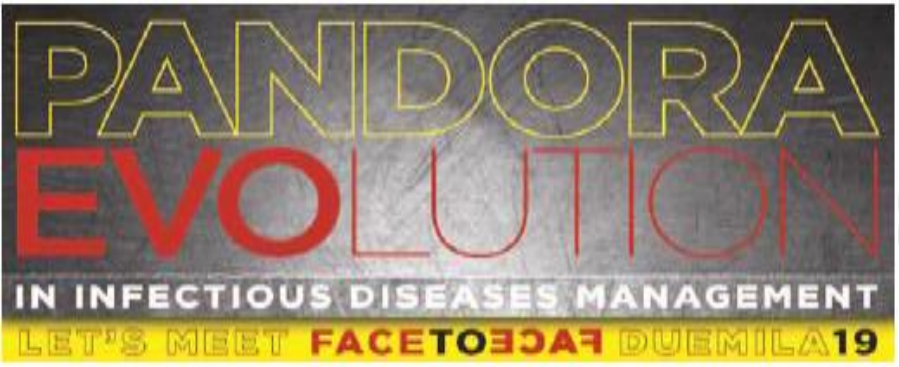
UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

Epidemiologia attuale e quadri clinici principali di febbre dengue,Chikungunya e Zika

Spinello Antinori

Dipartimento di Scienze Biomediche e Cliniche "Luigi Sacco"



Milano, 16 aprile 2019

Vecchie e nuove patologie: arbovirosi e lebbra

Arboviruses

At least 135 arboviruses that have been known to cause human disease

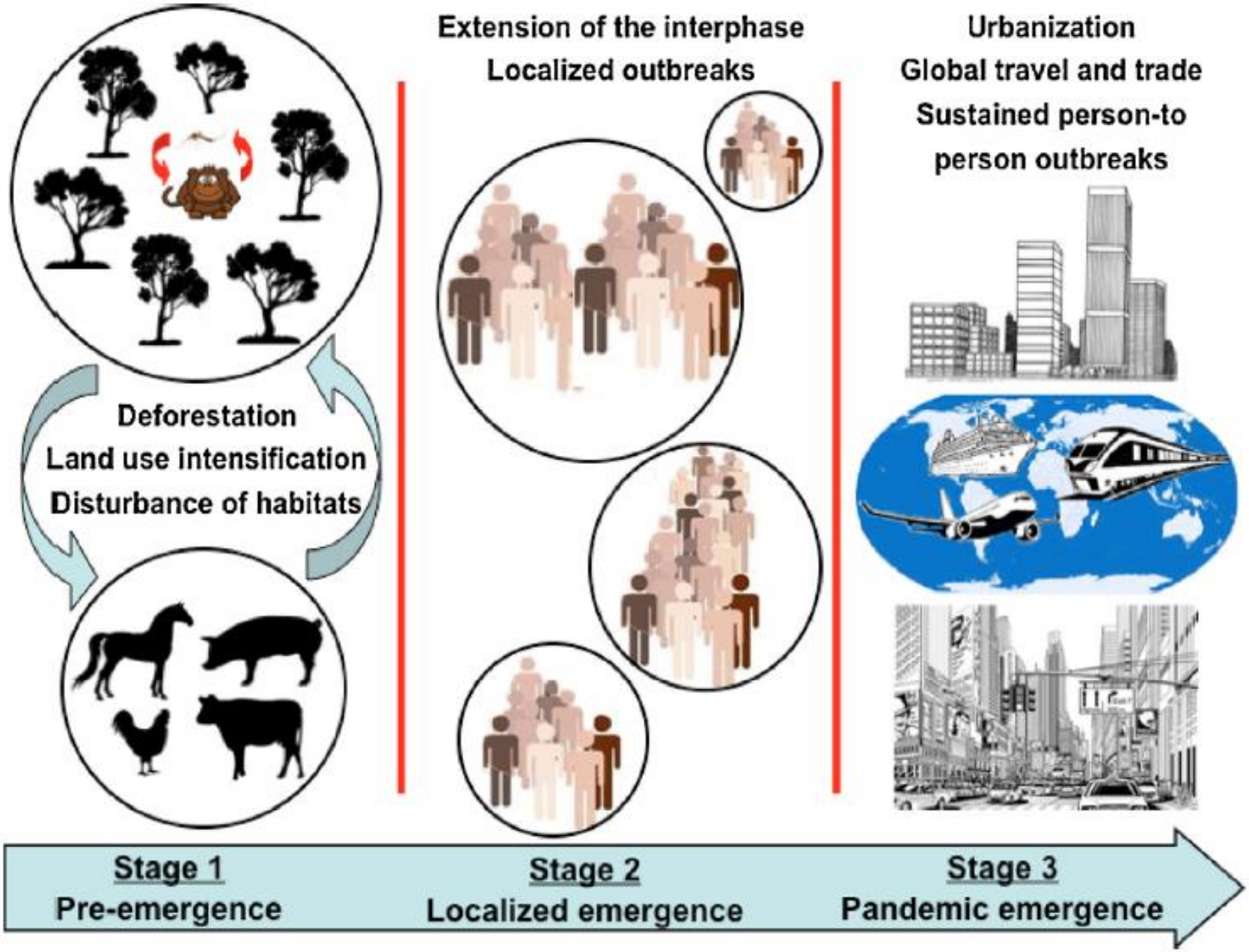
Arboviral infections can range from asymptomatic to fulminant fatal disease

The clinical symptoms are generally categorized as systemic febrile illness, hemorrhagic fever and invasive neurological disease

The vast majority of arboviruses are RNA viruses

Emerging arboviruses: Why today?

Ernest Gould[a,*], John Pettersson[c,d], Stephen Higgs[e,f], Remi Charrel[a,b], Xavier de Lamballerie[a,b]



Mayer S et al. Acta Tropica 2017; 166:155-63

Global risk mapping for major diseases transmitted by *Aedes aegypti* and *Aedes albopictus*

International Journal of Infectious Diseases 67 (2018) 25–35

Samson Leta[a,*], Tariku Jibat Beyene[a], Eva M. De Clercq[b], Kebede Amenu[a], Moritz U.G. Kraemer[c,d,e], Crawford W. Revie[f]

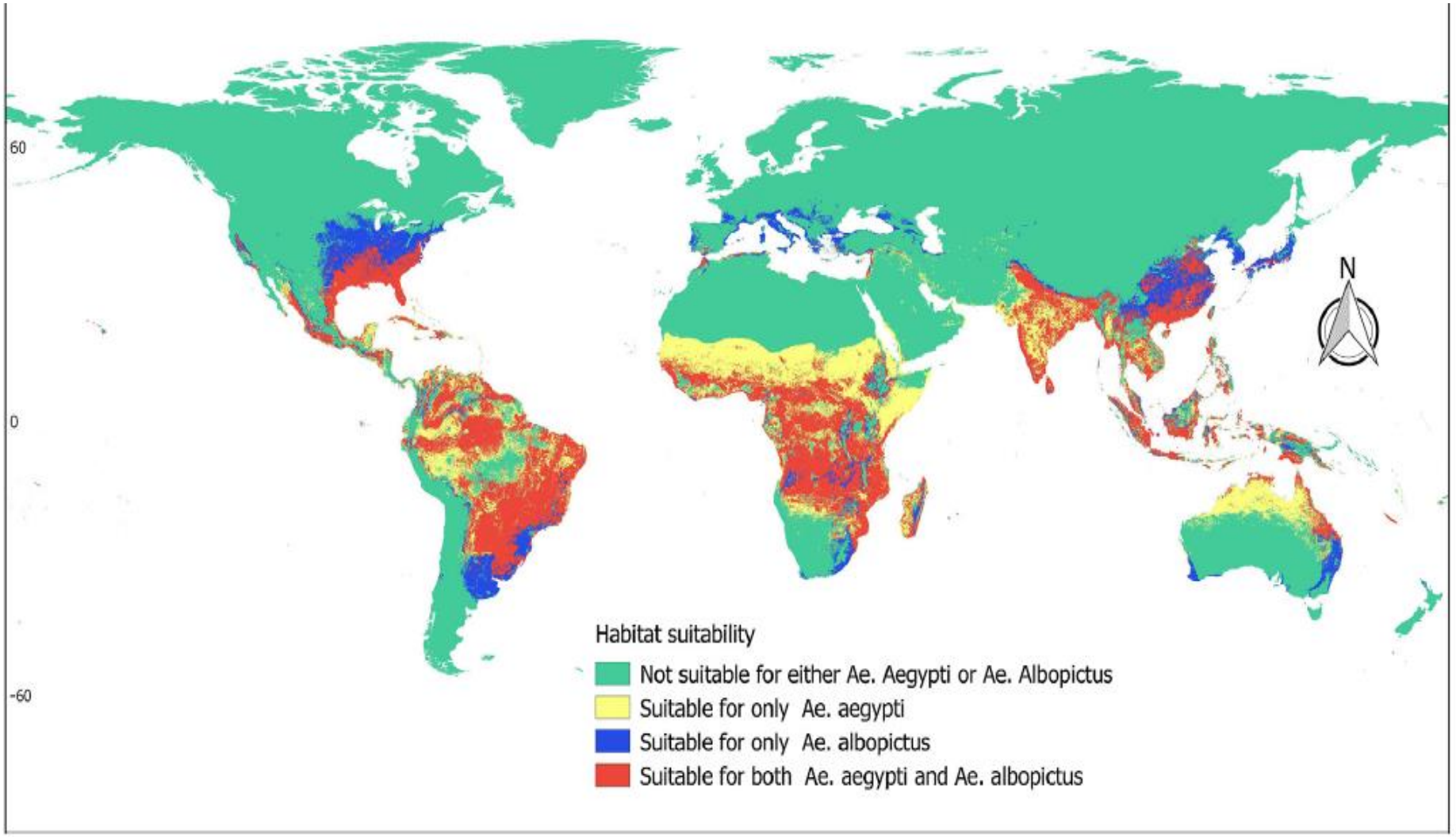


Figure 1. Global predicted habitat suitability of *Aedes aegypti* and *Aedes albopictus*.

Table 1

Number of countries/territories suitable for the vectors and number of countries/territories affected by the diseases, by region.

Region	Number of countries/ territories	Number of countries/territories suitable for			Number of countries/territories affected by				
		Aedes aegypti	*Aedes albopictus*	Either vector	Zika	Dengue fever	Yellow fever	Chikungunya fever	RVF
Africa	58	56	56	57	14	36	30	26	36
Americas[a]	56	52	44	52	48	46	13	46	0
Asia	52	45	43	49	11	15	0	20	3
Europe	56	12	32	32	0	3	0	3	0
Oceania[b]	28	23	22	25	12	11	0	11	0
Overall number of countries/ territories	250	188	197	215	85	111	43	106	39

RVF, Rift Valley fever.

[a] Includes Central America, North America, the Caribbean, and South America.

[b] Includes Australia and the Pacific islands.

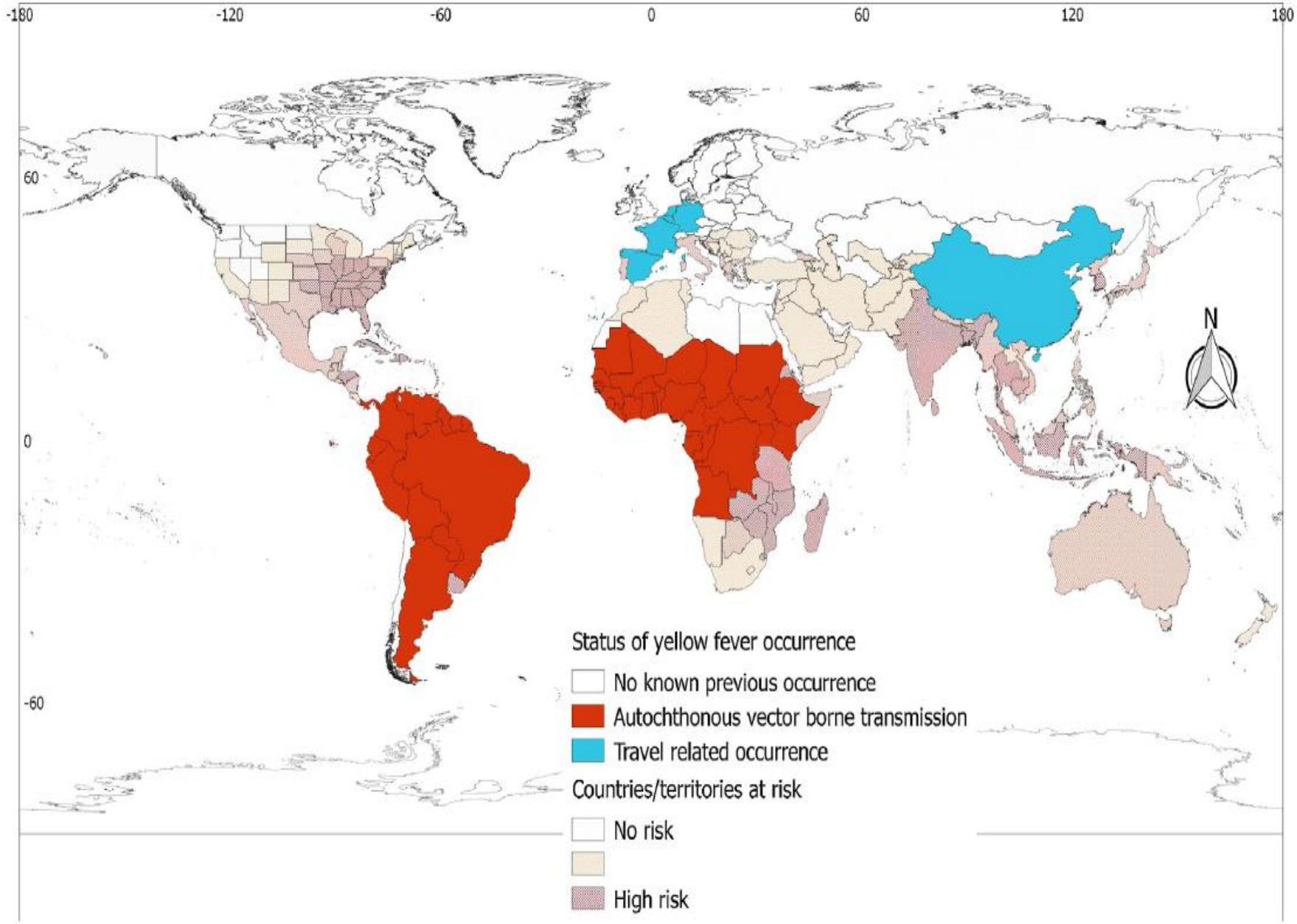


Figure 6. Global yellow fever occurrence. There are discrepancies between the global yellow fever risk and yellow fever occurrence. The discrepancies are apparent in the southern USA, Mexico, Caribbean countries, Southern Africa, Southern Europe, the Indian subcontinent, and Southeast Asian countries, as well as Oceania. It is emphasized that displaying occurrences at the country level overstates the distribution of the virus in Argentina.

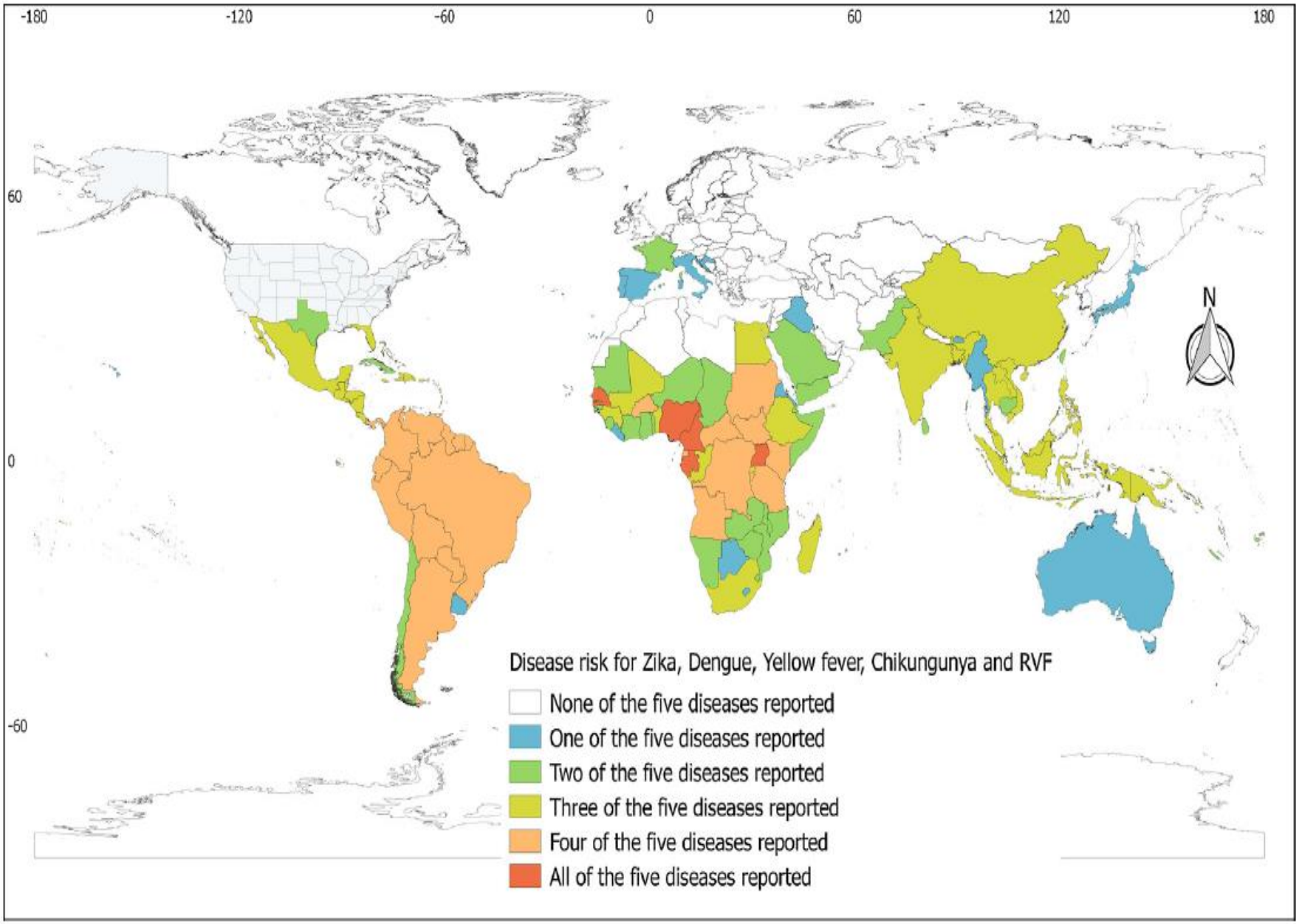


Figure 3. Global country-level occurrences of the selected arboviral diseases. The map depicts the occurrences of selected arboviral diseases from no occurrence, shown in white, to the occurrence of all of the selected arboviral diseases, shown in red.

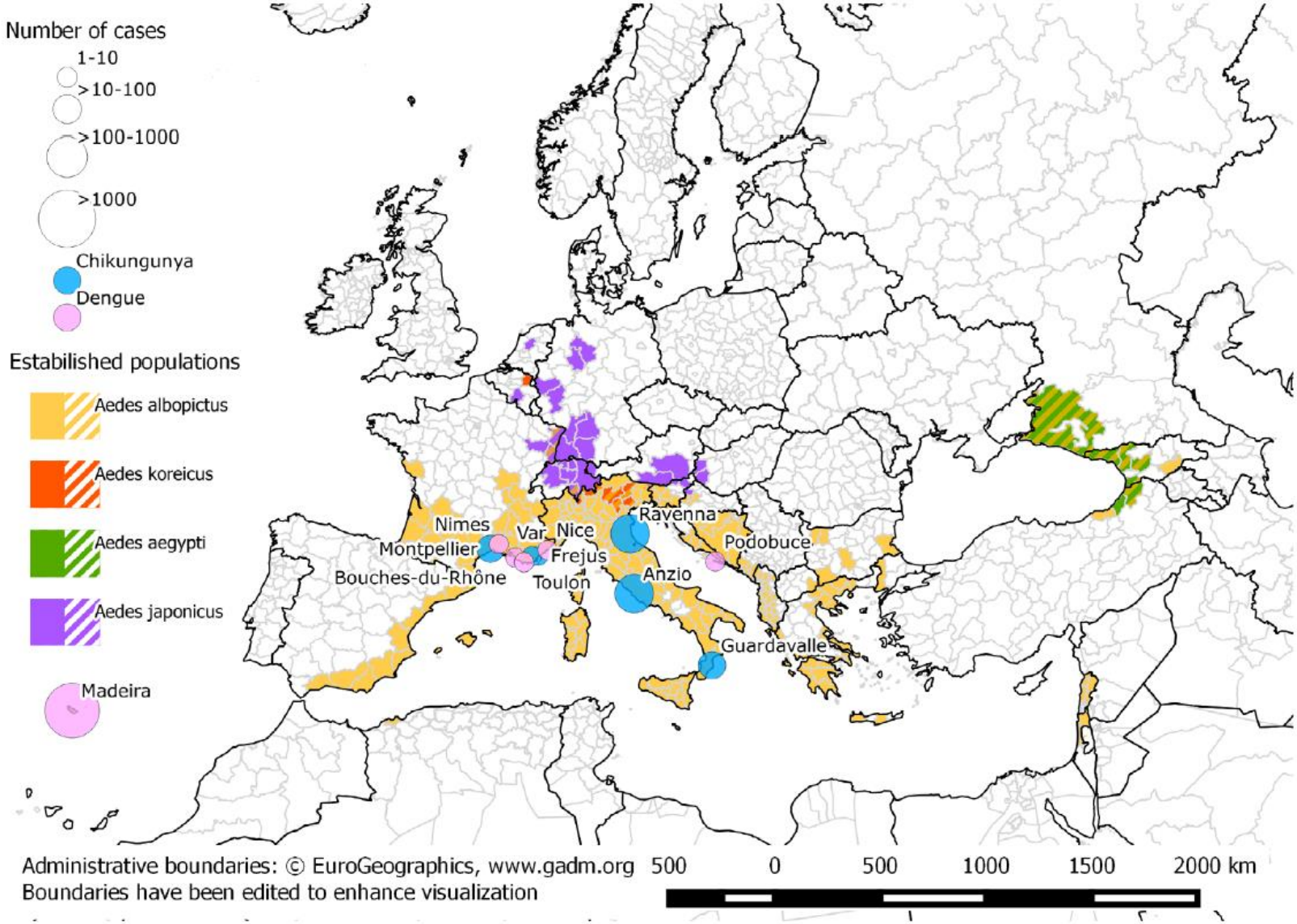
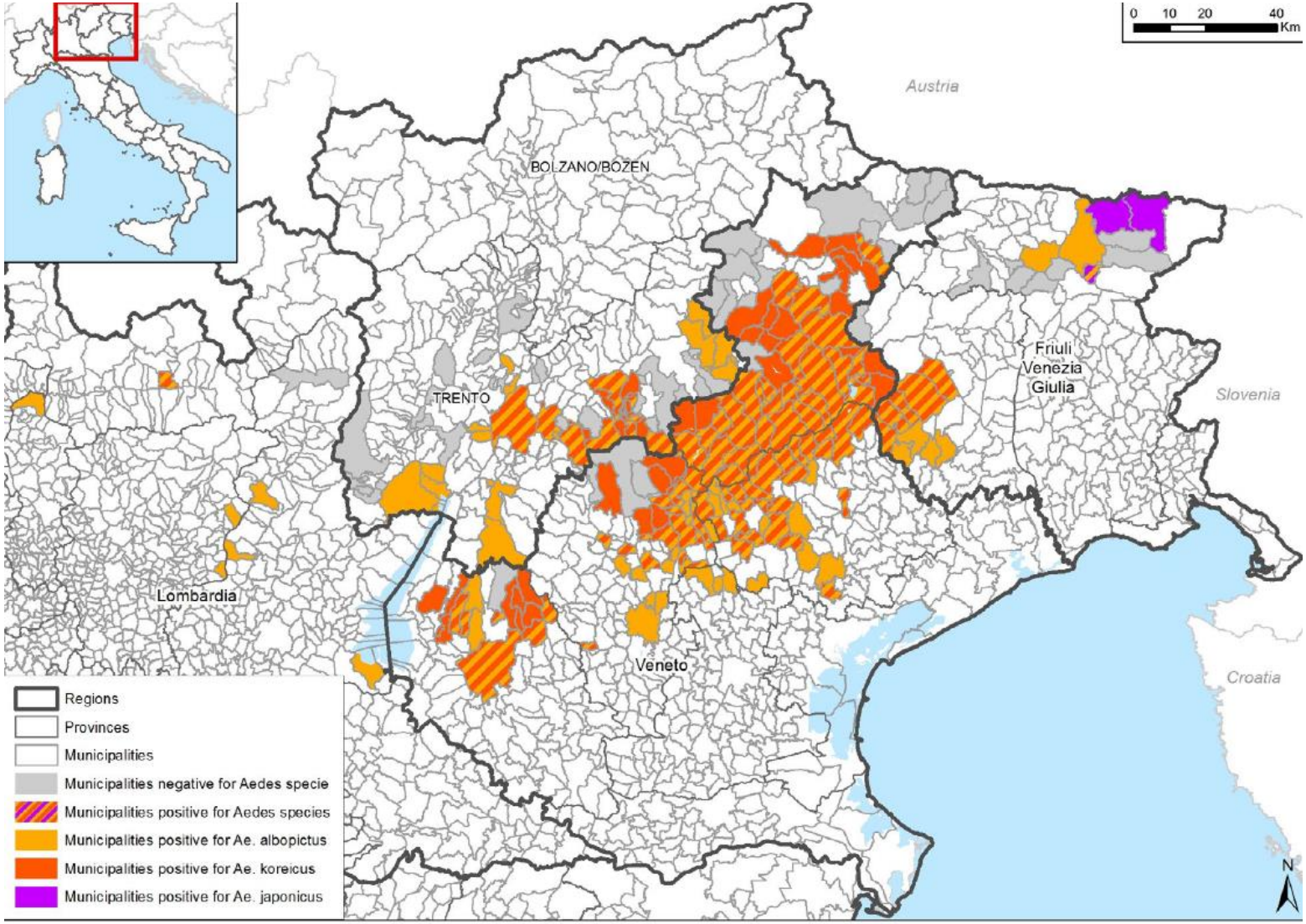


Figure 1. Distribution of invasive mosquito species in Europe (data collated from ECDC maps https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps) and locations and severity of autochthonous dengue and chikungunya outbreaks in Europe from 2007 [9,11,12,16,53–55,83–87]. Map created by Sandro Savino (University of Padua) and Silvia Ciocchetta (QIMR Berghofer).

