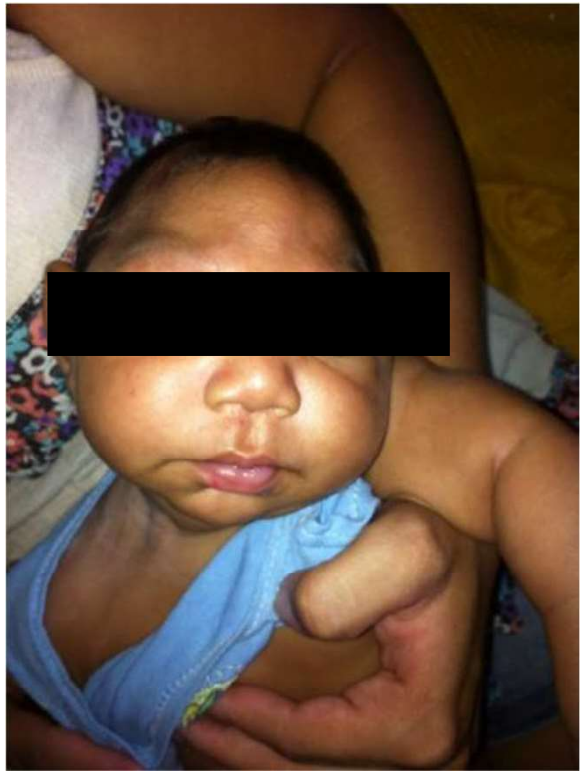


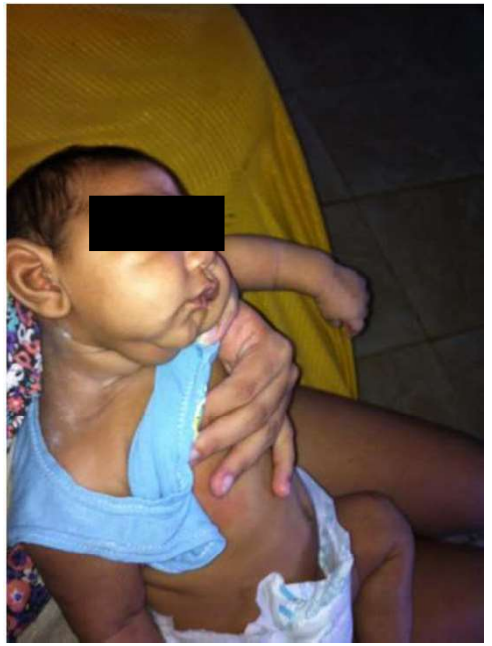
Although the patient was afebrile upon examination, both bulbar conjunctivas appeared congested.

CONJUNTIVITIS

EXANTHEMA







Microcephaly cases

MMWR Morbidity and Mortality Weekly Report

MMWR Morb Mortal Wkly Rep. 2018 Mar 23; 67(11): 340–341. PMCID: PMC5868208
Published online 2018 Mar 23. doi: 10.15585/mmwr.mm6711e1 PMID: 29565840

Fatal Yellow Fever in Travelers to Brazil, 2018

Davidson H. Hamer, MD,[✉1,2] Kristina Angelo, DO,[3] Eric Caumes, MD,[4] Perry J.J. van Genderen, MD, PhD,[5] Simin A. Florescu, MD, PhD,[6] Corneliu P. Popescu, MD,[6] Cecilia Perret, MD,[7] Angela McBride, BMBS,[8] Anna Checkley, MBChB, DPhil,[8] Jenny Ryan, MBBS,[9] Martin Cetron, MD,[10] and Patricia Schlagenhauf, PhD[11]

TABLE

Characteristics of five travelers to Brazil with yellow fever reported by GeoSentinel sites, January–March 2018*