The new European invader *Aedes* (*Finlaya*) *koreicus*: a potential vector of chikungunya virus

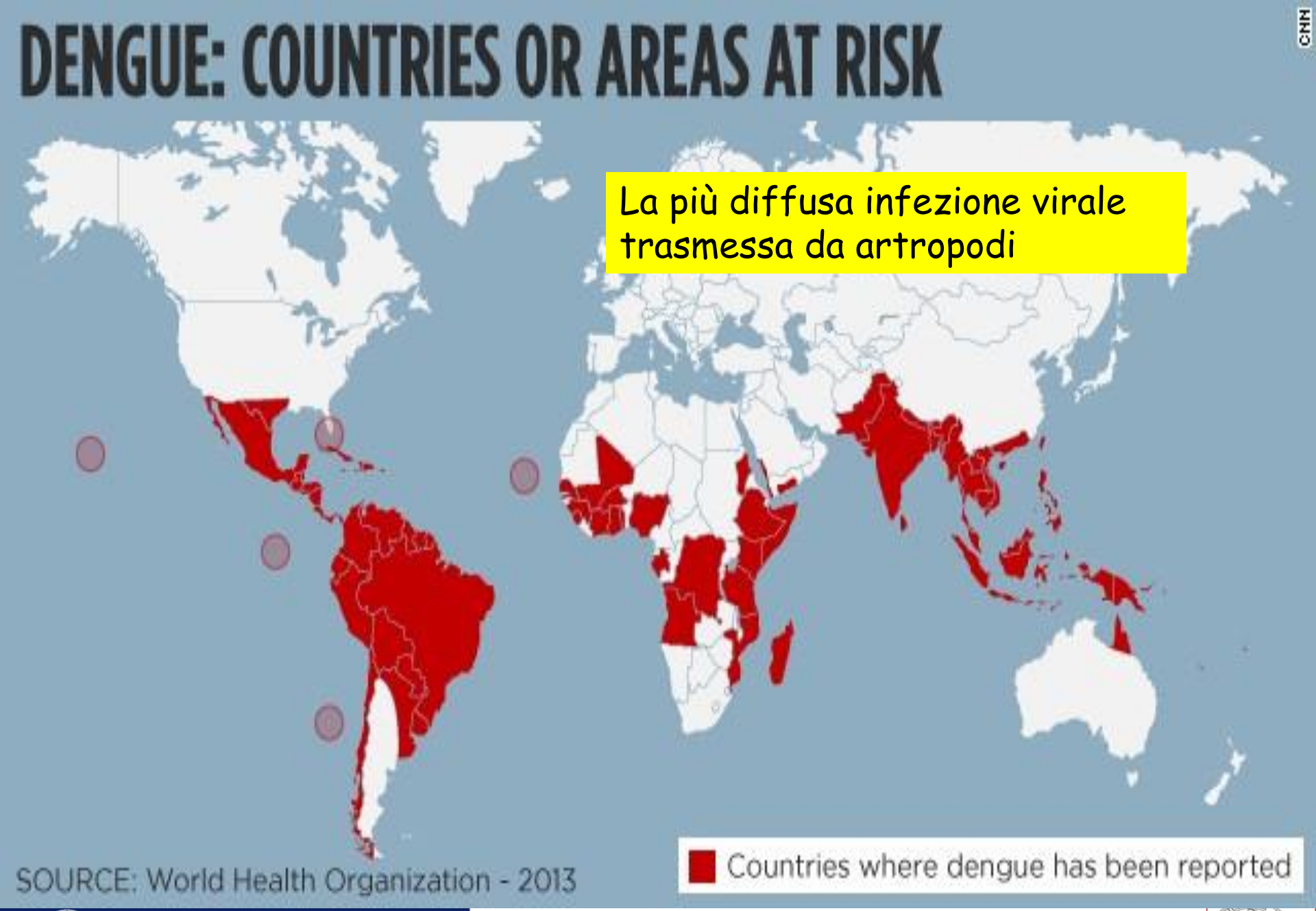
Silvia Ciocchetta[a,b], Natalie A. Prow[a], Jonathan M. Darbro[a], Francesca D. Frentiu[b], Sandro Savino[d], Fabrizio Montarsi[c], Gioia Capelli[c], John G. Aaskov[b] and Gregor J. Devine[a]



igure 2. Distribution of *Ae. koreicus*, *Ae. albopictus* and *Ae. japonicus* in northeastern Italy (data and map provided by Geograph nformation Systems office, IZSVe).

Examples of important arboviruses affecting humans.

Virus	Family	Vector	Vertebrate hosts
Chikungunya	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Primates, birds, cattle, and rodents
Mayaro	*Togaviridae*	Mosquitoes: Haemagogus spp.	Primates, other mammals, birds
Ross River	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Marsupials, other mammals, birds
O'nyong-nyong	*Togaviridae*	Mosquitoes: Anopheles spp.	?
Sindbis	*Togaviridae*	Mosquitoes: Aedes, Culex, and Culiseta spp.	Birds
Barmah Forest	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Birds? Marsupials, Others?
Eastern equine encephalitis	*Togaviridae*	Mosquitoes: Culiseta, Aedes, Coquillettidia, and Culex spp.	Birds, horses, other mammals
Western equine encephalitis	*Togaviridae*	Mosquitoes: Culex, Aedes, Ochlerotatus, and Coquillettidia spp.	Birds, horses, other mammals
Venezuelan equine encephalitis	*Togaviridae*	Mosquitoes: Culex, Ochlerotatus, Anopheles, Mansonia, Psorophora, Aedes spp. and others	Horses, Rodents, Other mammals, Birds
Dengue	*Flaviviridae*	Mosquitoes: Aedes spp	Primates
Yellow Fever	*Flaviviridae*	Mosquitoes: Aedes and Haemogogus spp.	Primates
West Nile	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Horses, Other Mammals
Japanese encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Pigs
Murray Valley encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds
Zika virus	*Flaviviridae*	Mosquitoes: Aedes spp	Primates
Rocio	*Flaviviridae*	Mosquitoes: Psorophora and Aedes spp	Birds
St. Louis encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Bats, Other Mammals
Kyasanur Forest disease	*Flaviviridae*	Ticks: Hemaphysalis spp.	Primates, Rodents, Other Mammals
Omsk hemorrhagic fever	*Flaviviridae*	Ticks: Dermacentor and Ixodes spp Mosquitoes:?	Rodents, Volves, Other Mammals
Tick-borne encephalitis	*Flaviviridae*	Ticks: Ixodes spp	Rodents, Goats, Sheep, Cows, Other Mammals, Birds?
Sandfly fever	*Bunyaviridae*	Sandflies: *Phlebotomus* spp.	Birds? Mammals?
Rift Valley fever	*Bunyaviridae*	Mosquitoes: Aedes, Ochlerotatus, Stegomyia, Anopheles, Culex, Neomelaniconion, Eretmapodites and others	Cows, Sheep, Camels, Goats and Other Mammals
La Crosse encephalitis	*Bunyaviridae*	Mosquitoes: Aedes spp	Rodents
Crimean-Congo hemorrhagic fever	*Bunyaviridae*	Ticks: *Hyalomma* spp	Cows, Sheep, Goats, Hares and Other Mammals
Oropouche	*Bunyaviridae*	Midges: Culicoides sp	Primates? Sloths? Birds?
Severe febrile thrombocytopenia syndrome	*Bunyaviridae*	Ticks: Haemaphysalis sp	?
Chandipura	*Rhabdoviridae*	Sandflies: *Phlebotomus* and *Sergentomyia* spp.	Hedgehogs, Others?
Bluetongue	*Reoviridae*	Midges: Culicoides spp	Sheep, Cows, Other Mammals


DENGUE: COUNTRIES OR AREAS AT RISK
CNN
La più diffusa infezione virale trasmessa da artropodi
SOURCE: World Health Organization - 2013
Countries where dengue has been reported

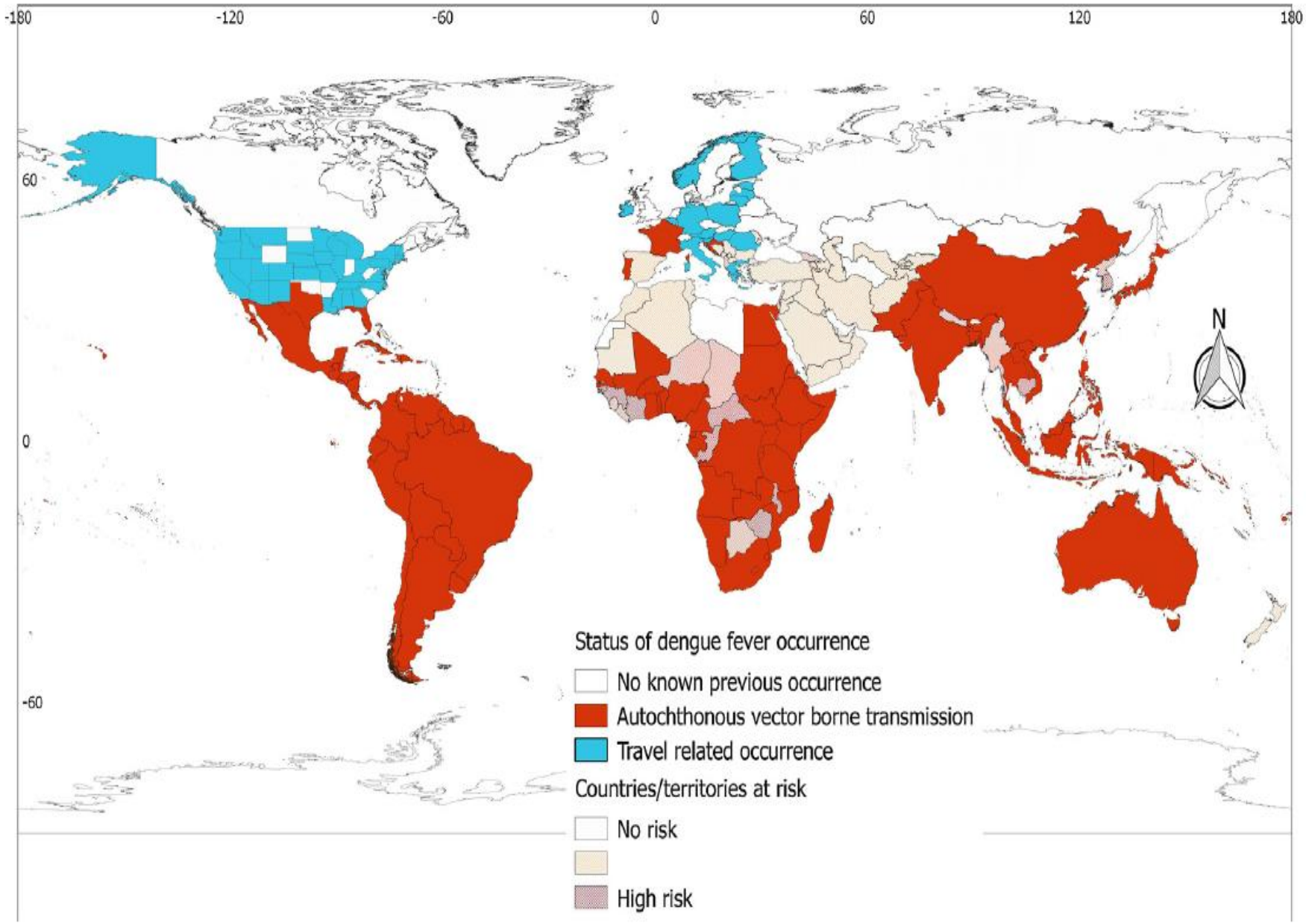
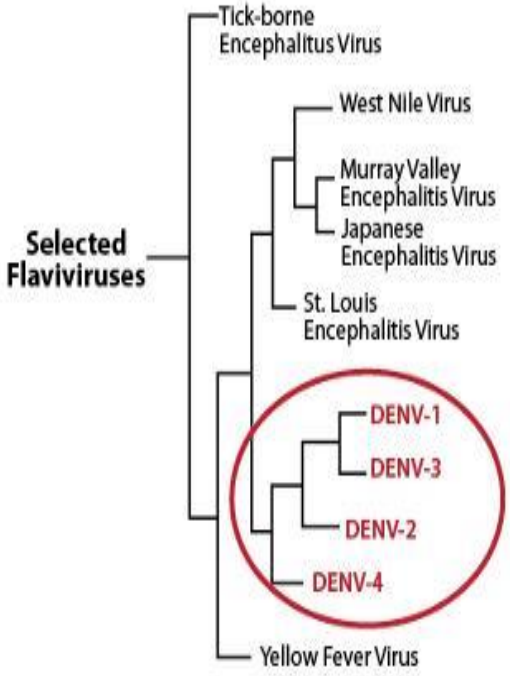


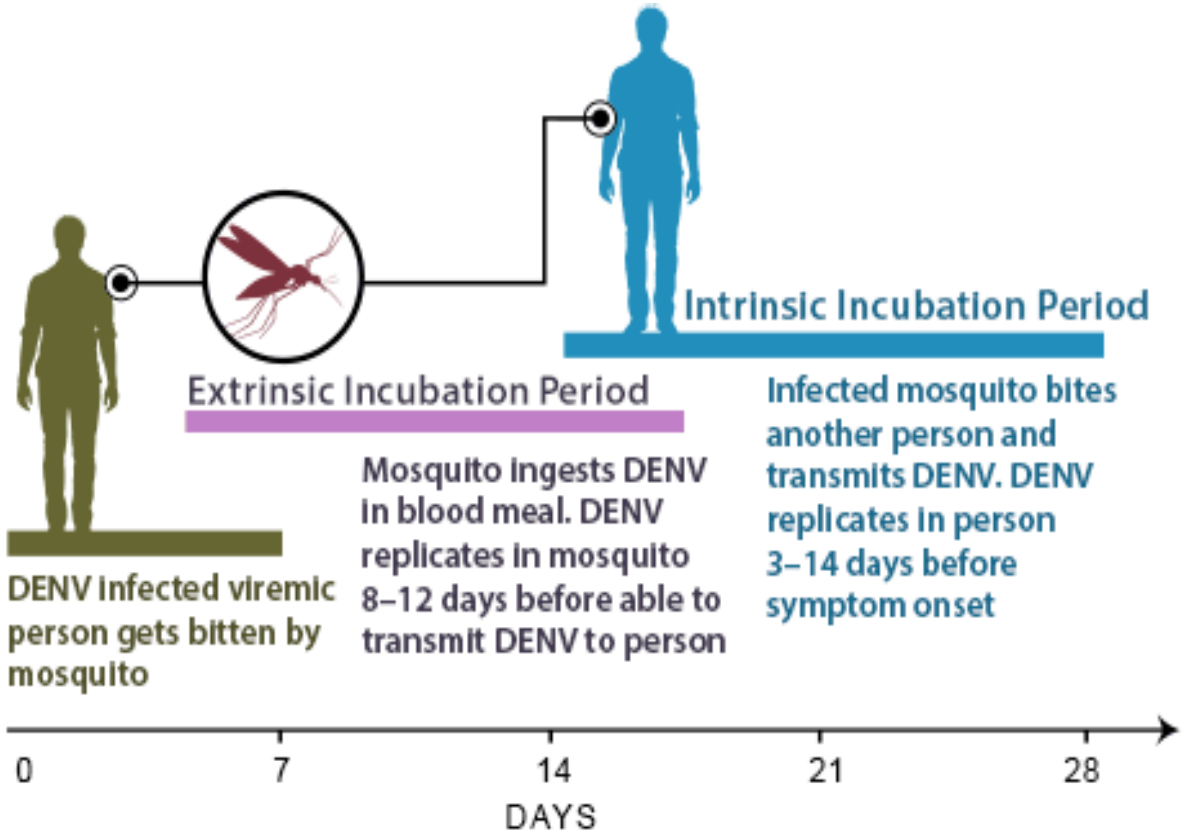
Figure 5. Global dengue fever occurrence. The global distribution of dengue fever corresponds well with the global dengue risk. The distribution of dengue fever extends to the temperate part of the world, with some European countries reporting its occurrence. It is emphasized that displaying occurrences at the country level overstates the distribution of the virus, especially in China, Argentina, and Chile.

Dengue fever

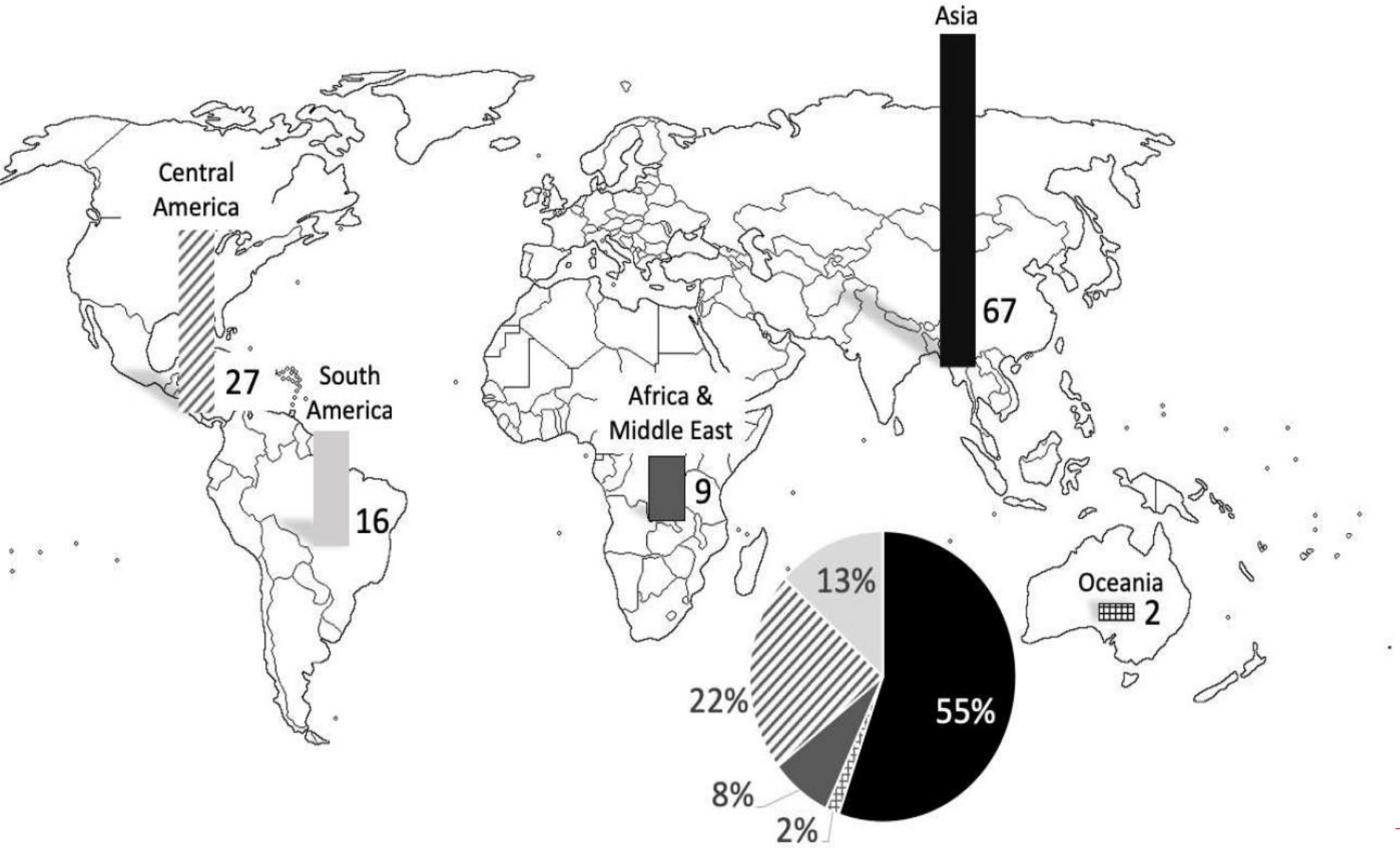
Aedes aegypti most efficient mosquito vector

Aedes albopictus one alternative mosquito vector

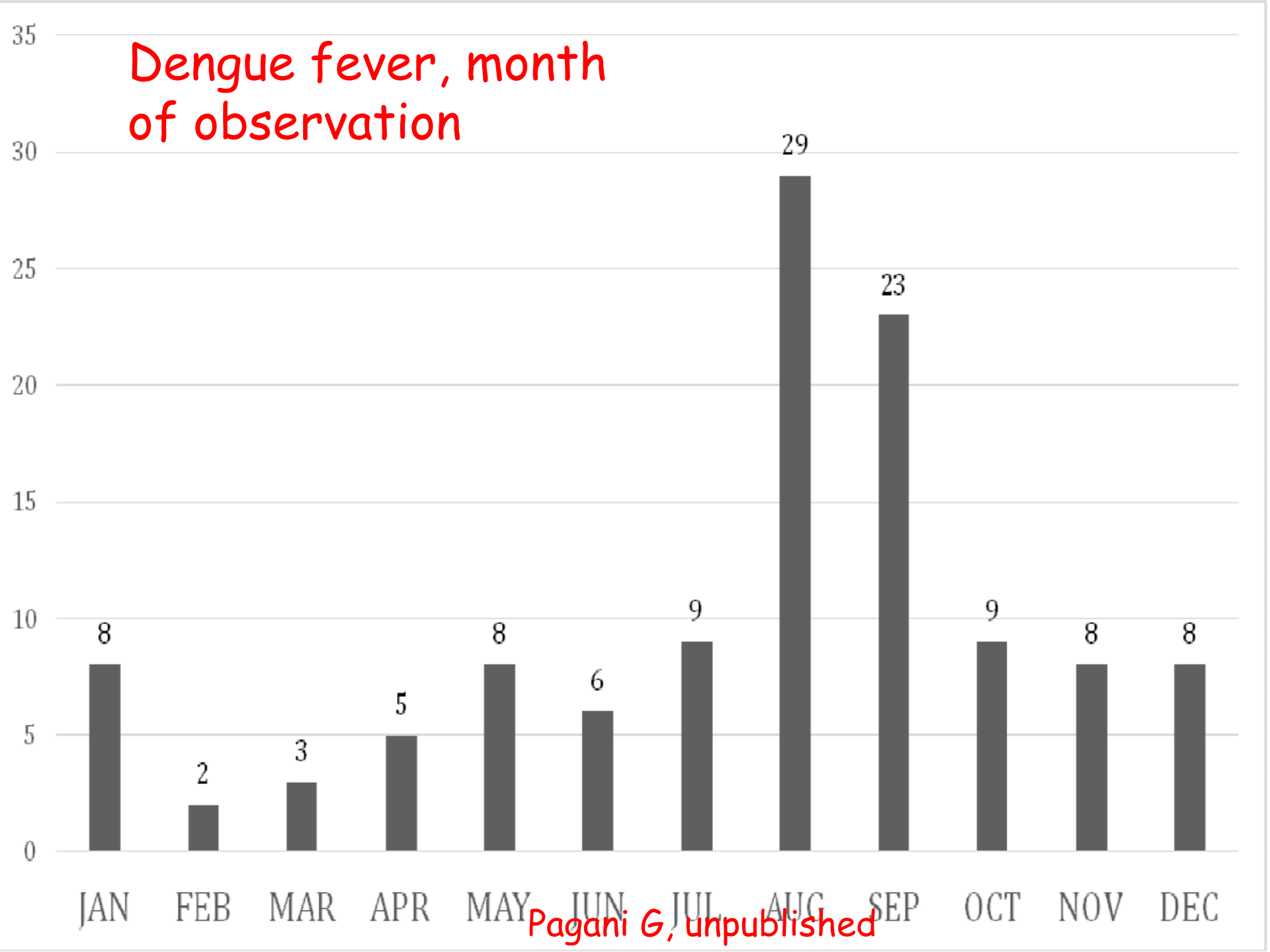




Dengue fever at L.Sacco ID department: geographic area of acquisition



Pagani G, unpublished


Dengue fever, month of observation
35
30
25
20
15
10
5
0
8
2
3
5
8
6
9
29
23
9
8
8
JAN
FEB
MAR
APR
MAY
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SEP
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Pagani G, unpublished

Figure 3. Distribution of dengue cases by month, EU/EEA, 2013–2016 and 2017

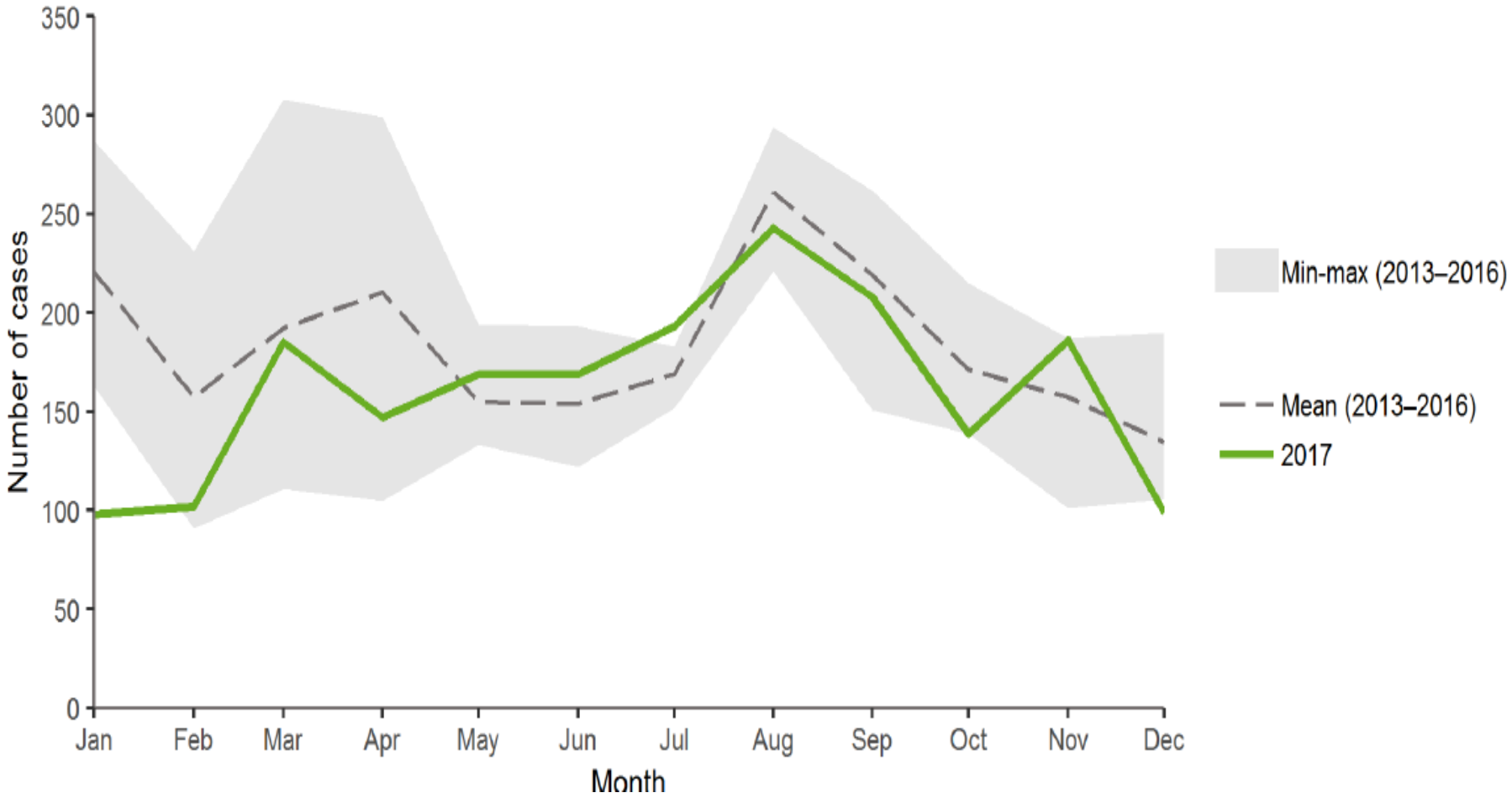


Table 1. Distribution of dengue cases and rates per 100 000 population by country and year, EU/EEA, 2013–2017

Country	2013		2014		2015		2016		2017			
	Reported cases	Rate	Reported cases	Rate	Reported cases	Rate	Reported cases	Rate	Reported cases	Rate	ASR	Confirmed cases
Austria	89	1.1	91	1.1	103	1.2	116	1.3	85	1.0	-	85
Belgium	139	1.2	110	1.0	108	1.0	114	1.0	77	0.7	-	77
Bulgaria	.	.	.	.	.	.	.	.	.	.	.	.
Croatia	3	0.1	2	0.0	-	-	2	0.0	0	0.0	0	0
Cyprus	.	.	.	.	.	.	.	.	.	.	.	.
Czech Republic	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Denmark	.	.	.	.	.	.	.	.	.	.	.	.
Estonia	0	0.0	9	0.7	12	0.9	9	0.7	8	0.6	-	8
Finland	80	1.5	38	0.7	54	1.0	66	1.2	25	0.5	-	25
France	271	0.4	212	0.3	167	0.3	297	0.4	264	0.4	-	240
Germany	877	1.1	624	0.8	723	0.9	956	1.2	635	0.8	-	635
Greece	1	0.0	4	0.0	2	0.0	2	0.0	1	0.0	-	1
Hungary	10	0.1	6	0.1	12	0.1	24	0.2	17	0.2	-	15
Iceland	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3	-	1
Ireland	15	0.3	21	0.5	8	0.2	18	0.4	10	0.2	-	10
Italy	142	0.2	79	0.1	103	0.2	106	0.2	95	0.2	-	95
Latvia	7	0.3	1	0.0	4	0.2	9	0.5	13	0.7	-	13
Liechtenstein	.	.	.	.	.	.	.	.	.	.	.	.
Lithuania	1	0.0	3	0.1	9	0.3	4	0.1	4	0.1	-	0
Luxembourg	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0
Malta	0	0.0	0	0.0	1	0.2	1	0.2	3	0.7	-	3
Netherlands	-	-	3	-	18	-	6	-	0	-	-	0
Norway	57	1.1	73	1.4	98	1.9	64	1.2	35	0.7	-	35
Poland	13	0.0	15	0.0	12	0.0	41	0.1	29	0.1	-	10
Portugal	-	-	-	-	14	0.1	13	0.1	11	0.1	-	10
Romania	6	0.0	6	0.0	7	0.0	8	0.0	7	0.0	-	7
Slovakia	4	0.1	0	0.0	2	0.0	4	0.1	2	0.0	-	2
Slovenia	8	0.4	2	0.1	3	0.1	6	0.3	5	0.2	-	5
Spain	0	0.0	0	0.0	168	0.4	261	0.6	128	0.3	-	49
Sweden	220	2.3	119	1.2	159	1.6	225	2.3	106	1.1	-	106
United Kingdom	571	0.9	376	0.6	423	0.7	468	0.7	465	0.7	-	386
EU/EEA	**2 514**	**0.5**	**1 794**	**0.4**	**2 210**	**0.5**	**2 821**	**0.6**	**2 026**	**0.4**	**-**	**1 818**

Clinical manifestations of dengue fever in Milano, L Sacco hospital

SIGNS/SYMPTOMS *(%)*	A.O. Sacco, MI	Laferl *et al.*	Lagi *et al.*	Trojanek *et al.*	Hoffmeister *et al.*	Tavakolipoor *et al.*	Calleri *et al.*	Riddell *et al.*
Fever	**99,2**	100	100	100	100	97,5	~100[e]	95,4
Arthralgia	**50,8**	63	63,9[a]	59,8	21,4	42[a]	~70[e]	27,3[a]
Rash	**50,8**	43	41,7	68,2	46,4	47,9	~50[e]	22,7
Headache	**50,8**	67	41,7	65,9	10,7[c]	49,6	~60[e]	18,2
Myalgia	**46,7**	63	[a]	62,1	62,5%	[a]	NR	[a]
Nausea	**26,2**	34	63,9[b]	NR	NR	NR	NR	NR
Diarrhea	**18**	30	NR	36,4	NR	42,9	NR	22,7
Vomit	**14,7**	19	[b]	15,9	3,6[d]	NR	NR	22,7

Table 2: European literature review - signs and symptoms.

[a]: arthralgia and/or myalgia; [b]: nausea and/or vomit; [c]: retro-ocular pain; [d]: persistent vomiting; [e]: precise numeric values not reported, percentages extrapolated from graphic; NR: data not reported.

LABORATORY VALUES	A.O. Sacco, MI	Laferl *et al.*	Lagi *et al.*	Trojanek *et al.*	Hoffmeister *et al.*	Tavakolipoor *et al.*	Riddell *et al.*
Plt (median)	**103 x10^9/µL**	66 x10^9/µL	NR	118 x10^9/µL	NR	NR	93 x10^9/µL
WBC (median)	**2685/µL**	2280/µL	NR	3200/µL	NR	NR	4000/µL
Hct (median)	**40,9%**	43,9%	NR	43,3%	NR	NR	41%
AST (median)	**62 U/L**	2,51xULN	NR	70 U/L	NR	NR	NR
ALT (median)	**46 U/L**	2,22xULN	NR	85,3 U/L	NR	NR	67 U/L
LDH (median)	**304 U/L**	1,31xULN	NR	294 U/L	NR	NR	NR
Thrombocytopenia (%)	**81,2**	72	72,2	12,9[a]	84	32,8	NR
Leukopenia (%)	**77,1**	89	66,7	14,4[b]	73,2	26,1	NR
AST > ULN (%)	**54,1**	79	NR	NR	NR	32,8	NR
ALT > ULN (%)	**45,9**	70	NR	NR	NR	34,5	NR
LDH > ULN (%)	**60,7**	73	NR	NR	NR	31,1	NR

Table 3: European literature review: laboratory values

[a]: <50x10^9/µL; [b]: <2000/µL; Plt: platelets; WBC: white blood cells; AST: aspartate aminotrasferase; ALT: alanine aminotrasferase; LDH: lactate dehydrogenase; ULN: Upper Limit

Pagani G, unpublished

Dengue: an update for clinicians working in non-endemic areas

Authors: Sophie Yacoub[A] and Bridget Wills[B]

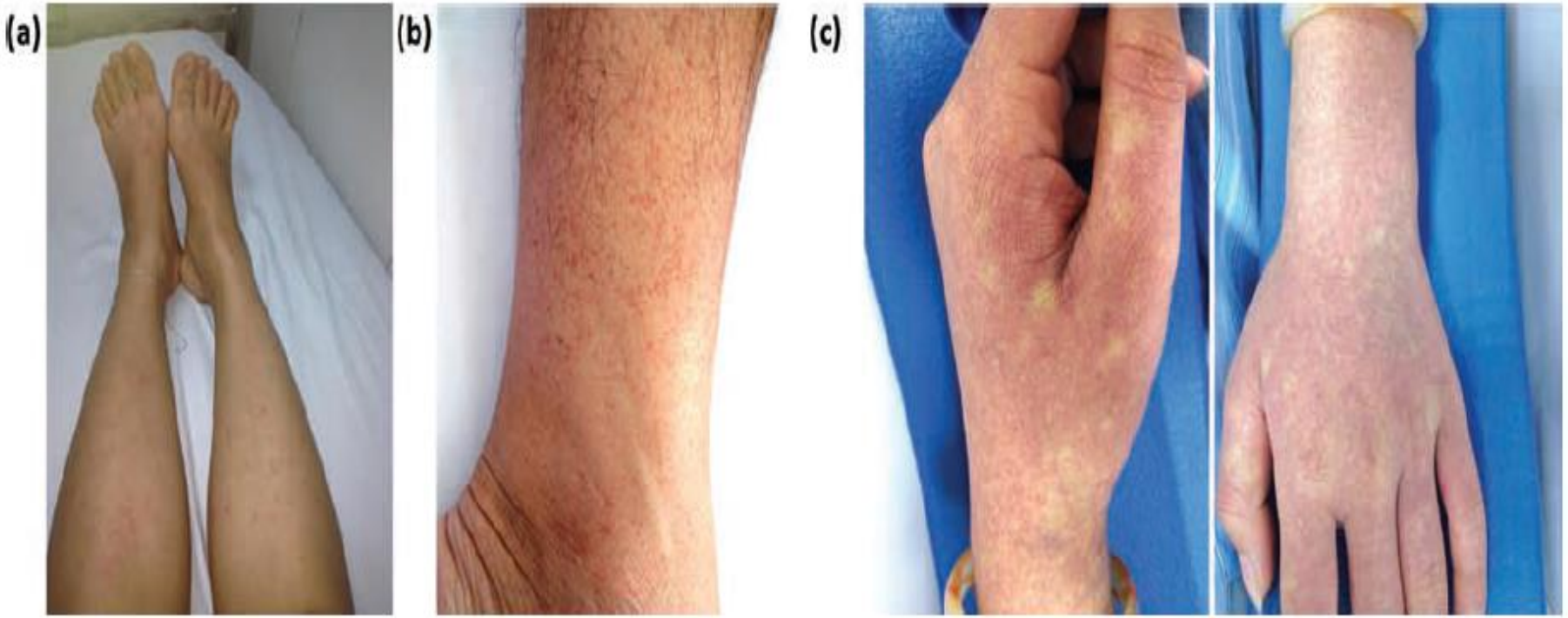
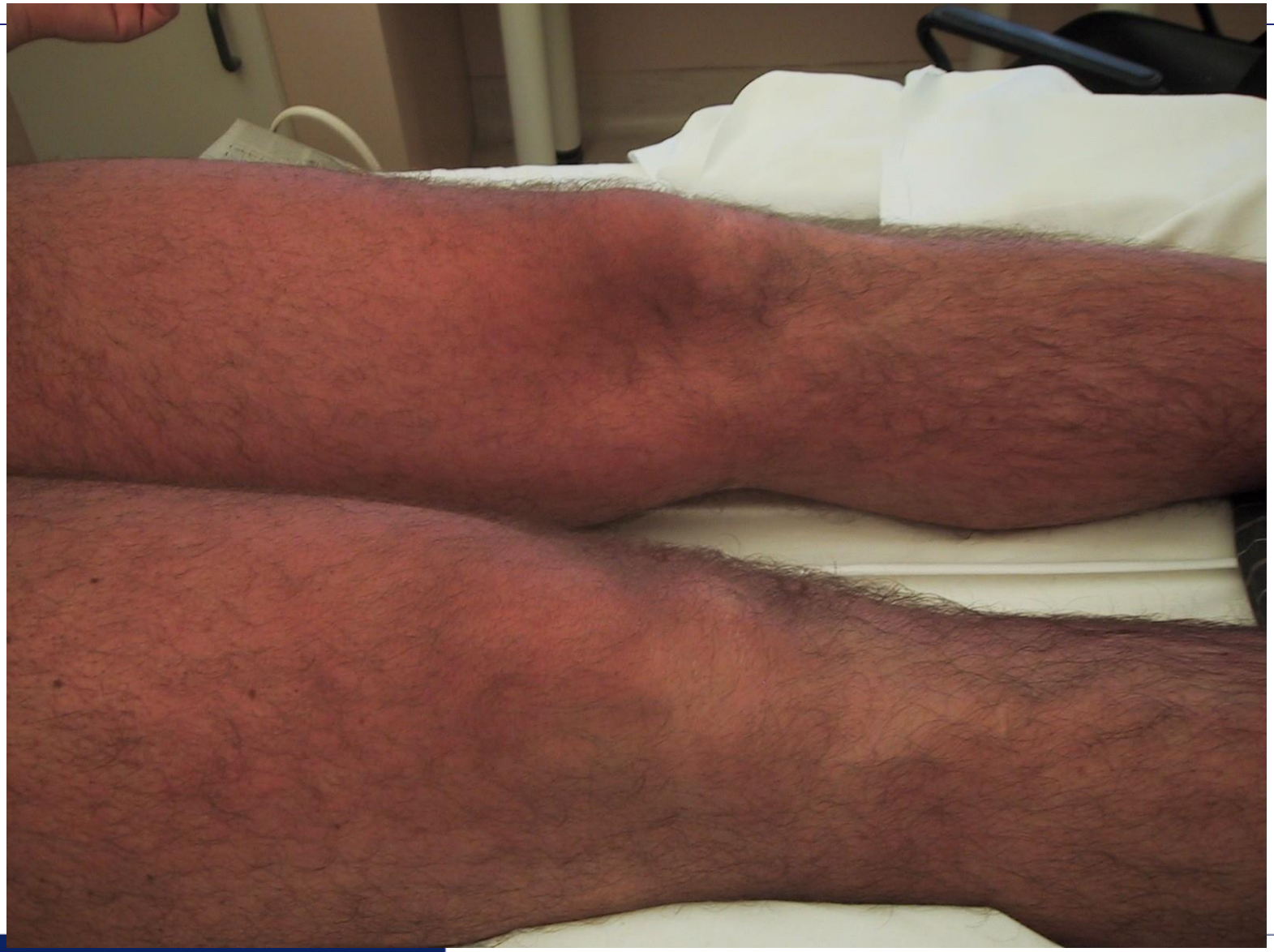
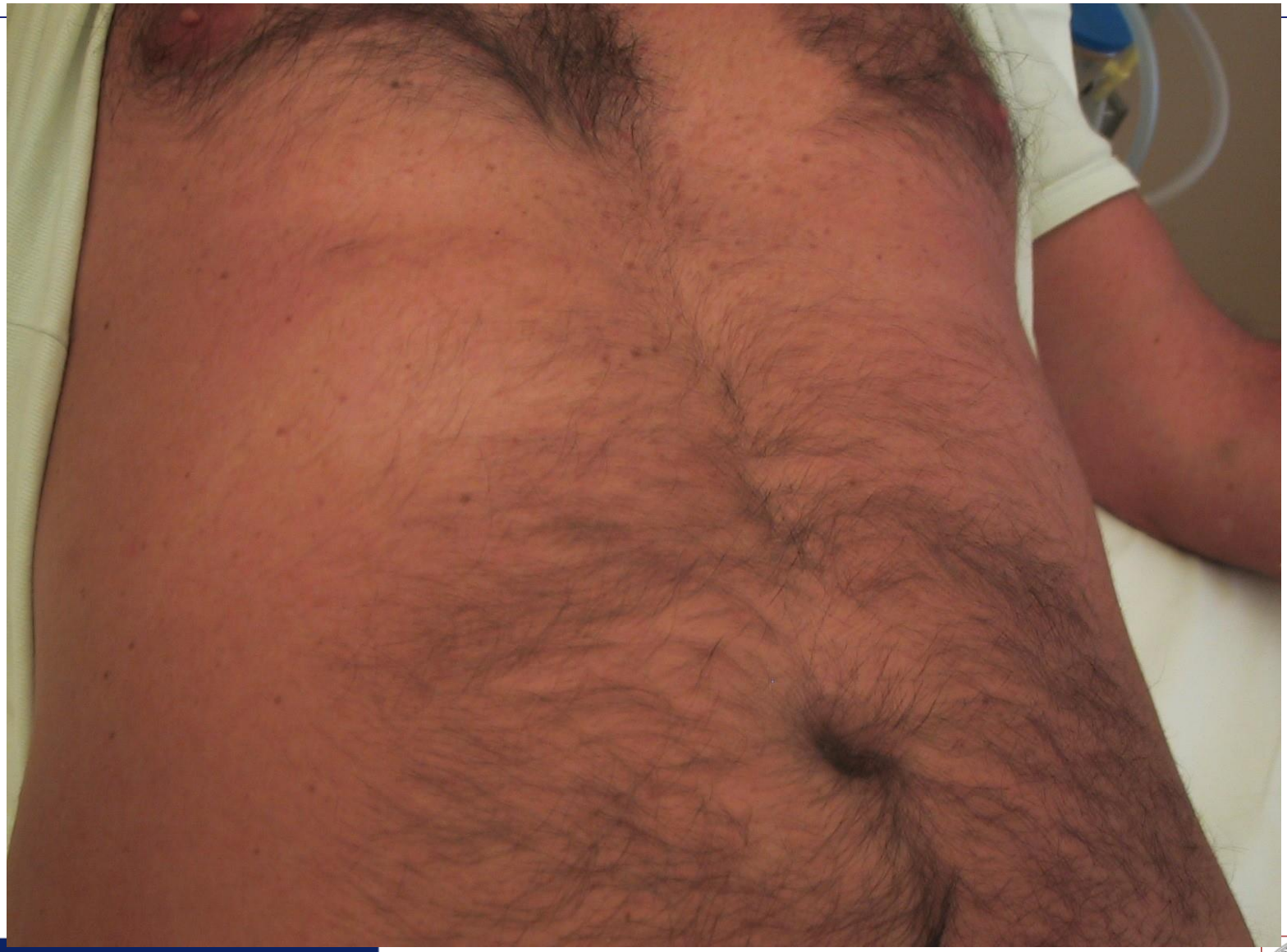


Fig 1. Spectrum of dengue associated rashes. (a) Macular-papular rash may be seen during the febrile phase; (b) petechial rash may develop during the febrile/critical phase particularly on arms and legs; (c) erythematous rash with 'islands of white' can be widespread and develop during the recovery phase.

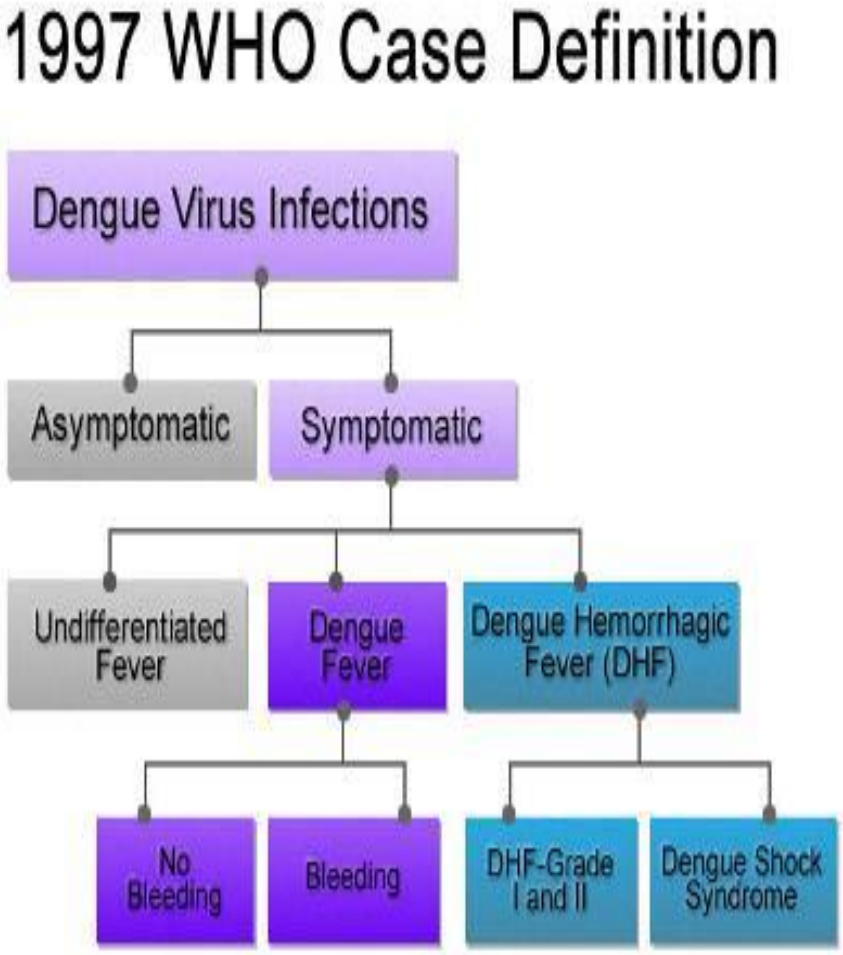
Dengue: *rash* cutaneo

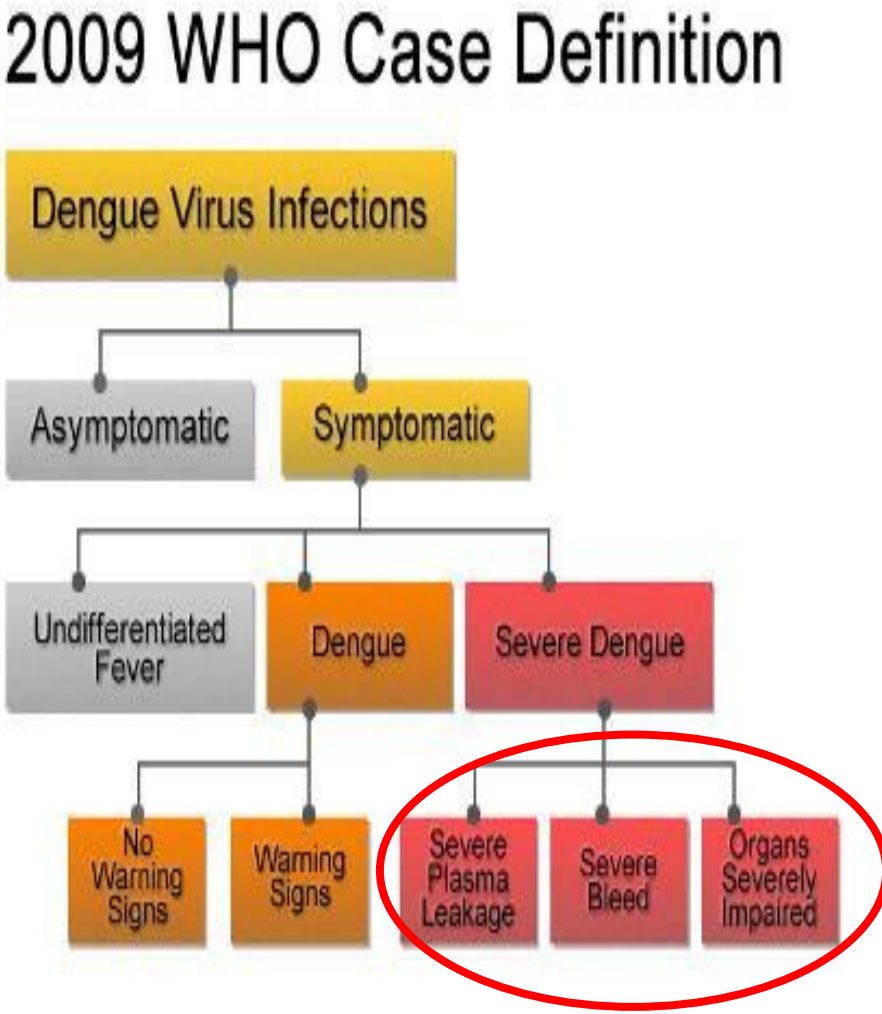


Dengue: *rash* cutaneo



Dengue fever WHO case definition



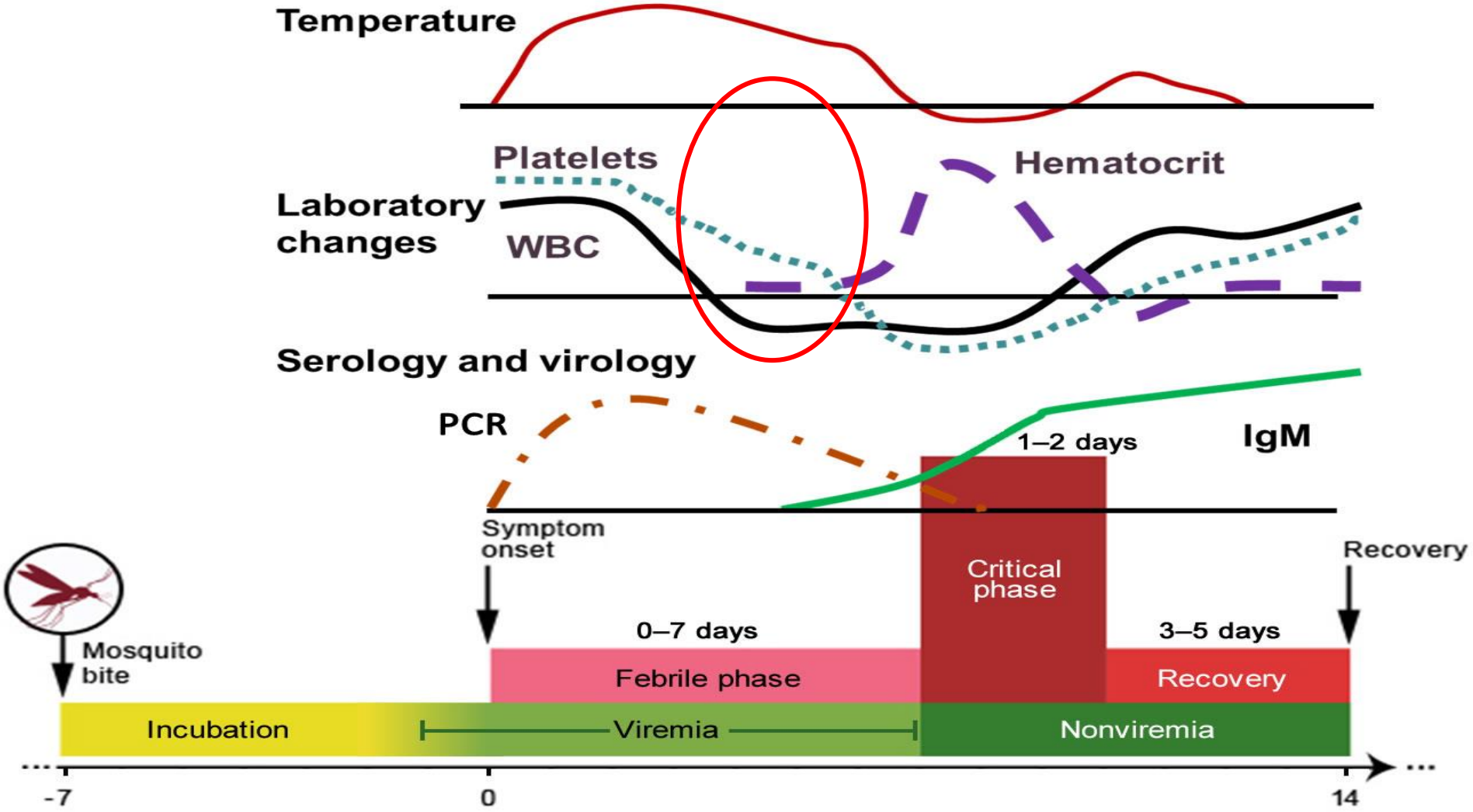


Dengue fever: warning signs

Box 1. Warning signs.