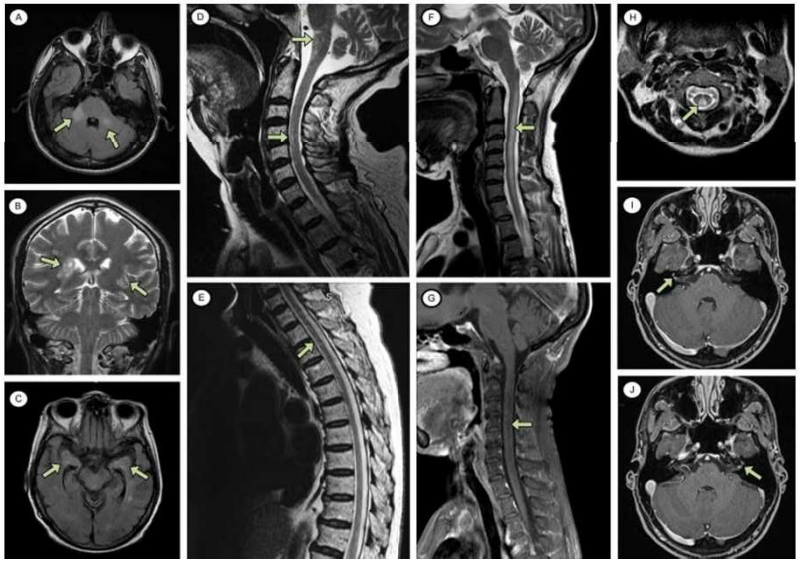
Characteristic	Patient 1 (man)	Patient 2 (woman)	Patient 3 (man)	Patient 4 (man)	Patient 5 (man)
Age (yrs)	46	42	34	44	33
Nationality	Dutch	French	Romanian	Swiss	German
Reporting site	Netherlands	France	Romania	Switzerland	United Kingdom
Area (state) of presumed yellow fever acquisition	Mairiporã (São Paulo)	(Minas Gerais)	Ilha Grande (Rio de Janeiro)	Ilha Grande (Rio de Janeiro)	Ilha Grande (Rio de Janeiro)
Characteristic	Patient 1 (man)	Patient 2 (woman)	Patient 3 (man)	Patient 4 (man)	Patient 5 (man)
Signs/Symptoms	Fever, headache, myalgia, nausea, vomiting, diarrhea	Fever	Fever, rash, myalgia, encephalopathy	Fever, petechial rash, arthralgia, vomiting, diarrhea	Fever, malaise, nausea, jaundice, hepatomegaly
Clinical/Laboratory findings	Hepatitis	Hepatitis, thrombocytopenia, neutropenia	Renal and hepatic failure	Renal and hepatic failure	Thrombocytopenia, renal and hepatic failure
Yellow fever diagnostic testing	Positive RT-PCR for YFV (urine, whole blood, plasma)	Positive RT-PCR (blood); positive IgM (initial diagnosis made in Brazil)	Positive PCR (serum, urine); YF IgM positive; IgG titers rising days 4–8	Positive PCR (blood)	Positive RT-PCR (serum, urine)
Yellow fever vaccination status	No	No	No	No	No
Outcome	Recovered	Recovered	Condition improving as of March 15, 2018	Died	Died

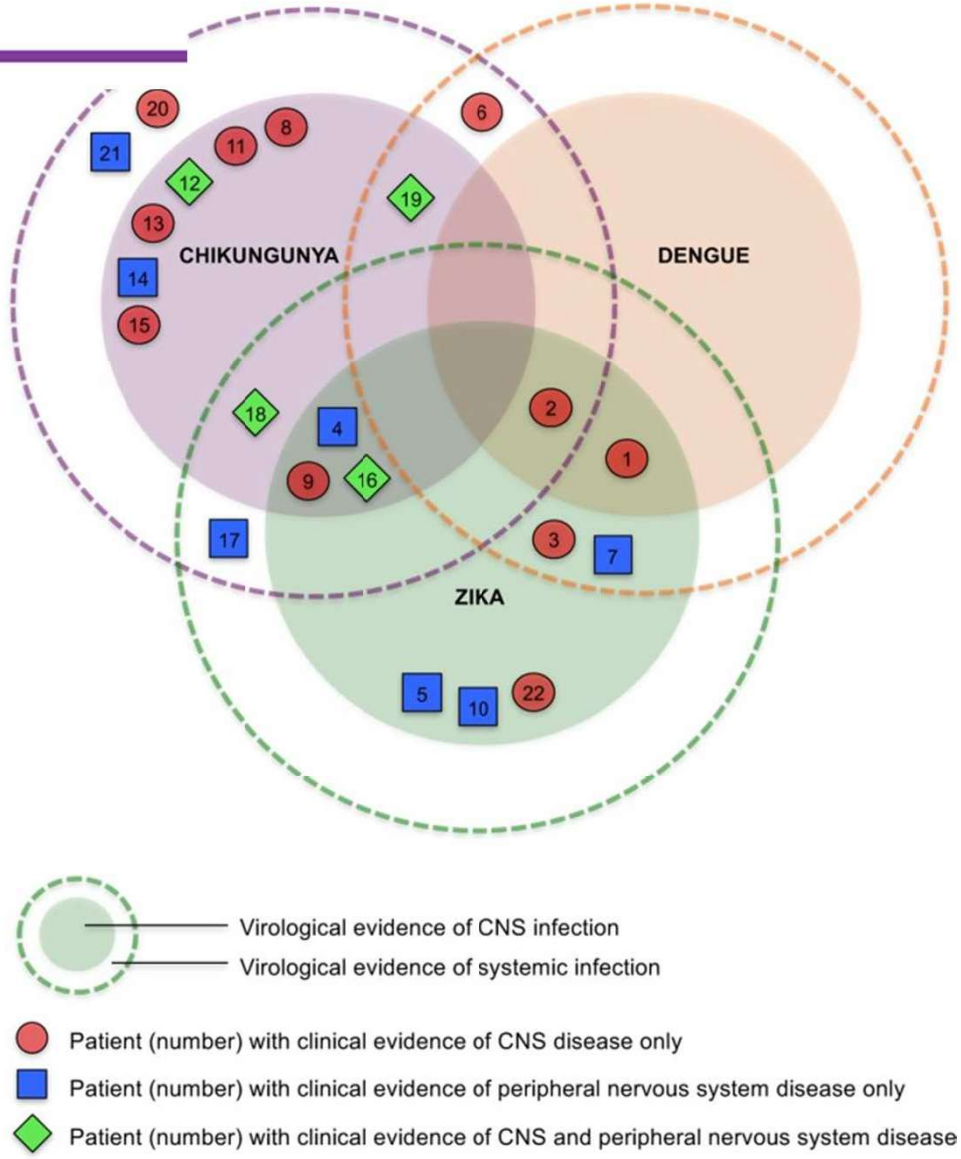
PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