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy/restlessness
- Liver enlargement >2 cm
- Increase in hematocrit concurrent with rapid decrease in platelet count

Dengue fever: natural history



Dengue Diagnostic Testing Results				
Diagnosis	**Acute Phase** (5 days or less after symptom onset)		**Convalescent Phase** (5 days or more after symptom onset)	
	PCR or NS1	**IgM anti-DENV**	**NS1**	**IgM anti-DENV**
Dengue Confirmed	+	+	+	+
	+	-	+	-
	Not tested or -	-*	**Not tested or -**	+*
Dengue Probable	-	+	-	+
Dengue Negative	-	-	-	-

Impact of Dengue Vaccination on Serological Diagnosis: Insights From Phase III Dengue Vaccine Efficacy Trials

Eric Plennevaux,[1] Annick Moureau,[2] José L. Arredondo-García,[3] Luis Villar,[4] Punnee Pitisuttithum,[5] Ngoc H. Tran,[6] Matthew Bonaparte,[7] Danaya Chansinghakul,[8] Diana L. Coronel,[9] Maïna L'Azou,[10] R. Leon Ochiai,[10] Myew-Ling Toh,[11] Fernando Noriega,[12] and Alain Bouckenooghe[13]

Vaccination with CYD-TDV induces anti-dengue IgM and IgG. As such, it is no surprise that it has an impact on the diagnosis of dengue based on these serological markers. Our observations from >18 000 febrile episodes, including >1200 VCD episodes, confirms the limited specificity and PPV of serological diagnosis of dengue, and the bias in the case of dengue vaccination [2]—specifically, vaccination-induced bias toward false-positive dengue diagnosis based on IgM serological diagnosis in individuals seronegative at baseline presenting with febrile episodes (false-positive rates of 33.0% and 14.7% in the CYD-TDV and control groups, respectively), as well as a larger vaccination-induced bias based on IgG serological diagnosis in these individuals (false-positive rates of 77.2% and 13.3%, respectively). The bias is observed up to month 4 after vaccination; however, the

The current immunological definitions of dengue infection based on IgM and IgG serology are inadequate in vaccinated individuals and need to be reevaluated urgently as the dengue vaccine is now available in several endemic countries. Dengue vaccination history would now be needed to help interpret diagnosis and surveillance results based on serology alone. New practical, dengue-specific diagnostic algorithms are needed, which may include, in addition to IgM and IgG, other assays or tests that are not affected by vaccine-induced immunity. The specific dengue NS1 antigen test and dengue PCR tests remain valid evidence of dengue infection.

Clin Infect Dis 2018;66:1164-72

Dengvaxia controversy: impact on vaccine hesitancy

Khunsha Fatima[1], Najah Irfan Syed[2]

The quest for a suitable vaccine for dengue has been ongoing for the last six decades [3]. In one such effort, Sanofi, one of the biggest multinational pharmaceutical companies, developed the world's first dengue vaccine – Dengvaxia. The vaccine is now approved in 19 countries and was used in vaccination campaigns in Philippines, involving more than 800 000 school children [4,5].

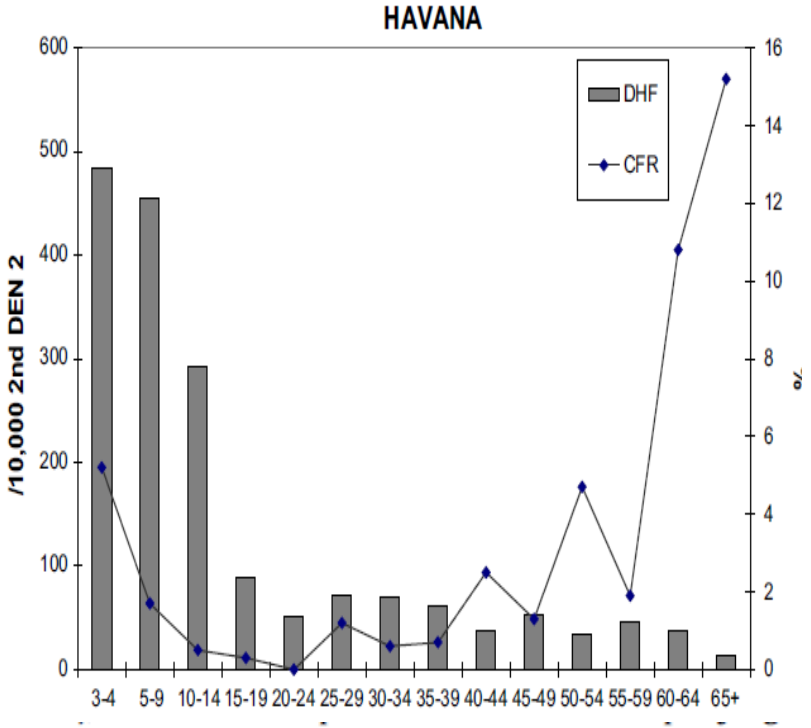
Soon after its authorization, Dengvaxia has now become a subject to controversy following Sanofi's recent analysis which suggests that the vaccine may put some people at an increased risk of a more severe form of dengue [5]. Dengvaxia was found to reduce the overall risk of severe dengue and hospitalizations due to this disease [4]. This protection, however, was more apparent in those who had a prior history of dengue infection. Sanofi recently

Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age

Vaccine 35 (2017) 6355–6358

Scott B. Halstead *

Uniformed Services University of the Health Sciences, Bethesda, MD, United States



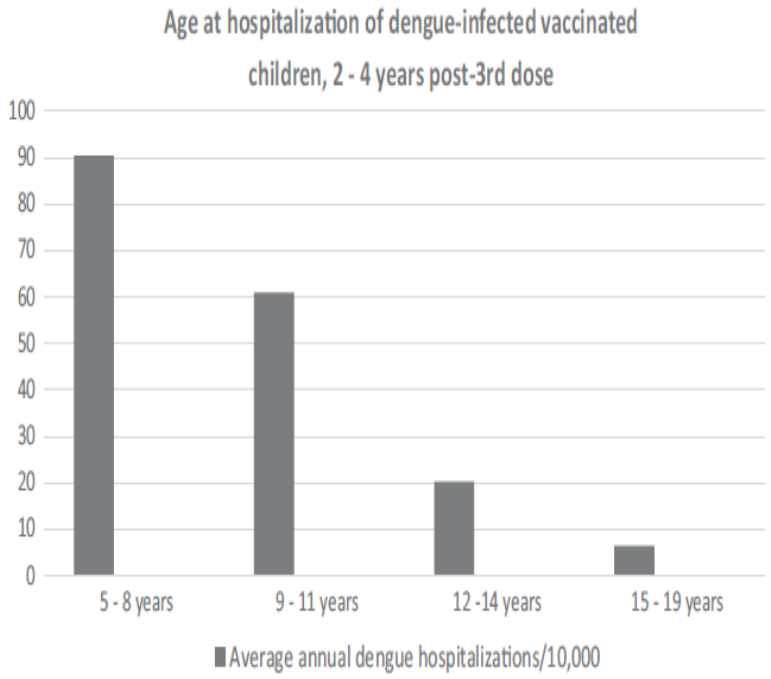


Fig. 2. Age-spe

closely similar to those in vaccinated children. However, the age specific hospitalization curves for these two populations differed. The curve for children vaccinated at ages 2–16 years closely resembled the 1981 age specific hospitalization rate curve for Cuban children infected with DENV 2 who were sensitized by a prior DENV 1 infection. The corresponding age specific hospitalization curve for placebos experiencing heterotypic secondary dengue infections peaked at age, 9–11 years. These differing epidemiological features support the conclusion that antibody dependent enhanced (ADE) dengue disease occurred in seronegatives who were sensitized by vaccine. As hospitalizations continue to occur in all age groups Dengvaxia consumers should be warned that sensitized vaccinated seronegatives will experience

Chikungunya virus

Chikungunya virus (CHIKV) first isolated in 1953 during an epidemic in Tanzania among the Makonde tribe

It is a mosquito-borne Alphavirus in the family TOGAVIRIDAE

Its name derives from a Makonde word that translate to " disease that bends up the joints"

Synovitis can be severe and highly destructive

CHIK is usually self-limiting and is rarely fatal but arthralgia is extremely painful and debilitating, typically lasting for 1 week but often much longer

Chikungunya virus

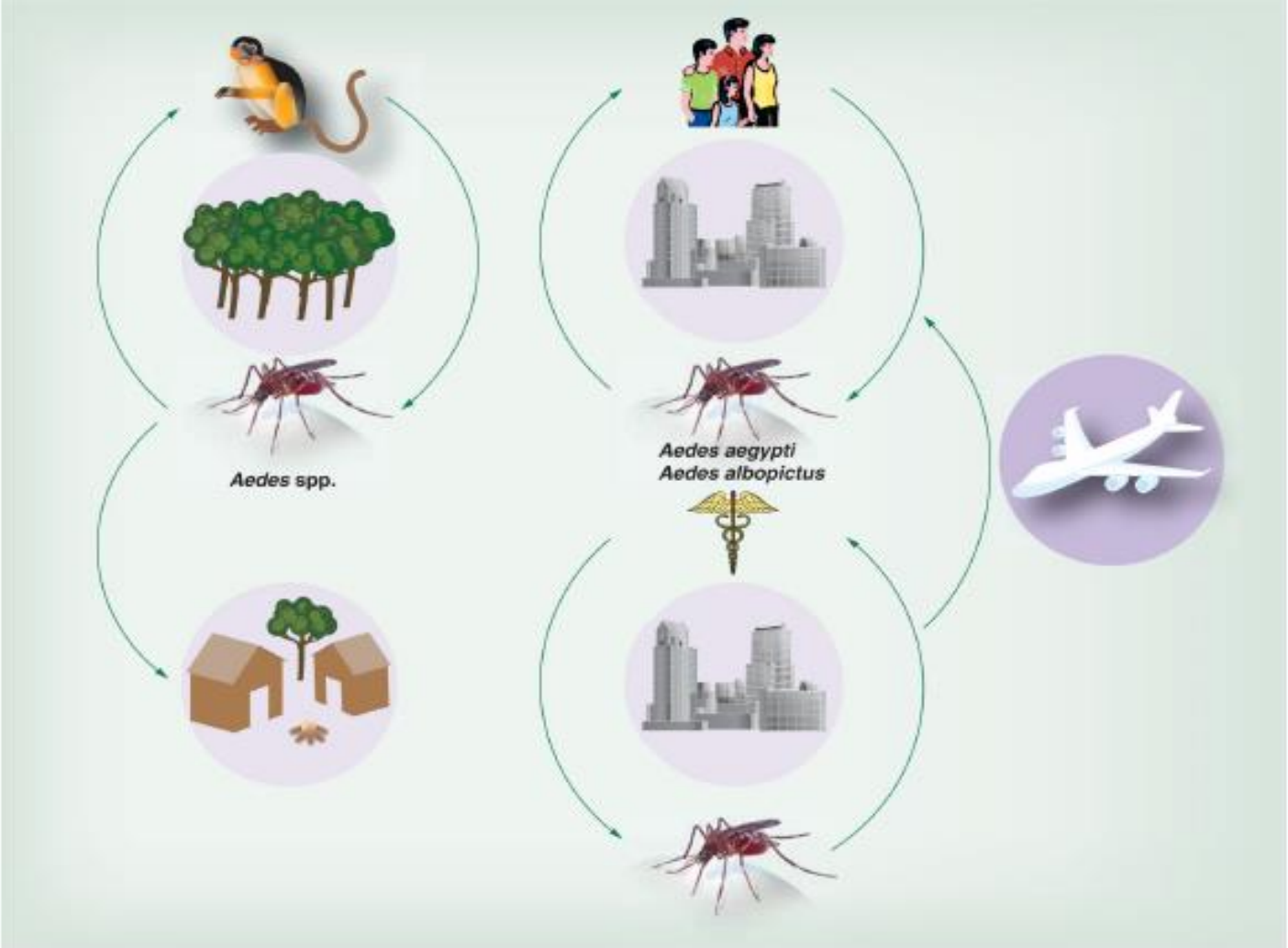


Figure 3. Chikungunya virus transmission cycles, including the progenitor sylvatic, enzootic cycle on the left and the emergent epidemic cycle on the right

Chikungunya Virus and the Global Spread of a Mosquito-Borne Disease

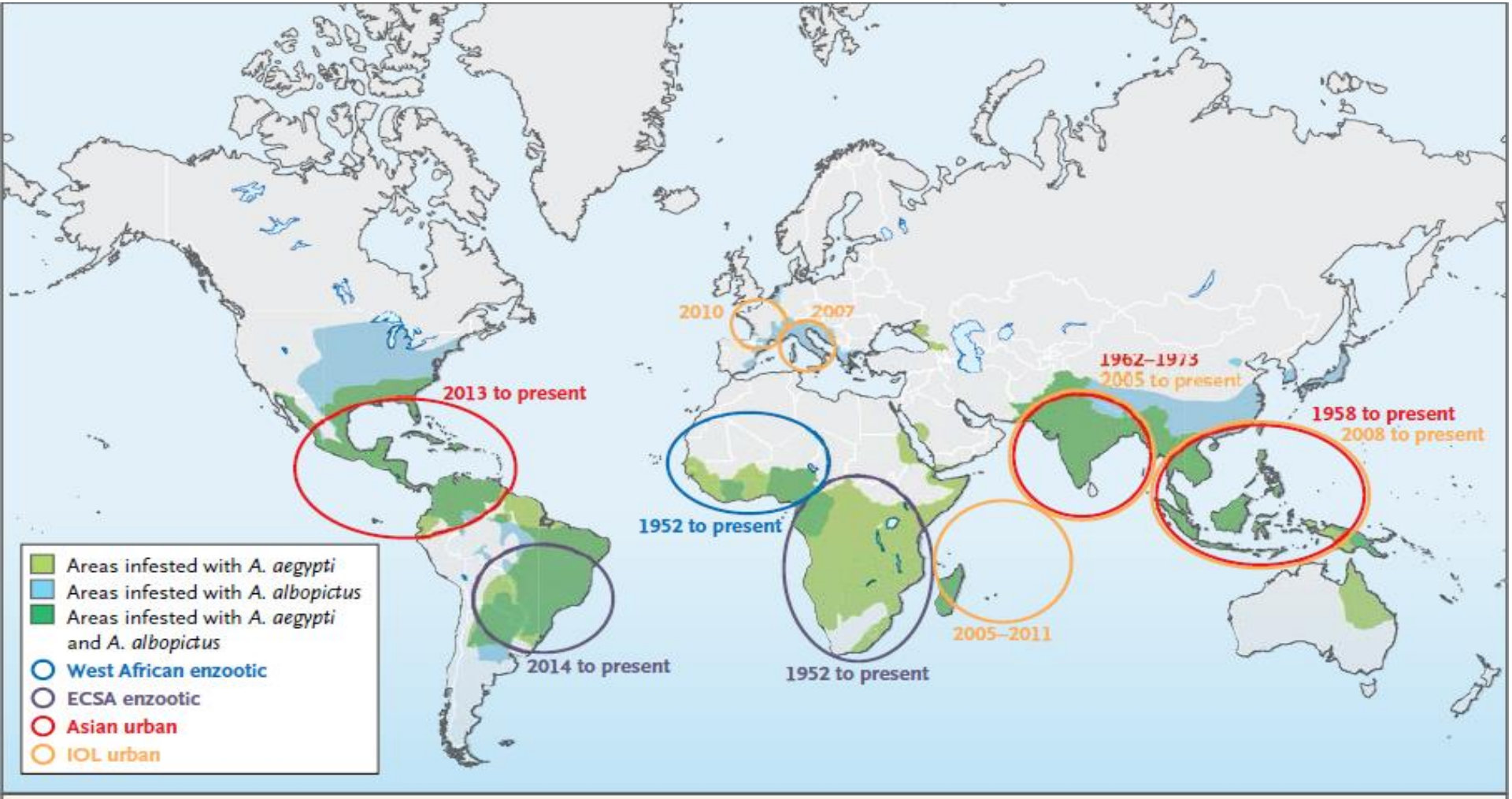


Figure 2. Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors.

The map shows the African origins of enzootic chikungunya virus strains and the patterns of emergence and spread of the Asian lineage and Indian Ocean lineage (IOL) of the virus during epidemics since the 1950s, based on phylogenetic studies.[4,5] The distributions of the peridomestic vectors, *Aedes aegypti* and *A. albopictus*, are also shown. ECSA denotes eastern, central, and southern African.

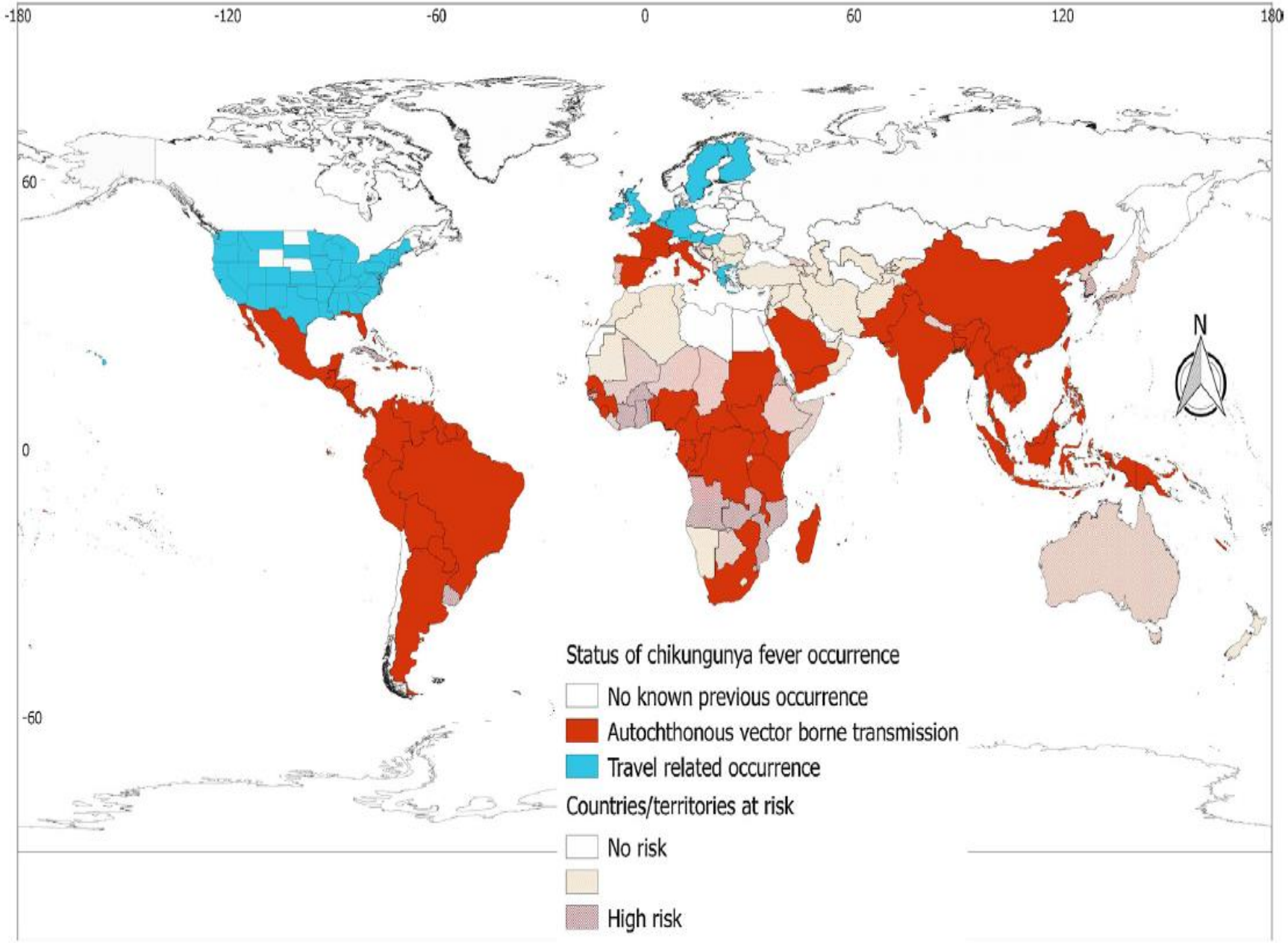


Figure 7. Global chikungunya fever occurrence. The global distribution of chikungunya fever corresponds well with the global chikungunya risk, with minor discrepancies in countries of Sub-Saharan Africa. The distribution of chikungunya fever extends to the temperate part of the world, with some European countries reporting its occurrence. It is emphasized that displaying occurrences at the country level overstates the distribution of the virus in Argentina.

Data table: Countries and territories where chikungunya cases have been reported

AFRICA
Benin
Burundi
Cameroon
Central African Republic
Comoros
Dem. Republic of the Congo
Equatorial Guinea
Gabon
Guinea
Kenya
Madagascar
Malawi
Mauritius
Mayotte
Nigeria
Republic of Congo
Reunion
Senegal
Seychelles
Sierra Leone
South Africa
Sudan
Tanzania
Uganda
Zimbabwe

ASIA
Bangladesh
Bhutan
Cambodia
China
India
Indonesia
Laos
Malaysia
Maldives
Myanmar (Burma)
Pakistan
Philippines
Saudi Arabia
Singapore
Sri Lanka
Taiwan
Thailand
Timor
Vietnam
Yemen

EUROPE
France
Italy

AMERICAS
Anguilla
Antigua and Barbuda
Argentina
Aruba
Bahamas
Barbados
Belize
Bolivia
Brazil
British Virgin Islands
Cayman Islands
Colombia
Costa Rica
Curacao
Dominica
Dominican Republic
Ecuador
El Salvador
French Guiana
Grenada
Guadeloupe
Guatemala
Guyana
Haiti
Honduras
Jamaica
Martinique
Mexico
Montserrat
Nicaragua
Panama
Paraguay
Peru
Puerto Rico
Saint Barthelemy
Saint Kitts and Nevis
Saint Lucia
Saint Martin
Saint Vincent & the Grenadines
Sint Maarten
Suriname
Trinidad and Tobago
Turks and Caicos Islands
United States
US Virgin Islands
Venezuela

OCEANIA/PACIFIC ISLANDS
American Samoa
Cook Islands
Federal States of Micronesia
French Polynesia
Kiribati
New Caledonia
Papua New Guinea
Samoa
Tokelau
Tonga

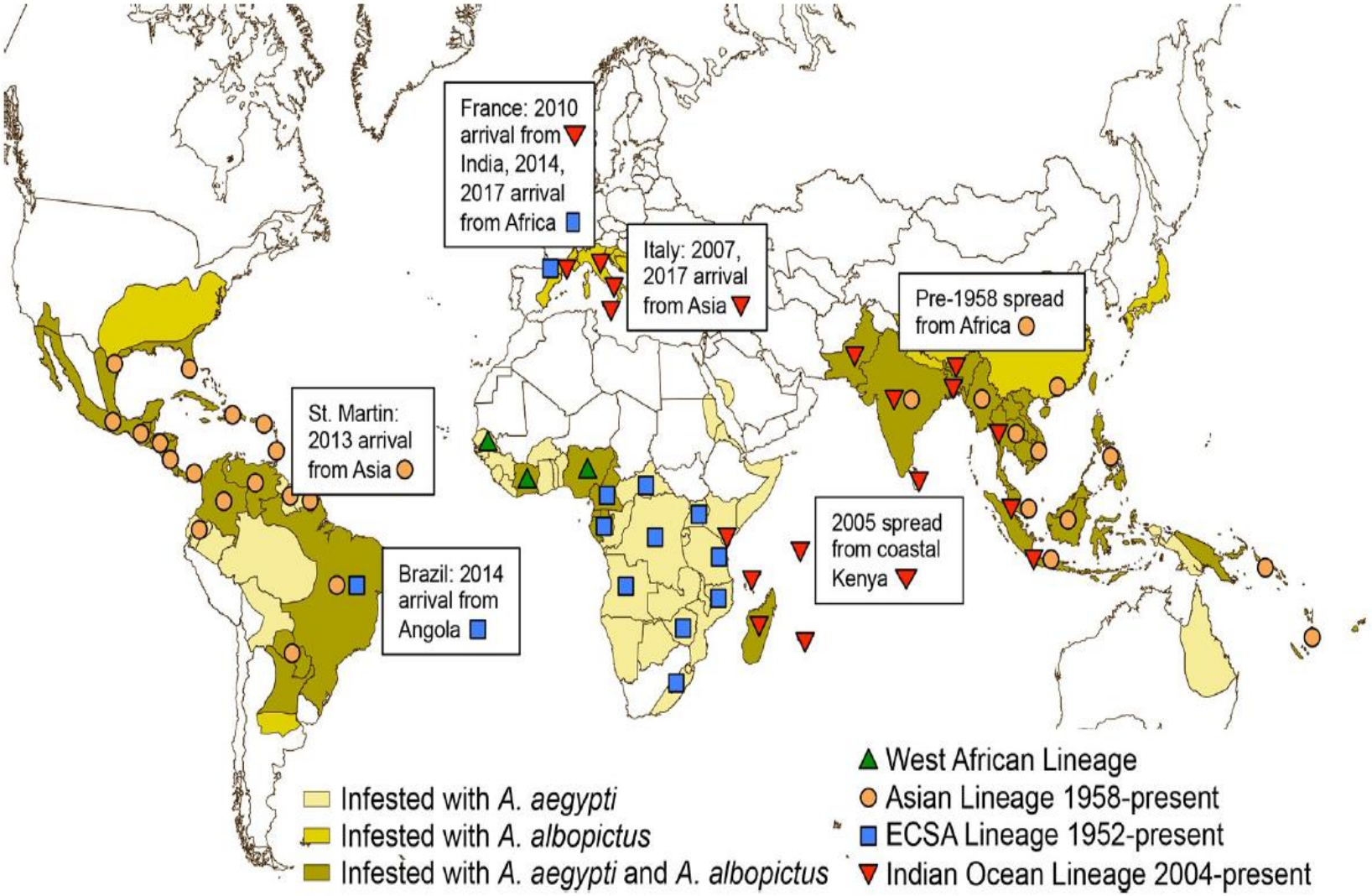


Fig 1. World map with countries where autochthonous (locally initiated) chains of CHIKV transmission have been identified. Data from World Health Organization (http://www.who.int/emergencies/diseases/chikungunya/en/) and Pan American Health Organization (https://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931&lang=en). CHIKV, chikungunya virus.

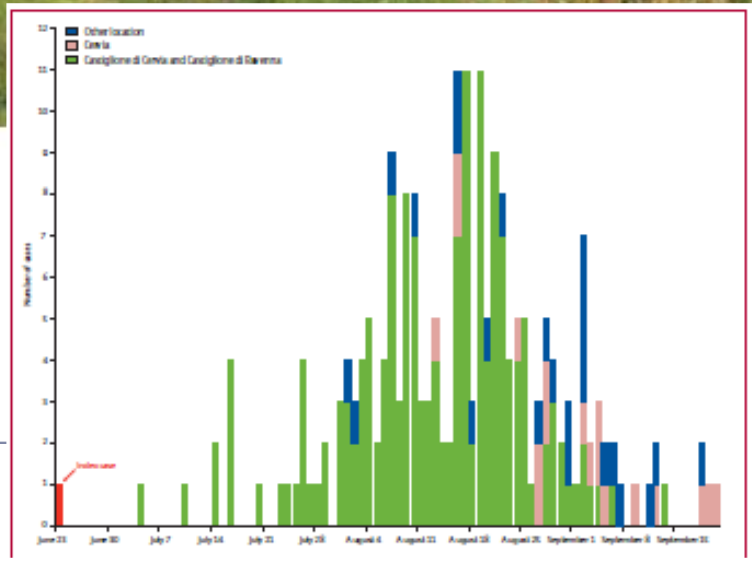
Infection with chikungunya virus in Italy: an outbreak in a temperate region

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

© ECDC

Riverbank, Castiglione di Cervia, province of Ravenna, 18 September 2007.



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Lancet 2007; 370: 1840–46

	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**

Local transmission of chikungunya in Rome and the Lazio region, Italy

PLOS ONE | https://doi.org/10.1371/journal.pone.0208896 December 21, 2018

Francesco Vairo[1], Alessia Mammone[1], Simone Lanini[1], Emanuele Nicastri[2], Concetta Castilletti[2], Fabrizio Carletti[2], Vincenzo Puro[1], Domenico Di Lallo[3], Vincenzo Panella[3], Donatella Varrenti[4], Paola Scaramozzino[5], Antonino di Caro[2], Paola Scognamiglio[1], Maria Rosaria Capobianchi[2]*, Giuseppe Ippolito[2], Chikungunya Lazio Outbreak Group[¶]

of the 402 probable or confirmed cases.

Demographic and clinical characteristics		Number of cases (%)
Age, years	0–34	81 (20.2%)
	35–50	95 (23.6%)
	51–64	99 (24.6%)
	>65	127 (31.6%)
Sex	Male	184 (45.8%)
	Female	218 (54.2%)
Body temperature	<37.8 °C	13 (3.2%)
	> = 37.8 °C	389 (96.8%)
Hospital admission	No	367 (90.6%)
	Yes	35 (9.4%)
Arthritis	No	243 (60.4%)
	Yes	159 (39.6%)
Headache	No	196 (48.8%)
	Yes	206 (51.2%)
Myalgia	No	148 (36.8%)
	Yes	254 (63.2%)
Retro orbital pain	No	353 (87.8%)
	Yes	49 (12.2%)
Conjuntivitis	No	342 (85.1%)
	Yes	60 (14.9%)
Rash	No	149 (37.1%)
	Yes	253 (62.9%)
Asthenia	No	91 (22.6%)
	Yes	311 (77.4%)
Arthralgia	No	17 (4.2%)
	Yes	385 (95.8%)

ITALIA: FOCOLAI AUTOCTONI DI INFEZIONE DA VIRUS CHIKUNGUNYA
(aggiornato al 26 settembre 2017)

186 casi notificati totali:

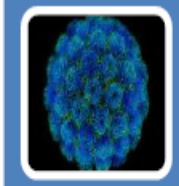
- 183 Regione Lazio
- 1 Regione Emilia-Romagna
- 1 Regione Marche
- 1 Paesi Europei (Francia)

112 casi confermati totali:

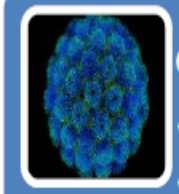
- 109 Regione Lazio
- 1 Regione Emilia-Romagna con legame epidemiologico Anzio
- 1 Regione Marche con legame epidemiologico Anzio
- 1 Paesi Europei (Francia) con legame epidemiologico Anzio

74 casi probabili totali:

- 74 Regione Lazio



- 91 (49 %) MASCHI
- 95 (51 %) FEMMINE



Gravità dell'infezione

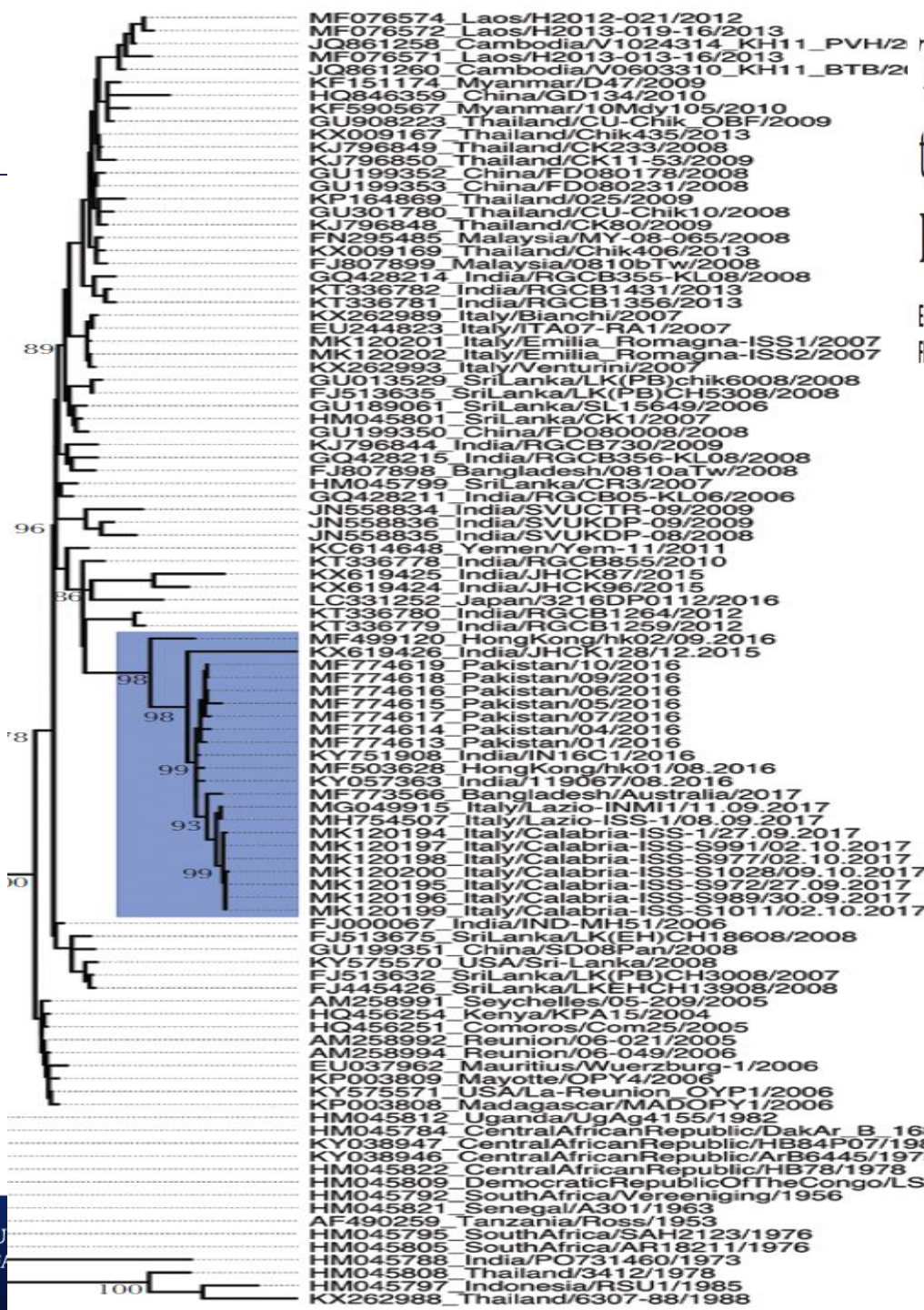
- Ospedalizzati 26 (14 %)
- Deceduti 0

Vector competence of *Aedes albopictus* for the Indian Ocean lineage (IOL) chikungunya viruses of the 2007 and 2017 outbreaks in Italy: a comparison between strains with and without the E1:A226V mutation

Claudia Fortuna[1,2], Luciano Toma[2,3], Maria Elena Remoli[1], Antonello Amendola[1], Francesco Severini[3], Daniela Boccolini[3], Roberto Romi[3], Giulietta Venturi[1], Giovanni Rezza[1], Marco Di Luca[3]

1. Istituto Superiore di Sanità, Department of Infectious Diseases, National Reference Laboratory for Arboviruses, Rome, Italy
2. These authors contributed equally to this article and share first authorship
3. Istituto Superiore di Sanità, Department of Infectious Diseases, Unit of Vector-borne Diseases, Rome, Italy

We compared the vector competence of an Italian population of *Aedes albopictus* for two strains of chikungunya virus (CHIKV), with and without E1:A226V mutation, responsible for outbreaks in 2007 in the Emilia Romagna region and 2017 in the Lazio and Calabria regions, respectively. *Ae. albopictus* showed similar vector competence for both viral strains indicating that E1:A226V mutation is not exclusively responsible for ability of CHIKV to replicate well in this mosquito species.



The Italian 2017 Outbreak Chikungunya Virus Belongs to an Emerging *Aedes albopictus*-Adapted Virus Cluster Introduced From the Indian Subcontinent

Erika Lindh,[1,2] Claudio Argentini,[1] Maria Elena Remoli,[1] Claudia Fortuna,[1] Giovanni Faggioni,[3] Eleonora Benedetti,[1] Antonello Amendola,[1] Giulia Marsili,[1] Florigio Lista,[3] Giovanni Rezza,[1] and Giulietta Venturi[1]

Chikungunya is back in Italy: 2007–2017

Giovanni Rezza*

Department of Infectious Diseases, Istituto Superiore di Sanità, Roma, Italy

Symptoms suggestive of chikungunya or dengue

↓

Travel to endemic area in the last two weeks or suspected autocthonous case

↓

<8 days after symptoms onset:
- PCR
- Serology (IgM) and PRNT
- Virus antigen (dengue virus)

≥8 days after symptoms onset:
- Serology (IgM/IgG) and PRNT
- Virus RNA in urine

Figure 2. Map of Italy with circles indicating the places where outbreaks of chikungunya occurred in 2007 (Emilia-Romagna Region) and in 2017 (Lazio and Calabria Region).

Journal of Travel Medicine, 2018, 1–4

Chikungunya

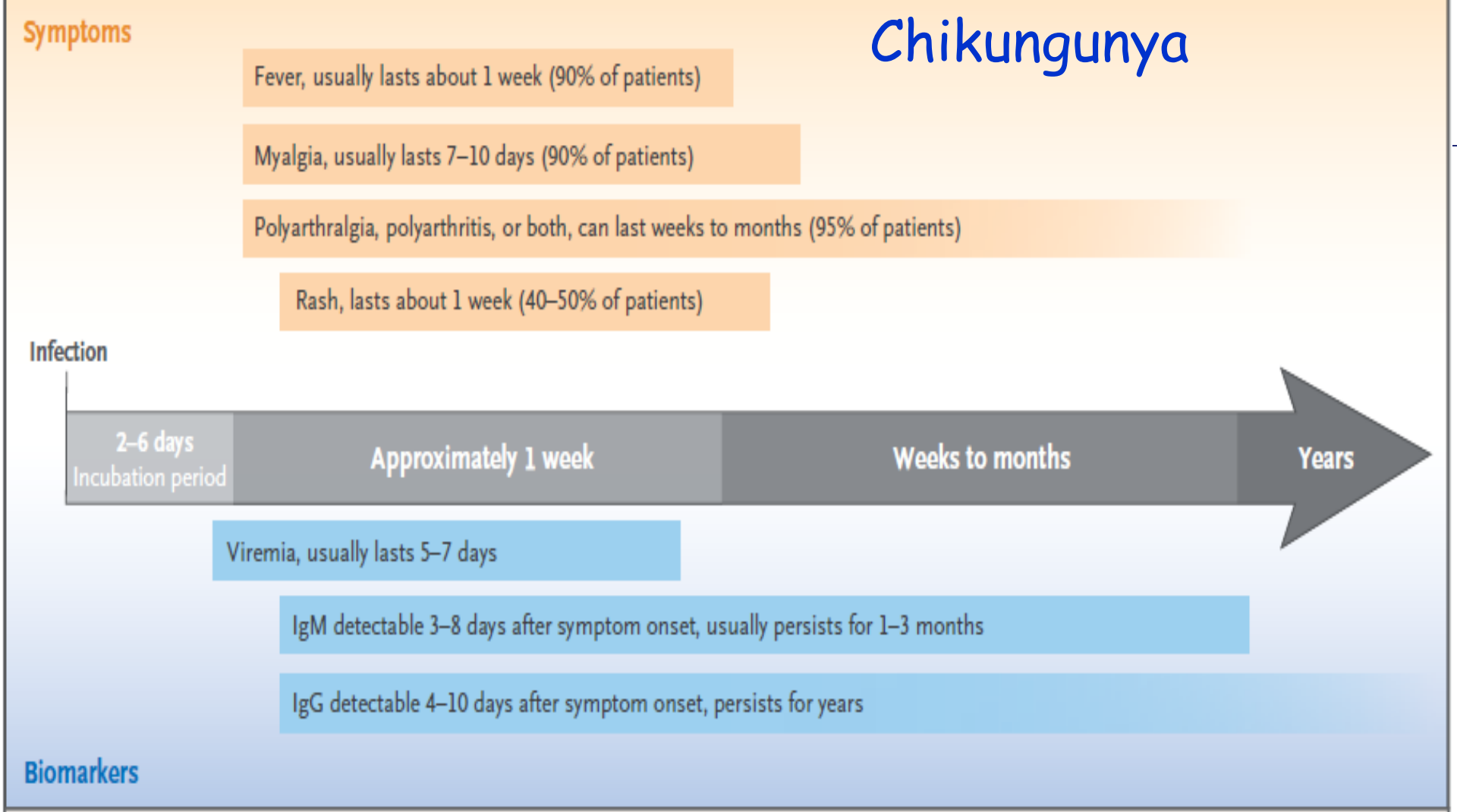
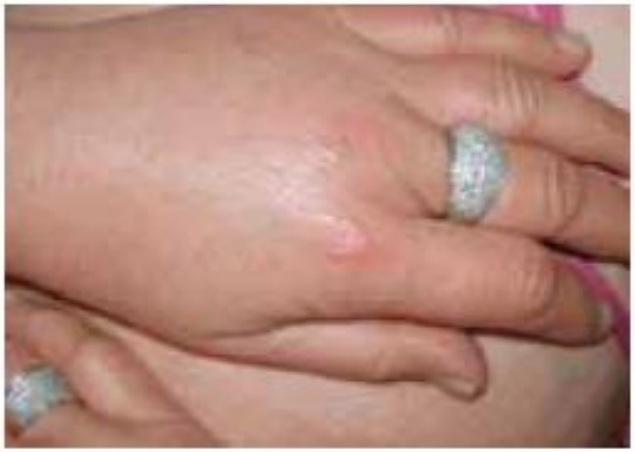


Figure 3. Timeline of Infection, Symptoms, and Biomarkers.

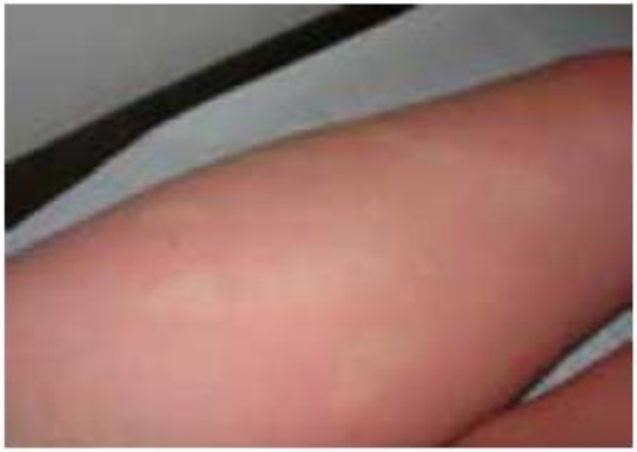
Shown is the chronology of viral replication in relation to the clinical and biologic signs of disease, including the biomarkers used in diagnostic assays to detect chikungunya virus infection (adapted from Suhrbier et al.[28]).

Clinical presentation. **Acute disease.**

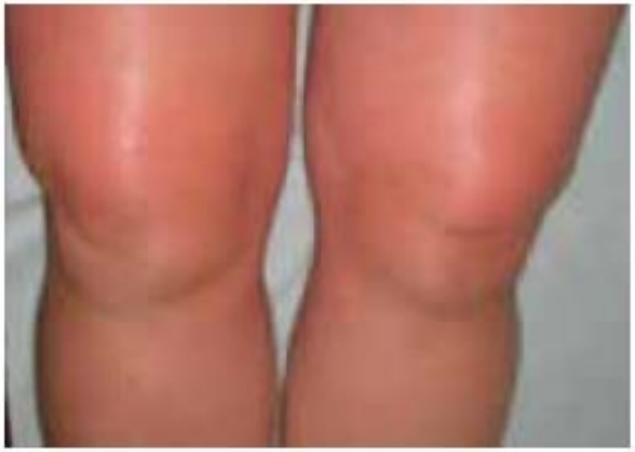
A. Edematous rash of the face



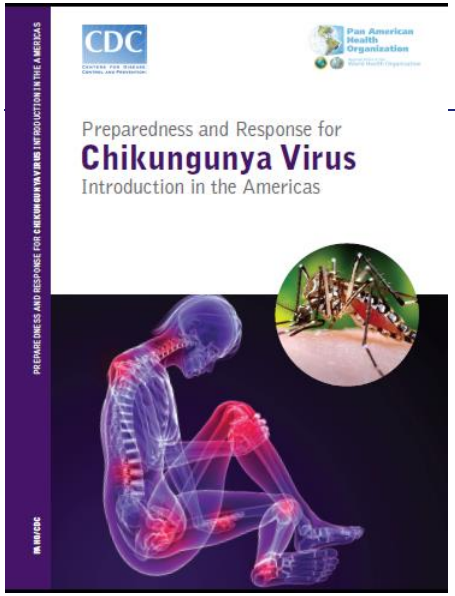
B. Edematous poylarthritis of the hands

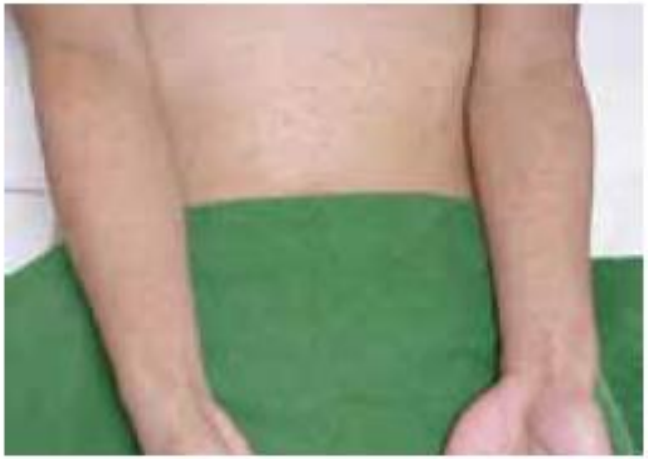


C. Erythema that blanches with pressure

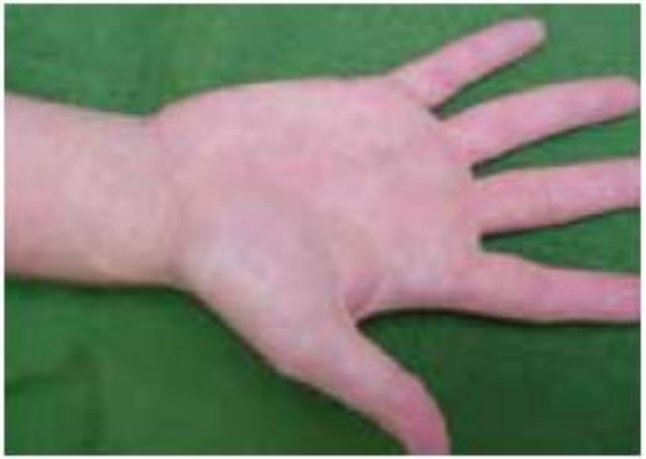


D. Periarticular swelling and joint effusion in knees

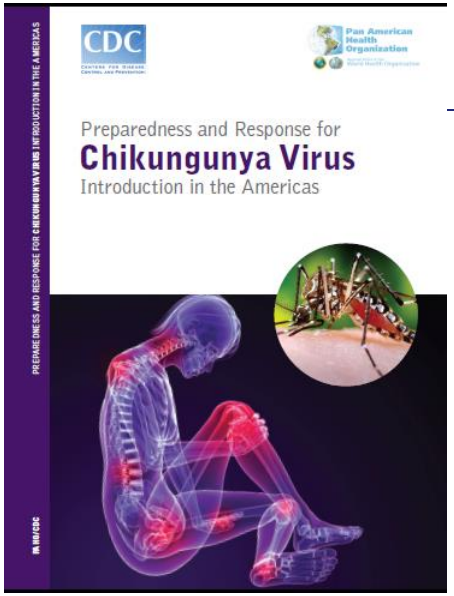


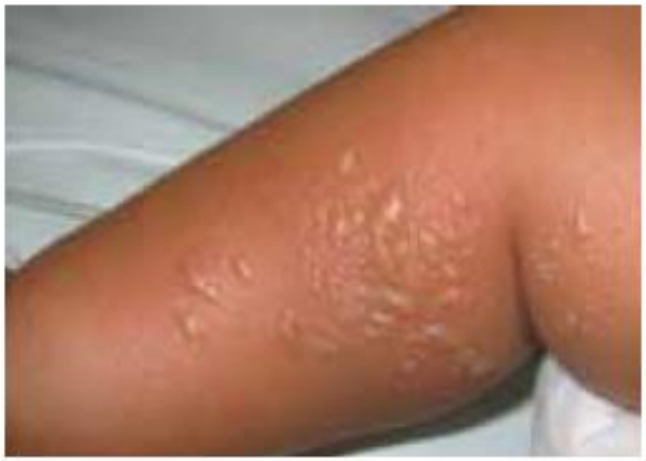


E. Maculopapular rash in trunk and extremities

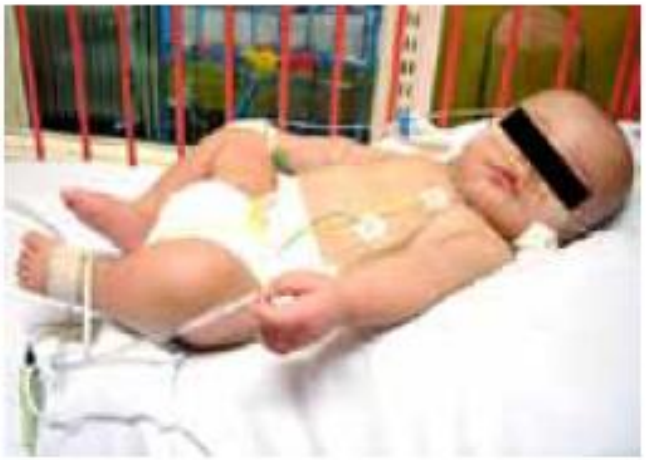


F. Maculopapular rash in extremities, including palms





G. Bullous lesions in infant leg



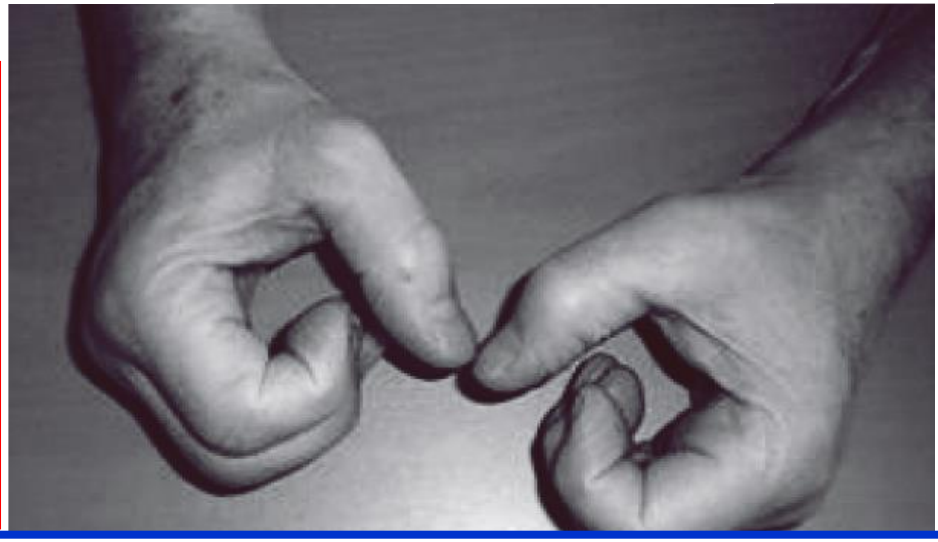
H. Infant with maculo-papular rash, petechial spots and erythema of upper and lower limbs associated with edema of the extremities

Clinical and laboratory features	Chikungunya virus infection	Dengue virus infection
Fever (>102°F or 39°C)	+++	++
Myalgias	+	++
Arthalgias	+++	+/-
Headache	++	++[b]
Rash	++	+
Bleeding dyscrasias	+/-	++
Shock	-	+
Leukopenia	++	+++
Neutropenia	+	+++
Lymphopenia	+++	++
Elevated hematocrit	-	++
Thrombocytopenia	+	+++

Emergence and treatment of chikungunya arthritis

Ravi B. Sutaria[a], *Jose K Amaral*[b], *and Robert T. Schoen*[a]

The transition from acute CHIKF to chronic CHIK arthritis is variable. Some patients have continuous symptoms, whereas others experience a biphasic illness, acute disease followed by transient remission, and then persistent arthritis [26]. Chronic CHIKV symptoms include arthralgia, arthritis, and edema involving hands, wrists, ankles, and knees, typically in a symmetrical pattern



In addition to arthritis, a variety of extra-articular manifestations occur with chronic CHIK. In one cohort, new-onset Raynaud's phenomenon developed in the second or third month in 20% of patients [31]. In another report, neurological symptoms including neuropathic pain syndromes, cerebral disorders, sensorineural impairment, and paresthesia's were reported, as well as depression [10]. Also present were carpal/tarsal/cubital tunnel syndromes, bursitis, tenosynovitis, and frank synovitis. Some patients had digestive disorders. Consid-

Late disease

Chronic CHIKV arthritis causes joint damage and impacts quality of life as severely as RA [46]. The goals of treatment of chronic CHIK arthritis include pain relief and preventing joint destruction. This phase of the illness is increasingly referred to as post-CHIK chronic inflammatory rheumatism (pCHIK-CIR) [29,33]. Treatment options for pCHIK-CIR include NSAIDs, corticosteroids, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide, methotrexate (MTX), and biologics [33] (Table 1).