The spectrum of neurological disease associated with Zika and chikungunya viruses in adults in Rio de Janeiro, Brazil: A case series

Ravi Mehta[1,2☯]*, Cristiane Nascimento Soares[3☯], Raquel Medialdea-Carrera[1,2☯], Mark Ellul[1,2,4], Marcus Tulius Texeira da Silva[5,6], Anna Rosala-Hallas[7], Marcia Rodrigues Jardim[8], Girvan Burnside[7], Luciana Pamplona[9], Maneesh Bhojak[4], Radhika Manohar[4], Gabriel Amorelli Medeiros da Silva[3], Marcus Vinicius Adriano[10], Patricia Brasil[11], Rita Maria Ribeiro Nogueira[12], Carolina Cardoso Dos Santos[12], Lance Turtle[1,2,4], Patricia Carvalho de Sequeira[12], David W. Brown[13,14], Michael J. Griffiths[1,2,15], Ana Maria Bispo de Filippis[12], Tom Solomon[1,2,4]*





Conclusions

Zika virus is associated with a wide range of neurological manifestations, including central nervous system disease. Chikungunya virus appears to have an equally important association with neurological disease in Brazil, and many patients had dual infection.

Treatment

There is no etiologic treatment for dengue, chikungunya, Zika virus and yellow fever

Prophylaxis

Bite prevention

Skin

Tissues

Acta Tropica 182 (2018) 257–263

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Current status, challenges and perspectives in the development of vaccines against yellow fever, dengue, Zika and chikungunya viruses

José V.J. Silva Jr.[a], Thaísa R.R. Lopes[b], Edmilson F. de Oliveira-Filho[a], Renato A.S. Oliveira[a,c], Ricardo Durães-Carvalho[a], Laura H.V.G. Gil[a,*]

[a] Department of Virology and Experimental Therapy, Aggeu Magalhães Institute, Oswaldo Cruz Foundation, Recife, PE, Brazil
[b] Virology Sector, Laboratory of Immunopathology Keizo Asami, Federal University of Pernambuco, Recife, PE, Brazil
[c] Department of Pharmaceutical Sciences, Federal University of Pernambuco, Recife, PE, Brazil

Table 1
General aspects of licensed vaccines and most advanced vaccine candidates against yellow fever, dengue, chikungunya and Zika viruses.