Chikungunya in the Americas

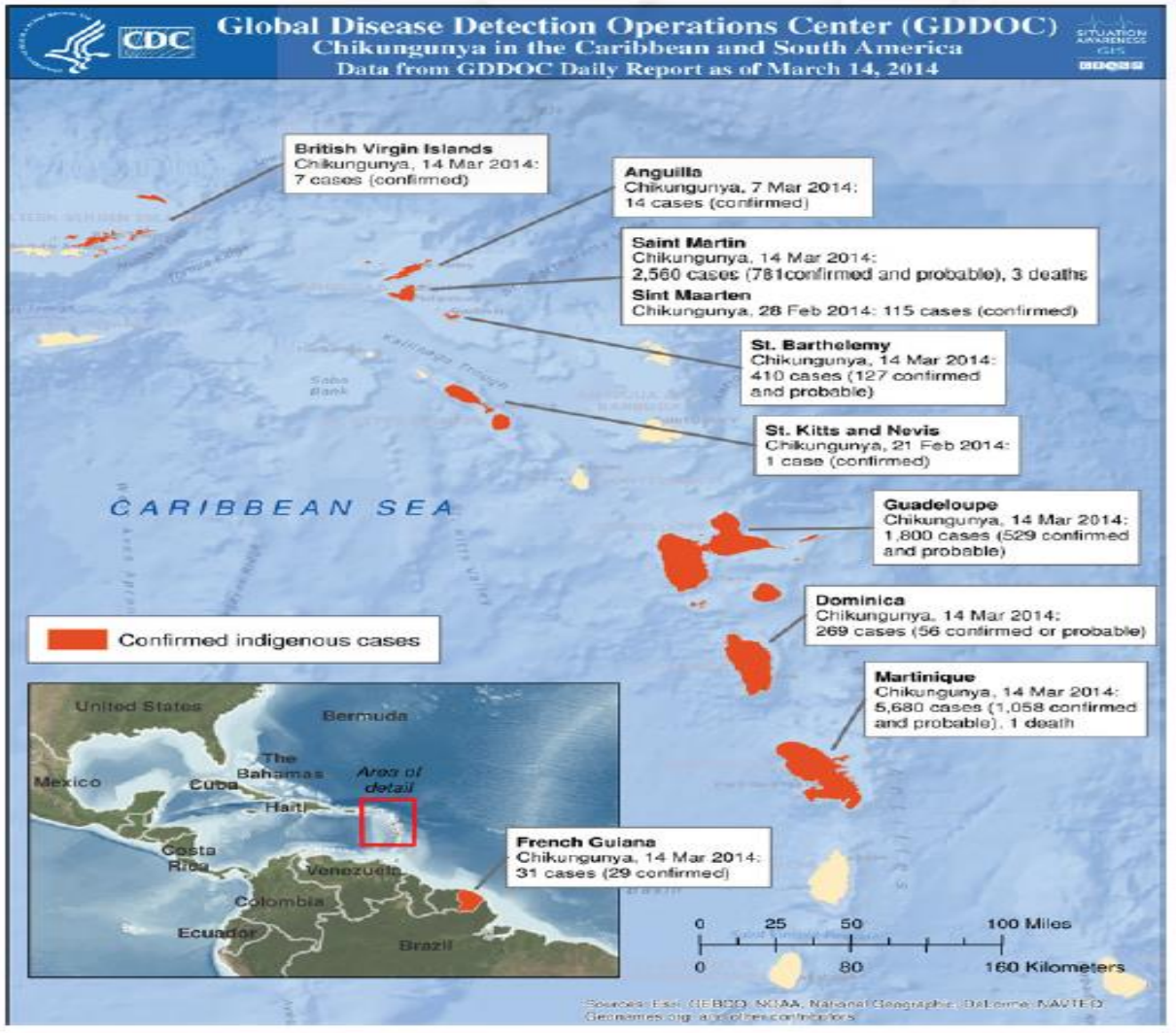
continued from page 3

Disease Prevention and Control, Public Health England, British and U.S. Virgin Islands, and Puerto Rico, have enabled international and domestic public health partners to share case report updates, coordinate laboratory testing, and review communication products. In addition to the official information received from PAHO and European colleagues, the GDD Operations Center scans the media for newly reported cases in media pending official confirmation for early notification of the CDC community regarding new areas reporting locally transmitted chikungunya cases.

As of March 14, more than 10,800 suspected cases and 2,727 laboratory confirmed cases of chikungunya since early December have been reported to PAHO from countries in and around the Caribbean. Local transmission has occurred in St. Martin, St. Maarten, St. Barthélemy, Guadeloupe, Martinique, the British Virgin Islands, Dominica, Anguilla, St. Kitts and Nevis, and French Guiana. Cases among travelers to the Caribbean have also been reported by several countries in the region.

The introduction of chikungunya into the Caribbean illustrates how quickly diseases can spread with international travel. The actions taken to date by CDC exemplify how the agency protects the United States and the world from infectious disease threats by building capacity and establishing networks to rapidly detect and respond to outbreaks in collaboration with international partners to ensure global health security.

For more information, please visit http://www.cdc.gov/chikungunya/.



Map of current outbreak in Caribbean by GRASP and GDDOC, "Chikungunya in the Caribbean and South America, data as of March 14, 2014."

TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 46. No. 5. September, 1952.

COMMUNICATIONS

ZIKA VIRUS

(I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

G. W. A. DICK,

The National Institute for Medical Research, London

S. F. KITCHEN,

Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.

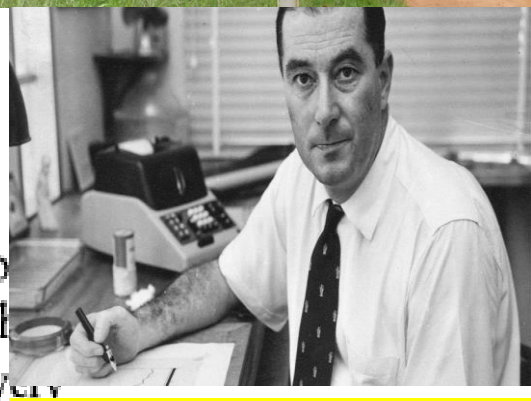
AND

A. J. HADDOW,

Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.

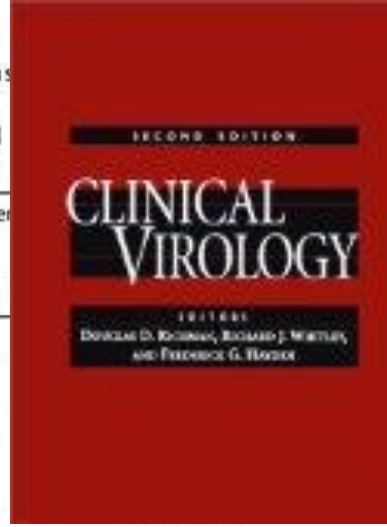
(*From the Virus Research Institute, Entebbe, Uganda.*)

of a fourth, Uganda S virus, is to be published (DICK and HADDOW). The purp
of this communication is to describe the isolation of yet another virus which
believed to be hitherto unrecorded. Particular interest attaches to the recov
of this virus, partly because it was encountered on two occasions separated
9 months, and partly because it was isolated independently by G.W.A.D. and later
by S.F.K. employing different methods, both of which were being used primarily
in the search for yellow fever virus in nature. This virus has been called Zika
virus after the geographical name of the area from where the isolations were made.



Zika virus co-discover **Alexander Haddow** at the Uganda Virus Institute circa

1960 when he was lab director

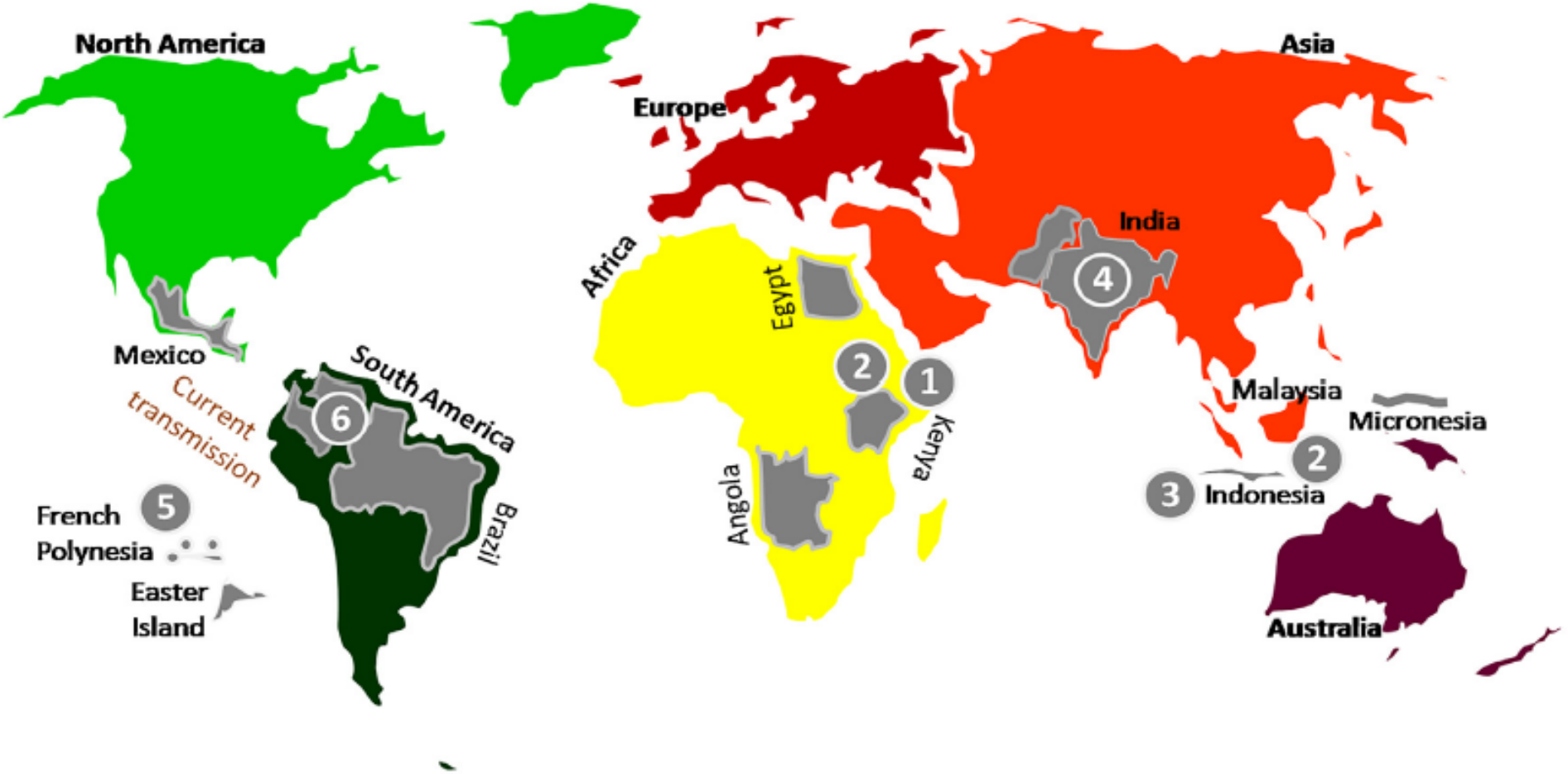


1997

TABLE 49-6. Flaviviruses Causing Sporadic Human Disease. The Recognition of These Diseases Has Often Occurred in the Setting of General Virus Investigations and Surveillance Projects. Infection (Disease) May be More Common Than Indicated, and the Clinical Spectrum May Differ From That Delineated by the Few Recognized Cases

Virus	Human Disease			Veterinary Disease Species Affected	Geographic Distribution	Transmission Cycle	Referer
	No. Cases	Clinical Features	Severity				
Banzi	<10	Nonspecific febrile illness	Self-limited	None known	Southern & East Africa	Mosquitoes (*Culex*)-rodents	162
Bussuquara	1	Fever, arthralgia	Self-limited	None known	Brazil, Colombia, Panama	Mosquitoes (*Culex*)-rodents	163
Edge Hill	1	Fever, myalgia, arthralgia	Self-limited	None known	Australia	Mosquitoes (*Aedes*)-wallabies	59
Ilheus	6	Fever, myalgia, encephalitis[c]	Potentially severe (no deaths)	None known	Brazil, Colombia, Panama, Trinidad	Mosquitoes (*Psorophora*)-birds	92
Kokobera	3	Fever, rash, arthralgia	Self-limited	None known	Australia, Papua New Guinea	Mosquitoes (*Culex*)-?	
Koutango	1[d]	Fever, rash, arthralgia	Self-limited	None known	West Central Africa	Ticks (several genera)-rodents	
Kunjin	<20	Fever, rash, encephalitis	Potentially severe (no deaths)	Horses (rare)[f]	Australia, Sarawak, Thailand	Mosquitoes (*Culex*)-birds	164
Langat	<10	Fever, encephalitis[c]	Potentially severe (no deaths)	None known	Malaysia, Thailand, USSR	Ticks (*Ixodes*)-rodents	
Louping ill	39[e]	Similar to CEE[g]	Potentially severe (no deaths)	Sheep[h]	United Kingdom, Ireland	Ticks (*Ixodes*)-sheep, grouse	165, 166
Modoc	1	Aseptic meningitis	Self-limited	None known	Western U.S., Canada	Rodent-rodent[i]	49
Negishi	3+[j]	Encephalitis	Potentially fatal	None known	Japan, China	Ticks-?	167
Rio Bravo	6 (11)	Febrile illness, meningitis, orchitis	Self-limited	None known	Western U.S., Mexico	Bat-bat[i]	168
Sepik	1	Febrile illness, (hospitalized)	Self-limited	None known	New Guinea	Mosquitoes (*Mansonia*)-?	
Spondweni	3[k]	Fever, arthralgia, rash	Self-limited	None known	South & West Africa	Mosquitoes (*Aedes*)	169
Usutu	1	Fever, rash	Self-limited	None known	South, Central Africa	Mosquitoes (*Culex*)-birds	
Wesselsbron	<20	Fever, arthralgia, rash, encephalitis	Potentially severe (no deaths)	Sheep[l]	Sub-Saharan Africa, Thailand	Mosquitoes (*Aedes*)-?	170
Zika	14+	Fever, rash, arthralgia	Self-limited	None known	West, East, Central Africa, Indonesia	Mosquitoes (*Aedes*)-monkeys	171

Zika virus infected areas according to time



1. 1947: first documented in monkeys in Uganda
2. 1960: first human case
3. 1970s: cases in Indonesia, India, Pakistan and Malaysia
4. 2007: epidemic in Micronesia
5. 2013: epidemic in French Polynesia
6. 2014 – 2016: spread throughout America

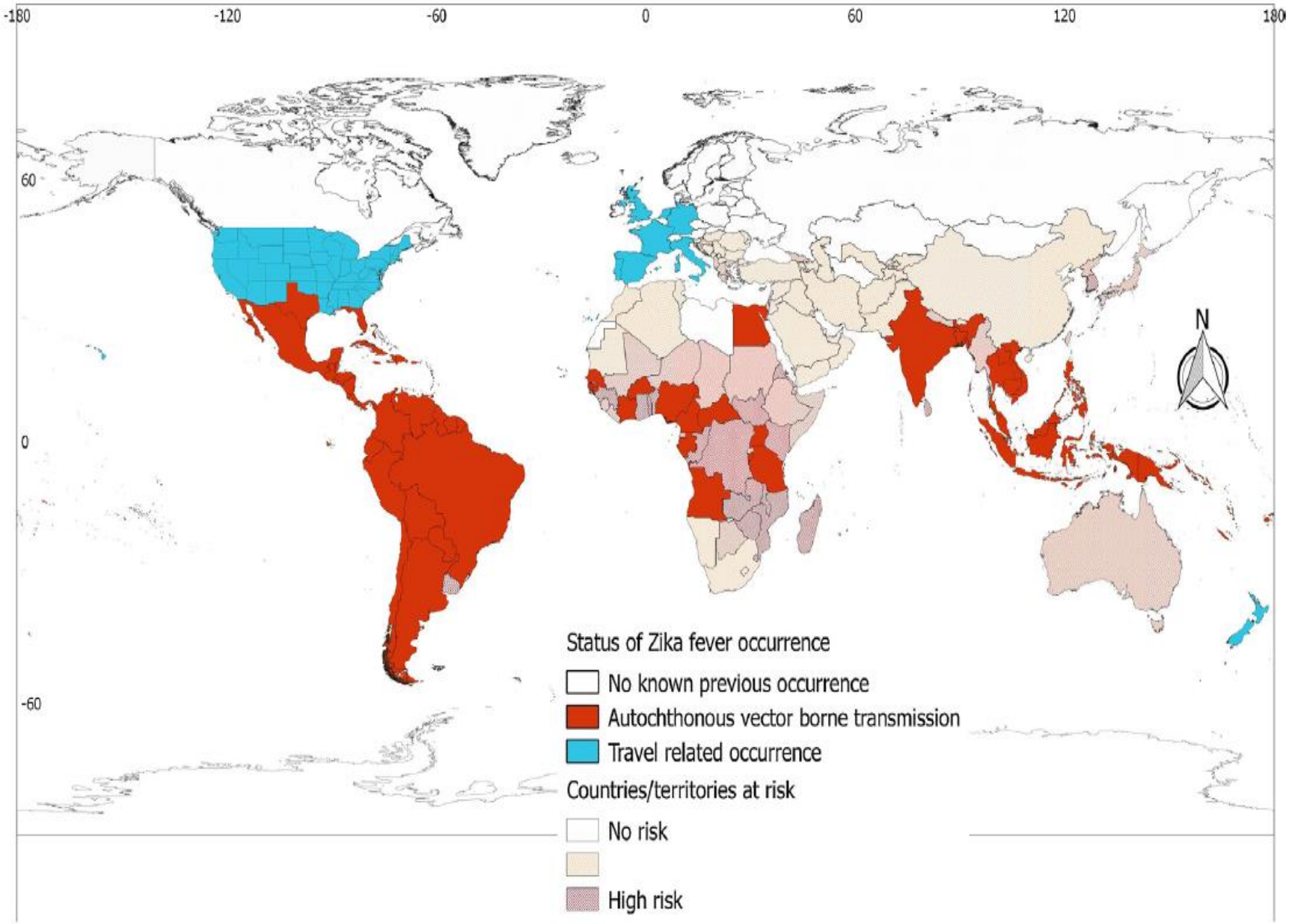
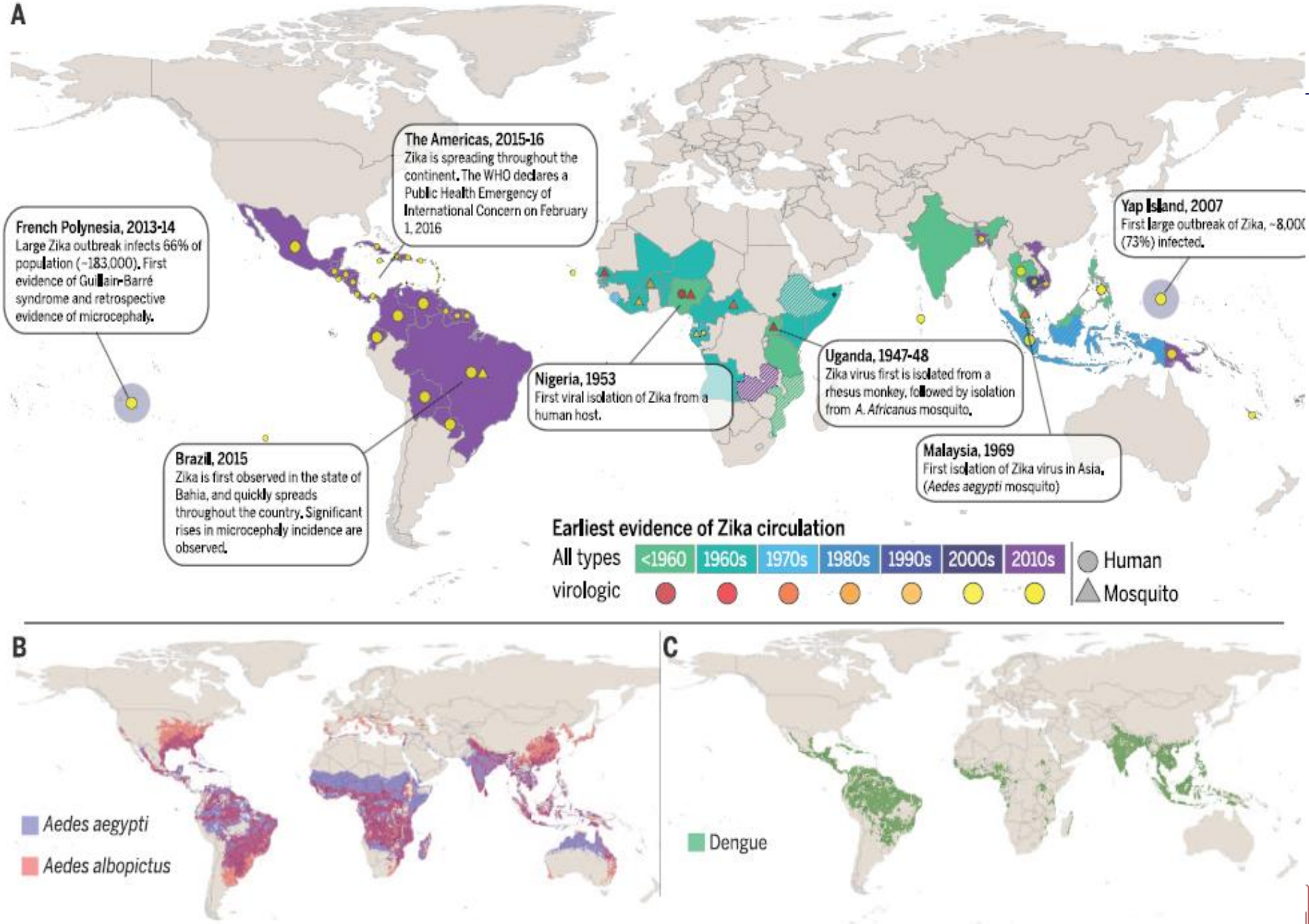


Figure 4. Global Zika fever occurrence. The global distribution of Zika fever corresponds well with the global Zika risk. Discrepancies are apparent in Sub-Saharan Africa, where there is a high risk of Zika fever but few occurrence reports. It is emphasized that displaying occurrences at the country level overstates the distribution of the virus, especially in countries such as Argentina and Chile.

Further spread of Zika virus across America


A
The Americas, 2015-16
Zika is spreading throughout the continent. The WHO declares a Public Health Emergency of International Concern on February 1, 2016
French Polynesia, 2013-14
Large Zika outbreak infects 66% of population (~183,000). First evidence of Guillain-Barré syndrome and retrospective evidence of microcephaly.
Brazil, 2015
Zika is first observed in the state of Bahia, and quickly spreads throughout the country. Significant rises in microcephaly incidence are observed.
Nigeria, 1953
First viral isolation of Zika from a human host.
Uganda, 1947-48
Zika virus first is isolated from a rhesus monkey, followed by isolation from A. Africanus mosquito.
Yap Island, 2007
First large outbreak of Zika, ~8,000 (73%) infected.
Malaysia, 1969
First isolation of Zika virus in Asia, (Aedes aegypti mosquito)
Earliest evidence of Zika circulation
All types
virologic
<1960
1960s
1970s
1980s
1990s
2000s
2010s
Human
Mosquito
B
Aedes aegypti
Aedes albopictus
C
Dengue

Zika virus transmission worldwide

9 April 2019

Europe

No vector-borne locally acquired ZIKV disease cases had been reported by EU/EEA countries in Europe as of week 12, 2019.

Between 2015 and week 12 of 2019, 22 EU/EEA Member States reported 2 398 travel-associated ZIKV infections through the European Surveillance System (TESSy)1. France reported 48% of the cases, Spain 15% and the UK 9%. The latest week of disease onset reported was week 4, 2019. Since 2015, 12 countries have reported 139 travel-associated Zika cases among pregnant women. Two cases of microcephaly associated with these pregnancies, one from Spain and one from Slovenia, were reported in the literature [36,37]. An additional case of congenital ZIKV infection was reported in the pregnancy of a Finnish woman [38].

An overview of the number of laboratory-confirmed travel-associated ZIKV disease cases by year and probable place of infection is presented in Annex 1. The number of travel-associated cases has substantially decreased since 2016 when 2 059 travel-associated cases were reported. During the peak of the outbreak in 2016, the majority of the travel-associated cases were reported in travellers returning from Guadeloupe (n=463; 22%), Martinique (n=413, 20%) and the Dominican Republic (n=153; 7%).

In 2017, 264 travel-associated cases were reported to TESSy and only 47 in 2018. In 2017 and 2018, most cases were reported from Cuba (n=116; 44% (2017) and n=20; 43% in (2018)). In 2019, three cases were reported to TESSy as of week 12 in 2019. The travel-related cases from 2019 reported to TESSy up to week 12 have all been reported in travellers returning from Thailand: two from Denmark and one from Norway (see Annex 1).

In addition, 25 sexual transmission events from returning travellers to their partners in the EU/EEA have been reported in TESSy. These event were reported by eight Member States during the period 2015–2019. Of these, the majority were reported as occurring in 2016 (n=21; 84%). One was reported in 2017, two in 2018 and one in 2019. The case from 2019 contracted the infection from a partner who was infected in Thailand, presumably as a result of mosquito-borne transmission.

Zika virus transmission

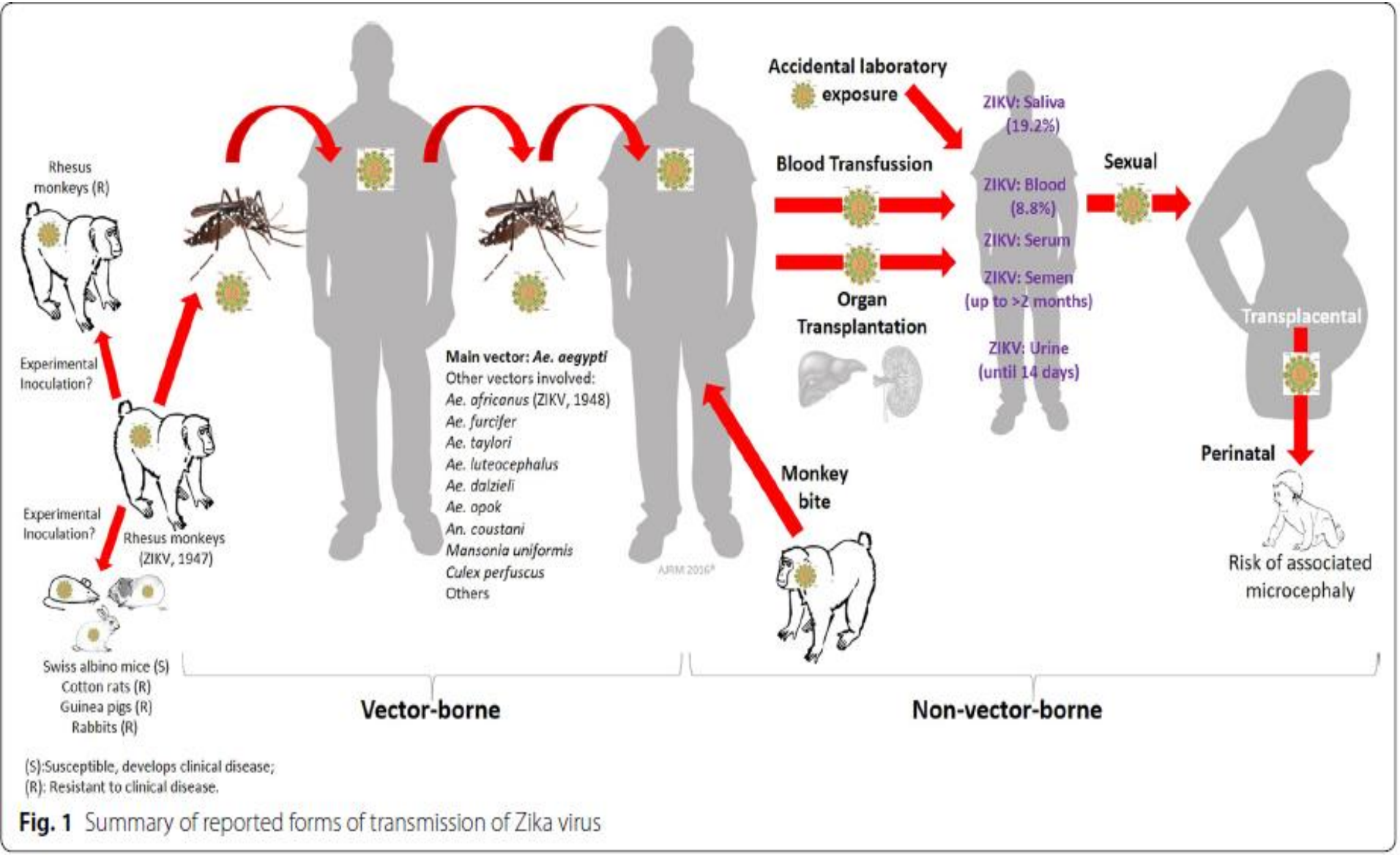
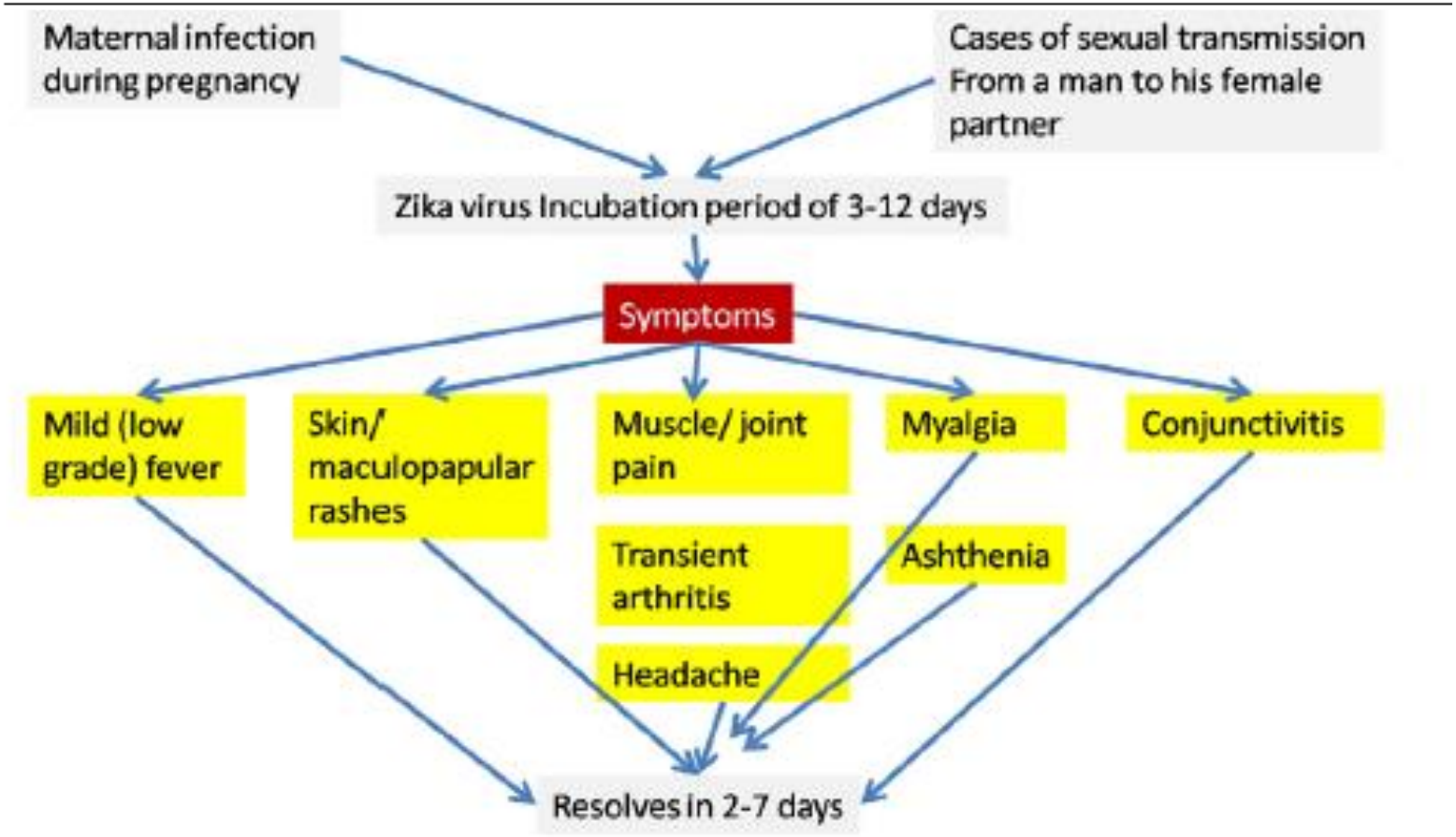


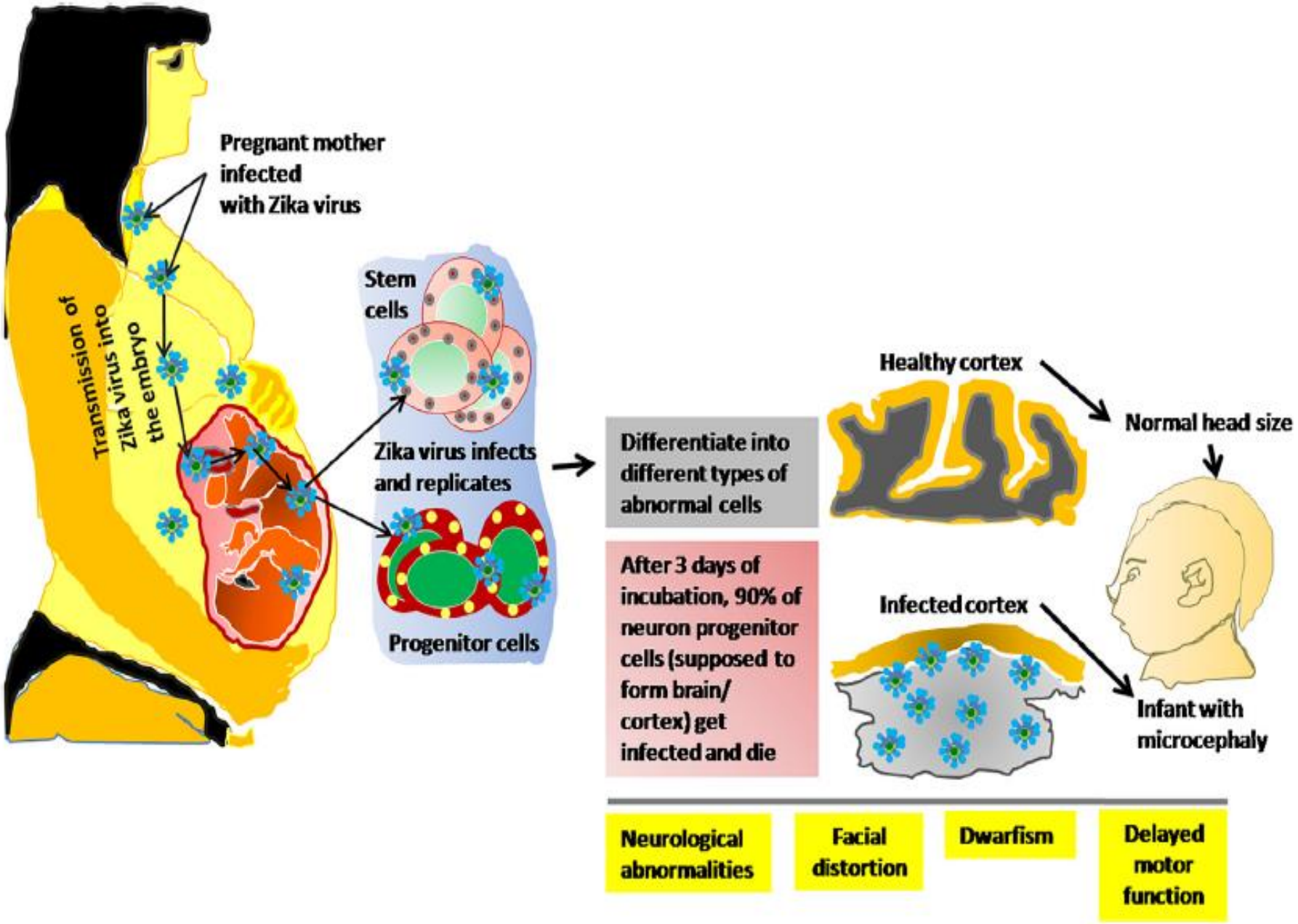
Fig. 1 Summary of reported forms of transmission of Zika virus

Zika virus: Epidemiological study and its association with public health risk

Rashed Noor*, Tasnia Ahmed

Department of Microbiology, Stamford University Bangladesh, 51 Siddeswari Road, Dhaka 1217, Bangladesh




Pregnant mother infected with Zika virus
Transmission of Zika virus into the embryo
Stem cells
Zika virus infects and replicates
Progenitor cells
Differentiate into different types of abnormal cells
After 3 days of incubation, 90% of neuron progenitor cells (supposed to form brain/ cortex) get infected and die
Healthy cortex
Normal head size
Infected cortex
Infant with microcephaly
Neurological abnormalities
Facial distortion
Dwarfism
Delayed motor function

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

Duffy MR et al. N Engl J Med 2009; 360:2536-43

Clinical, laboratory and virological data from suspected ZIKV patients in an endemic arbovirus area

Tatiana Elias Colombo[a,b], Cássia Fernanda Estofolete[a], Andréia Francesli Negri Reis[c], Natal Santos da Silva[d], Morgana Lima Aguiar[b], Eliana Márcia Sotello Cabrera[a], Izalco Nuremberg Penha dos Santos[c], Fabiana Rodrigues Costa[c], Lilian Elisa Arão Antônio Cruz[c], Patrícia Lopes Rombola[c], Ana Carolina Bernardes Terzian[a], Maurício Lacerda Nogueira[a,*]

Clinical characteristics and laboratory assays of patients with laboratory-confirmed ZIKV and DENV.

Sign/Simptom	Confirmed ZIKV (n = 96)[a] n(%) or mean	Confirmed DENV (n = 67)[a] n(%) or mean	*p* value
Fever	71 (74.0)	53 (79.1)	0.45
Edema/Arthralgia	74 (77.1)	47 (70.1)	0.32
Myalgia	71 (74.0)	50 (74.6)	0.92
Non-purulent conjunctivitis	67 (69.8)	43 (64.2)	0.45
Headache	63 (65.6)	49 (73.1)	0.31
Abdominal pain	11 (11.5)	16 (23.9)	0.04
Nausea	26 (27.1)	24 (35.8)	0.23
Cough	17 (17.7)	5 (7.5)	0.06
Sore throat	15 (15.6)	10 (14.9)	0.90
Diarrhea	13 (13.5)	7 (10.4)	0.55
Vomiting	11 (11.5)	7 (10.4)	0.84
Leukopenia	4 (7.8)	10 (34.5)	0.003
Thrombocytopenia	1 (2.0)	6 (20.7)	0.01[b]
Hemoconcentration	1 (2.0)	1 (3.4)	1.00[b]

p value was calculated using Pearson's chi-square test (*p* value ≤ 0.05 is considered statistically significant).

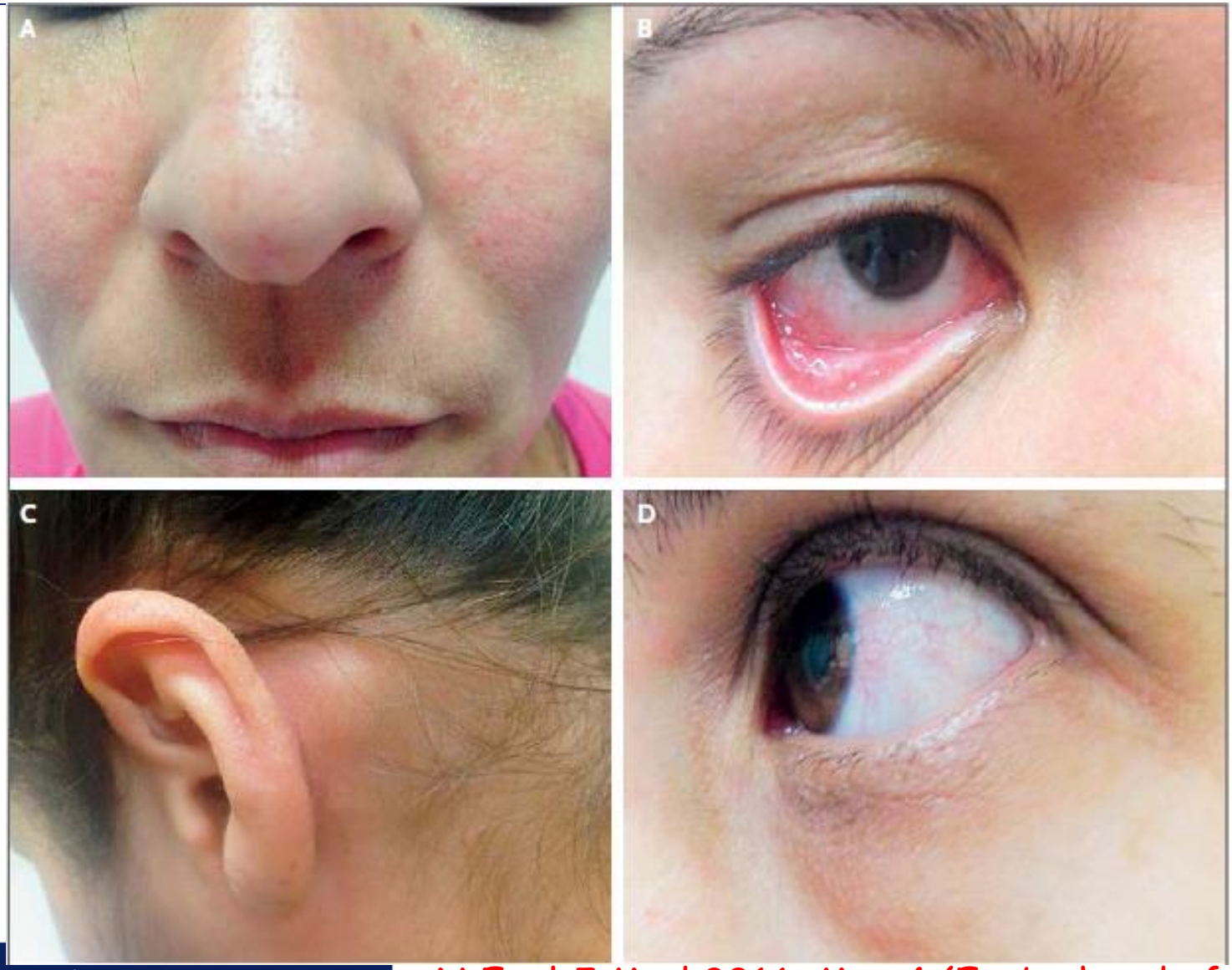
[a] Four cases of co-infection (ZIKV/DENV-2) were excluded.

[b] Fisher's exact teste.

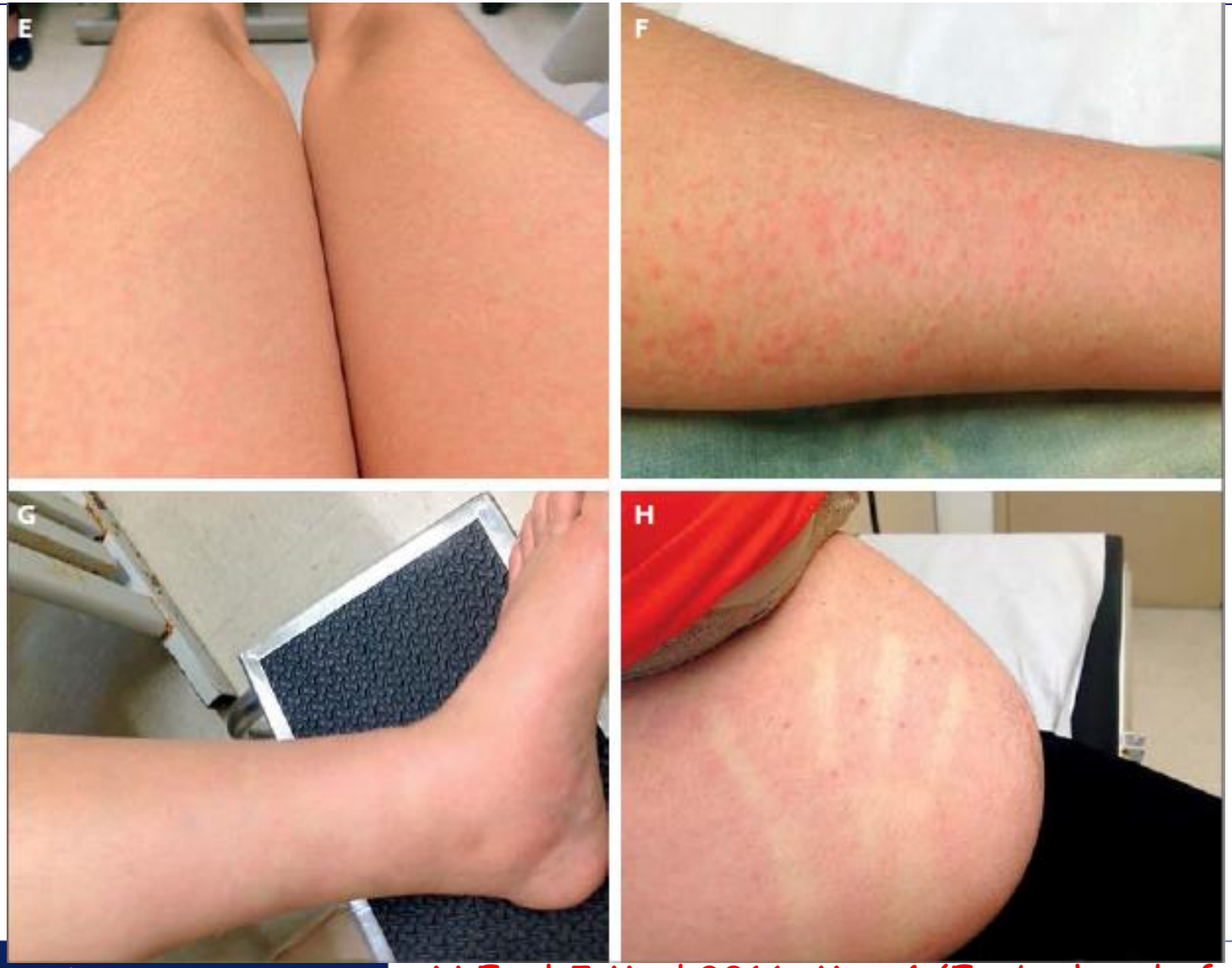
Laboratory findings in Zika infection: The experience of a reference centre in North-West Italy

Elisa Burdino[a,*], Maria Grazia Milia[a], Tiziano Allice[a], Gabriella Gregori[a], Tina Ruggiero[a], Guido Calleri[b], Filippo Lipani[c], Anna Lucchini[c], Giulietta Venturi[d], Giovanni Di Perri[c], Valeria Ghisetti[a]

Characteristic	ID# 1	ID# 2	ID# 3	ID# 4	ID# 5	ID# 6	ID# 7	ID# 8	ID# 9[a]	ID# 10	ID# 11[b]	ID# 12[b]	ID# 13
Travelling from	Venezuela	Venezuela	Dominican Republic	Dominican Republic	Dominican Republic	Puerto Rico	Dominican Republic	Dominican Republic	Sexual transmission[a]	Mexico	Costa Rica	Costa Rica	Dominican Republic
Age (yrs)	29	31	40	30	20	29	21	18	19	28	21	23	32
Sex	Male	Female	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female	Male
Pregnancy	/	No	No	/	/	/	No	/	No	/	/	No	/
Stay duration	> 15 days	> 15 days	30 days	15 days	30 days	15 days	30 days	30 days	15 days	4 months	15 days	15 days	15 days
Date of returning to Italy	Jan 9	Jan 9	Apr 8	May 26	July 11	July 4	July 14	July 14	July 25	August 23	August 29	August 29	August 18
Date of symptom onset	Jan 6	Jan 4	Apr 11	May 30	July 6	July 11	July 7	July 4	July 17	August 19	August 26	August 27	August 22
Date of sampling	Jan 11	Jan 11	Apr 17	Jun 3	July 15	July 15	July 18	July 18	July 28	August 29	August 29	August 29	August 26
Symptom													
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maculopapular rash	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Itching	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No
Conjunctivitis	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No
Headache	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No
Retroorbital pain	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No
Arthralgia/Myalgia	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No
Diarrhea	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Malaise/Fatigue	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	No
Laboratory test (reference)													
Leukopenia (WB Count < 4,000 µl)	3500	Normal	3880	Normal	NA	Normal	NA	NA	NA	Normal	3610	2320	Normal
Thrombocytopenia (PLTS Count < 140,000 µl)	Normal	Normal	Normal	Normal	NA	Normal	NA	NA	NA	NA	123,000	Normal	Normal
Liver function[c]	Normal	ALT x 4	Normal	Normal	NA	Normal	NA	NA	NA	NA	Normal	Normal	ALT x 2
Treatment	Paracetamol	Paracetamol	Steroid	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy
Outcome	Recovery (1 week)	Recovery (4 days)	Recovery (2 days)	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery (1 week)	Recovery (1 week)	Recovery



N Engl J Med 2016, Mar 4 (Epub ahead of print)



N Engl J Med 2016, Mar 4 (Epub ahead of print)