Virus Family	Main difficulty	Vaccines						
		Licensed			Under development			
		Identification/seed	Manufacter[1]	Strategy	Identification/seed	Manufacter	Current status	Strategy
Yellow fever Flaviviridae	–	YFV-17DD	Bio-Manguinhos (Fiocruz)	Attenuation by passage in animal, tissue and cell culture	XRX-001	Xcellerex[2]	Phase I (Completed)	YFV-17D inactivated
		YFV-17D-204	Sanofi Pasteur Pasteur Institute Chiron/Novartis	Attenuation by passage in animal, tissue and cell culture	–	–	–	–
		YFV-17D-213	Federal State Unitary Enterprise of Chumakov Institute	Attenuation by passage in animal, tissue and cell culture				
Dengue Flaviviridae	Multiple serotypes	CYD-TVD	Sanofi Pasteur	Live attenuated chimeric	TV003	NIH/NIAID/Butantan Institute	Phase III (In progress)[3]	Live attenuated chimeric
					TDV	Inviragen/Takeda	Phase III (In progress)[4]	Live attenuated chimeric
Chikungunya Togaviridae	High virulence	–	–	–	TSI-GSD-218	USAMRIID/Salk Institute for Biological Studies	Phase II (Completed)	Attenuation by passages in cell culture
					VRC–CHKVLP059-00-VP	NIAID	Phase II (In progress)[5]	VLP
Zika Flaviviridae	GBS[10] Neurotropism ZVCS[11]	–	–	–	GLS–5700	Inovio	Phase I (In progress)[6]	DNA
					VRC 5288 (ZKADNA085-00-VP)	NIAID	Phase I (In progress)[7]	DNA
					VRC 5283 (VRC-ZKADNA090-00-VP)	NIAID	Phase I[8]/II[9] (In progress)	DNA

YELLOW FEVER VACCINE

4

INTERNATIONAL CERTIFICATE* OF VACCINATION OR PROPHYLAXIS

This is to certify that [name] .....

date of birth ..... sex .....

nationality .....

national identification document, if applicable .....

whose signature follows .....

has on the date indicated been vaccinated or received prophylaxis against: (name of disease or condition)

.....

in accordance with the International Health Regulations.

Vaccine or prophylaxis Vaccin ou agent prophylactique	Date Date	Signature and professional status of supervising clinician Signature et titre du clinicien responsable	Manufacturer and batch no. of vaccine or prophylaxis Fabricant du vaccin ou de l'agent prophylactique et numéro du lot	Certificate valid from: until: Certificat valable à partir du : jusqu'au :	Official stamp of the administering centre Cachet officiel du centre habilité
1.					
2.					
3.					

* Requirements for validity of certificate on page 2.

5

CERTIFICAT* INTERNATIONAL DE VACCINATION OU DE PROPHYLAXIE

Nous certifions que [nom] .....

né(e) le ..... de sexe .....

et de nationalité .....

document d'identification national, le cas échéant .....

dont la signature suit .....

a été vacciné(e) ou a reçu des agents prophylactiques à la date indiquée contre: (nom de la maladie ou de l'affection)

.....

conformément au Règlement sanitaire international.

* Voir les conditions de validité à la page 3.

- **Certification becomes valid 10 days following primary dose of YF vaccine**

- **Effective July 2016, YF 10 year booster requirement will be eliminated and a completed ICVP will be valid for a lifetime, including ICVPs filled out more than 10 years ago**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2015 VOL. 372 NO. 2

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

ABSTRACT

BACKGROUND

In light of the increasing rate of dengue infections throughout the world despite vector-control measures, several dengue vaccine candidates are in development.

METHODS

In a phase 3 efficacy trial of a tetravalent dengue vaccine in five Latin American countries where dengue is endemic, we randomly assigned healthy children between the ages of 9 and 16 years in a 2:1 ratio to receive three injections of recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo at months 0, 6, and 12 under blinded conditions. The children were then followed for 25 months. The primary outcome was vaccine efficacy against symptomatic, virologically confirmed dengue (VCD), regardless of disease severity or serotype, occurring more than 28 days after the third injection.

RESULTS

A total of 20,869 healthy children received either vaccine or placebo. At baseline, 79.4% of an immunogenicity subgroup of 1944 children had seropositive status for one or more dengue serotypes. In the per-protocol population, there were 176 VCD cases (with 11,793 person-years at risk) in the vaccine group and 221 VCD cases (with 5809 person-years at risk) in the control group, for a vaccine efficacy of 60.8% (95% confidence interval [CI], 52.0 to 68.0). In the intention-to-treat population (those who received at least one injection), vaccine efficacy was 64.7% (95% CI, 58.7 to 69.8). Serotype-specific vaccine efficacy was 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4. Among the severe VCD cases, 1 of 12 was in the vaccine group, for an intention-to-treat vaccine efficacy of 95.5%. Vaccine efficacy against hospitalization for dengue was 80.3%. The safety profile for the CYD-TDV vaccine was similar to that for placebo, with no marked difference in rates of adverse events.

CONCLUSIONS

The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD in five Latin American countries where dengue is endemic. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01374516.)

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