Brief communication

Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urine

Koh Shinohara, MD[1], Satoshi Kutsuna, MD[1]*, Tomohiko Takasaki, MD[2], Meng Ling Moi, PhD[2], Makiko Ikeda, PhD[2], Akira Kotaki, PhD[2], Kei Yamamoto, MD[1], Yoshihiro Fujiya, MD[1], Momoko Mawatari, MD[1], Nozomi Takeshita, MD[1], Kayoko Hayakawa, MD[1], Shuzo Kanagawa, MD[1], Yasuyuki Kato, MD[1], and Norio Ohmagari, MD[1]

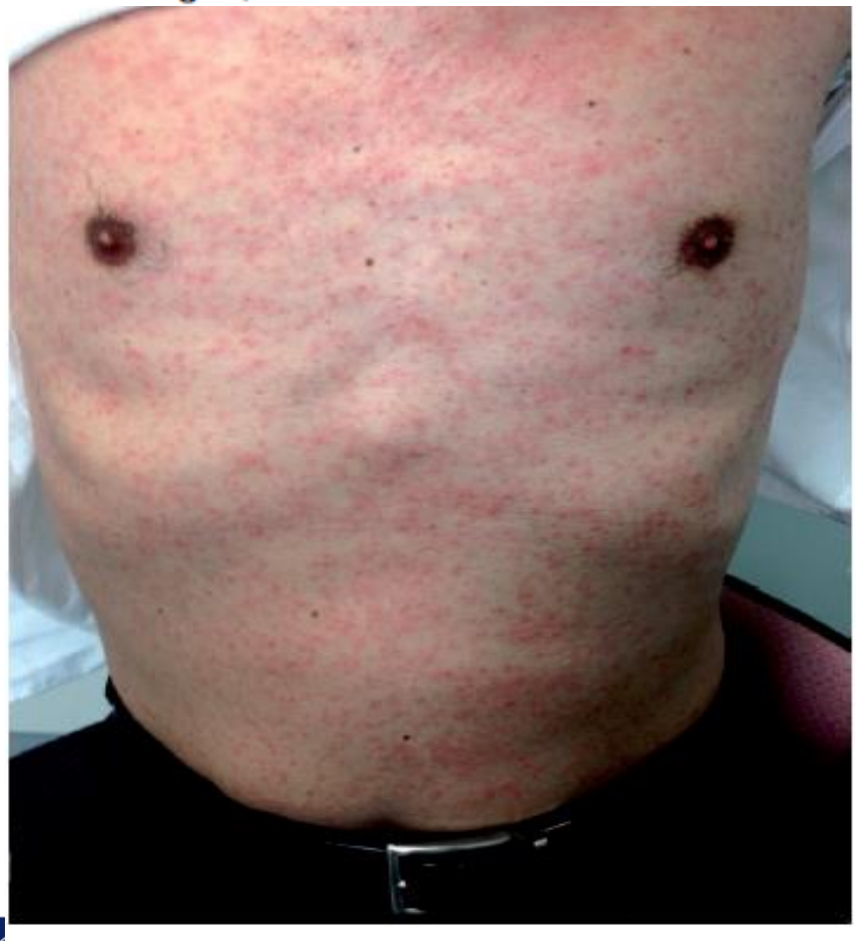


Figure 1. Maculopapular rash on the trunk in a case of imported ZIKV infection from Thailand, Japan, July 2014

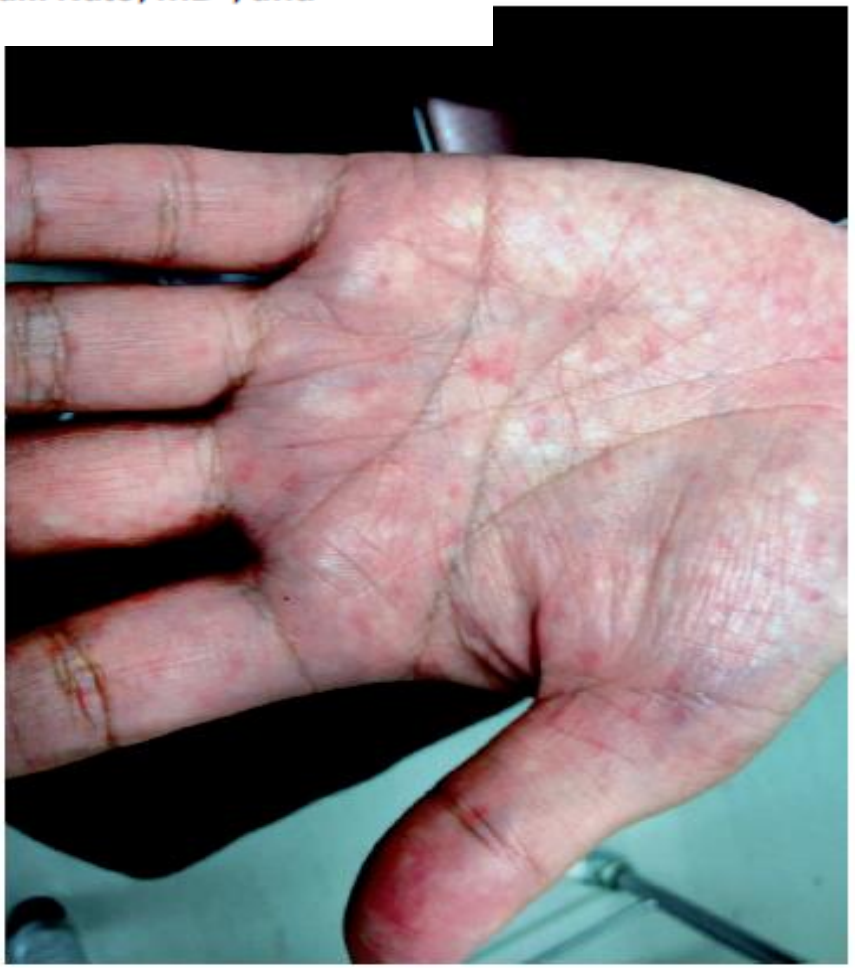


Figure 2. Maculopapular rash on the hand in a case of imported ZIKV infection from Thailand, Japan, July 2014

Zika Virus as a Cause of Neurologic Disorders

Nathalie Broutet, M.D., Ph.D., Fabienne Krauer, M.Sc., Maurane Riesen, M.Sc., Asheena Khalakdina, Ph.D., Maria Almiron, M.Sc., Sylvain Aldighieri, M.D., Marcos Espinal, M.D., Nicola Low, M.D., and Christopher Dye, D.Phil.

Studies of Guillain–Barré Syndrome or Microcephaly in Association with Zika Virus Infection, According to Study Design and Date of Publication.*

Study Type	Countries (Yr of Publication)	No. of Studies	Main Findings	Strengths	Weaknesses
Guillain–Barré syndrome					
Ecologic	French Polynesia (2015), Pacific Islands (2016)	2	French Polynesia: 8750 suspected Zika cases; 52% of 885 tested Zika-positive in saliva or blood; 73 with neurologic or autoimmune complications, including GBS; Pacific islands: AFP surveillance in children not associated with Zika emergence	French Polynesia: temporal ecologic association; studies cover several Pacific island countries	Mostly clinical diagnoses; AFP surveillance in children only and aggregated to yearly level
Surveillance	Brazil, Colombia, El Salvador, Venezuela (2016)	1	GBS cases in countries with reported Zika virus circulation: Brazil, 1708; Colombia, 201; El Salvador, 118 in 6 wk (vs. monthly average of 15); Venezuela, 252 in 1 mo	Covers multiple countries in the Americas	Ecologic association; no report of numbers of Zika cases; inconsistent or no GBS comparison data
Case reports	French Polynesia (2014), Puerto Rico (2016)	2	Patients with rash followed by GBS diagnosis; serum positive for ZIKV IgM; some other infections excluded in one case	Laboratory-confirmed ZIKV infections	Other infections not completely excluded
Case–control	French Polynesia (2016)	1	Cases: 42 people hospitalized with GBS during Zika outbreak; control group 1: 98 hospital inpatients with nonfebrile illness in same period; control group 2: 70 patients with RT-PCR–confirmed ZIKV infection; comparison of ZIKV antibodies, GBS vs. control group 1: OR, 59.7 (95% CI, 10.4–∞).	Two control groups; strong association	Cross-reactivity between DENV and ZIKV; few other infections investigated

N Engl J Med March 10,2016

Zika Virus as a Cause of Neurologic Disorders

Nathalie Broutet, M.D., Ph.D., Fabienne Krauer, M.Sc., Maurane Riesen, M.Sc., Asheena Khalakdina, Ph.D., Maria Almiron, M.Sc., Sylvain Aldighieri, M.D., Marcos Espinal, M.D., Nicola Low, M.D., and Christopher Dye, D.Phil.

Microcephaly

Ecologic	Brazil: Paraíba, Bahia (2016)	2	Paraíba: retrospective review 2012–2015: 16,208 births; higher-than-expected (2–8%) incidence of microcephaly; Bahia: ecologic association between reports of acute rash, March–June 2015 and microcephaly cases October 2015–January 2016	Temporal associations; large number of births; Bahia data suggest association with late first and early second trimester	Ecologic associations only; no confirmed Zika cases; alternative explanations not excluded
Case reports or case series	French Polynesia (2015)	1	Retrospective review of 2013–2014 Zika outbreak period: 17 cases of congenital brain malformations, including microcephaly	Temporal association with Zika outbreak; other congenital brain abnormalities observed	No documented maternal infection; retrospective; most not tested for ZIKV; no control group
Case reports or case series	Brazil: several states (2015–2016)	11	93 Cases of microcephaly, 70 with history of maternal symptoms (laboratory-confirmed in 1 of 3 tested); 9 with ZIKV in amniotic fluid, fetal or neonatal brain; 4 with ZIKV in brain but not other organs	Biologic evidence of ZIKV in fetal or neonatal brain tissues and neurotropism	Most maternal ZIKV exposures were self-reported; other congenital infections not always excluded; no control group
Case reports or case series	Various countries (2016)	1	9 Women returning to United States from Zika-affected countries, August 2015–February 2016; all reported symptoms, all laboratory-confirmed recent ZIKV infection; 2 early pregnancy losses, 2 terminations, 1 microcephaly, 2 healthy newborns, 2 still pregnant	Temporal association; biologic evidence of maternal ZIKV infections	Alternative explanations not excluded; no control group
Cohort study	Brazil: Rio de Janeiro (2016)	1	88 Women with rash during pregnancy, 72 ZIKV-positive on RT-PCR; ultrasound normal in all 16 ZIKV-negative women; ultrasound abnormal in 12 of 42 ZIKV-positive women at all stages of pregnancy (29%); microcephaly mostly in association with intrauterine growth restriction	Temporal association; biologic evidence; strong association with abnormal ultrasound or neonatal outcome	Small study; control group presumed to have other causes for rash; some congenital infections not excluded

N Engl J Med March 10,2016

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

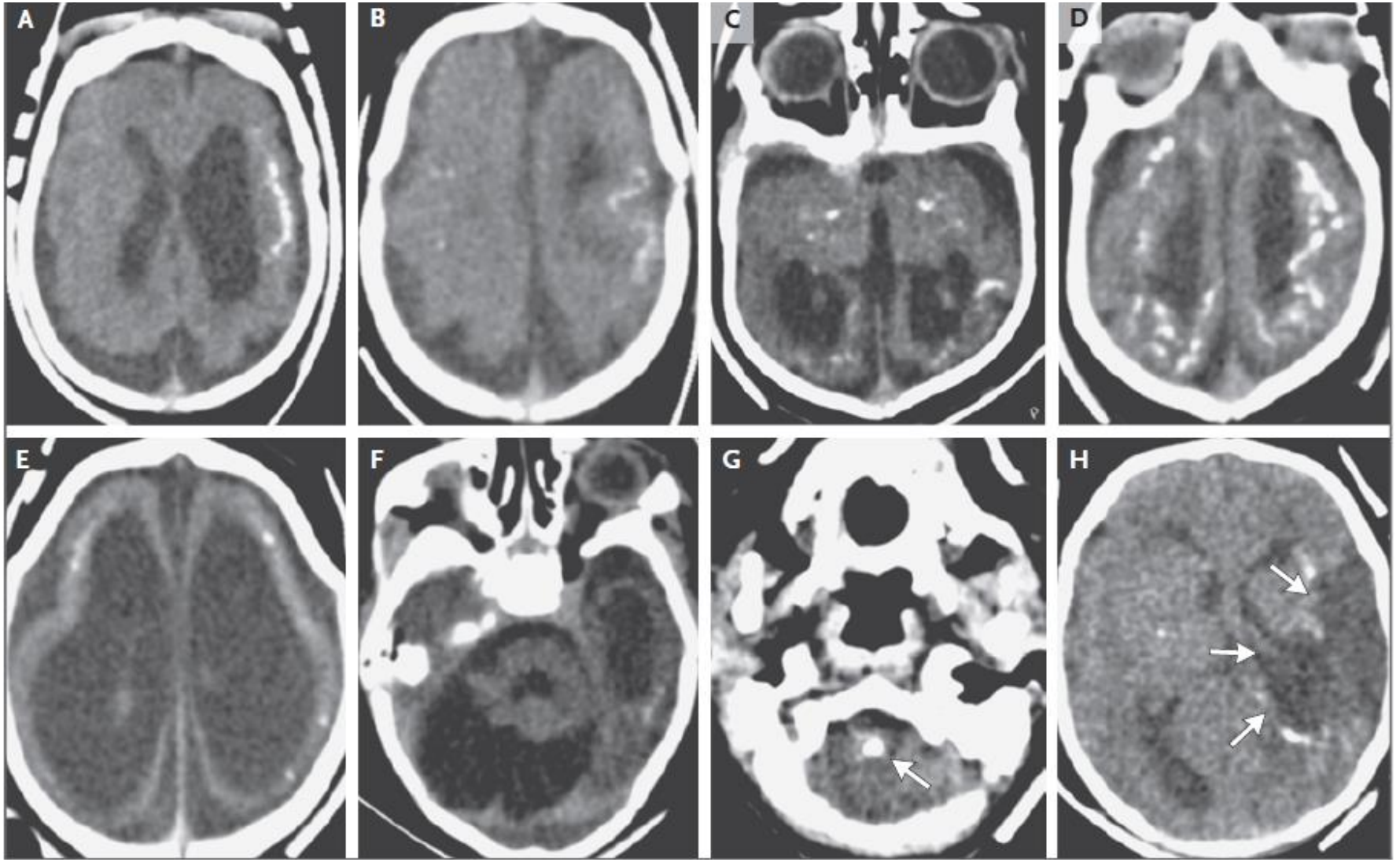
Computed Tomographic Findings in Microcephaly Associated with Zika Virus

23 infants with congenital microcephaly (clinical & epidemiological data compatible with Zika infection

Head CT obtained at a mean age of 36 days (range 3 days-5 months)

- Intracranial calcifications (all infants): frontal lobe (69-78%); parietal lobe (83-87%)
- Corticomedullary calcifications (all infants): basal ganglia (57-65%), thalamus (39-43%)
- Ventriculomegaly (all infants): severe 53%
- Hypogyration cerebral cortex: 78% severe
- Cerebellar hypoplasia (74%)
- Hypodensity of white matter (87%)

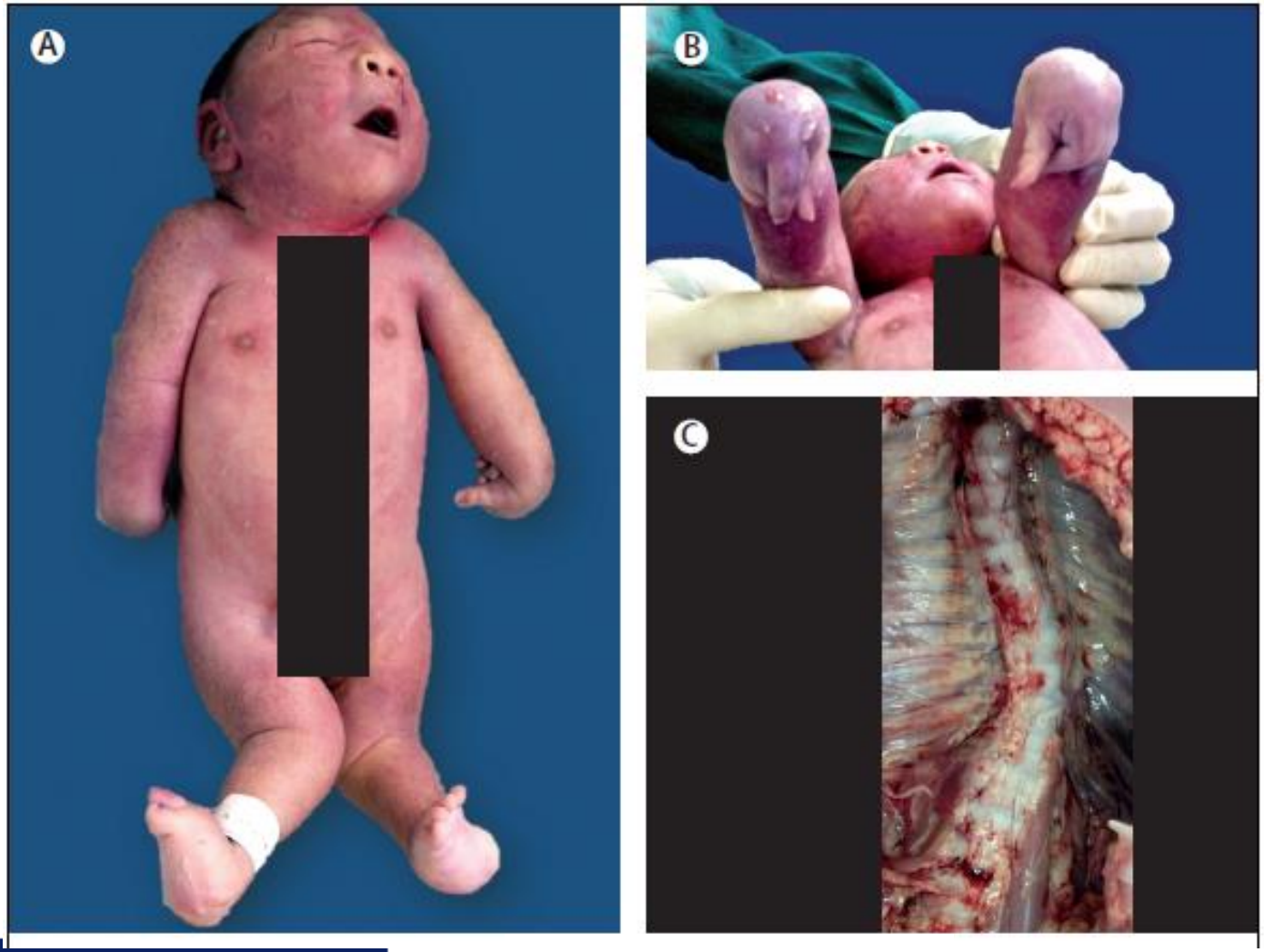
Computed Tomographic Findings in Microcephaly Associated with Zika Virus



Hazin AN et al. N Engl J Med May 13, 2016

Pathology of congenital Zika syndrome in Brazil: a case series

Roosecelis Brasil Martines, Julu Bhatnagar*, Ana Maria de Oliveira Ramos, Helaine Pompeia Freire Davi, Silvia D'Andretta Iglezias, Cristina Takami Kanamura, M Kelly Keating, Gillian Hale, Luciana Silva-Flannery, Atis Muehlenbachs, Jana Ritter, Joy Gary, Dominique Rollin, Cynthia S Goldsmith, Sarah Reagan-Steiner, Yokabed Ermias, Tadaki Suzuki, Kleber G Luz, Wanderson Kleber de Oliveira, Robert Lanciotti, Amy Lambert, Wun-Ju Shieh, Sherif R Zaki*



Lancet 2016; 388: 898–904

Zika Fetal Neuropathogenesis: Etiology of a Viral Syndrome

PLOS | NEGLECTED TROPICAL DISEASES

Zachary A. Klase[1], Svetlana Khakhina[1], Adriano De Bernardi Schneider[2], Michael V. Callahan[3,4], Jill Glasspool-Malone[5,6], Robert Malone[5,6]*

Table 1. Selected viral TORCH pathogens and associated morbidity. After [75].

Viral TORCH Pathogen	Symptoms	First or Second Trimester Teratogen	Third Trimester Teratogen	Primary microcephaly	Spontaneous abortion or fetal death
Rubella virus (German measles)	Defects in multiple organ systems, including the ophthalmic (cataracts and microphthalmia), cardiac, and neurological (deafness, mental retardation), and increased risk of type 1 diabetes in childhood	+	-	+	+
Cytomegalovirus	Mental retardation, sensorineural hearing loss, jaundice, hepatosplenomegaly, petechiae, preterm birth, preeclampsia, and fetal growth restriction	+	-	+	+
Herpes simplex virus	Encephalitis, sepsis, cataracts, pneumonitis, myocarditis, hepatosplenomegaly, chorioretinitis, and mental retardation	+	+	+	+
Varicella zoster virus (chickenpox)	Skin lesions, neurological and eye defects, limb hypoplasia, fetal growth restriction, and defects of multiple organ systems	+	-	+/-	+
Zika virus	Microcephaly, facial disproportionality, cutis gyrata, hypertonia and/or spasticity, hyperreflexia, and irritability; abnormal neuroimages include calcifications, ventriculomegaly, and lissencephaly	+	+	+	+

Zika virus-associated neurological disorders: a review

Abelardo Q. C. Araujo,[1,2] Marcus Tulius T. Silva[1] and Alexandra P. Q. C. Araujo[3]

Table 1 Clinical and neurological findings of the most common arboviruses

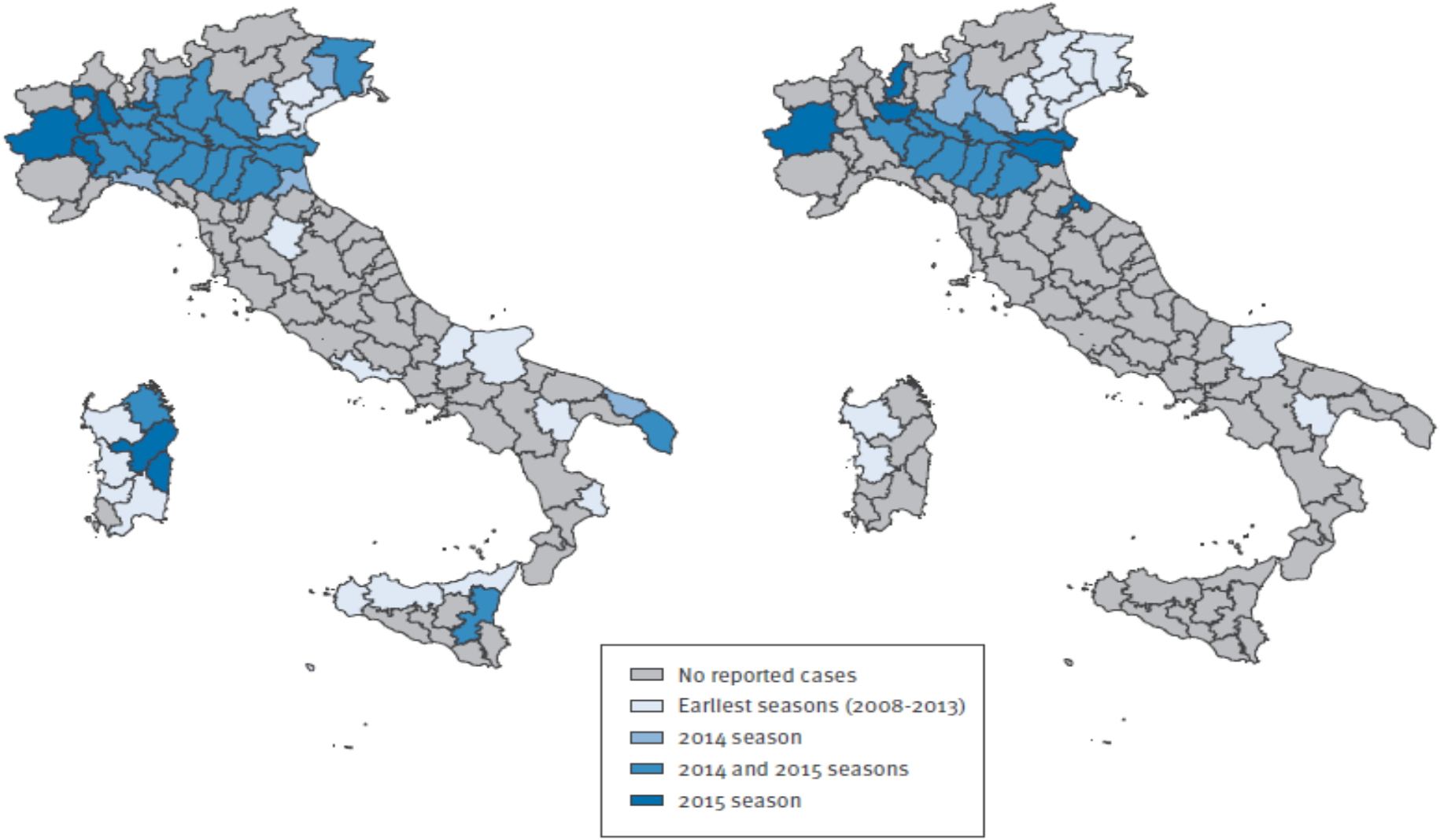
Virus/symptoms	Zika virus	Dengue virus	Chikungunya virus	West Nile virus
Fever	+	+ + + +	+ + + +	+ +
Rash	+ + + +	+ +	+ +	+ +
Myalgia	+ +	+ + +	+ +	+ +
Arthralgia	+ +	+	+ + + +	+
Peri-articular oedema	+ +	+	+ + +	-
Conjunctival hyperaemia	+ + +	+	+	+ +
Headache	+ +	+ + +	+ +	
Neurological syndromes	Microcephaly, GBS, meningoencephalitis, myelitis	Encephalopathy, seizures, GBS, mononeuropathy, myelitis	Meningoencephalitis, acute flaccid paralysis, GBS, sensorineural hearing loss	Meningitis, encephalitis, acute flaccid paralysis, brachial plexopathy, demyelinating neuropathy, motor axonopathy, axonal polyneuropathy, motor radiculopathy, myasthenia gravis, cranial nerve palsies

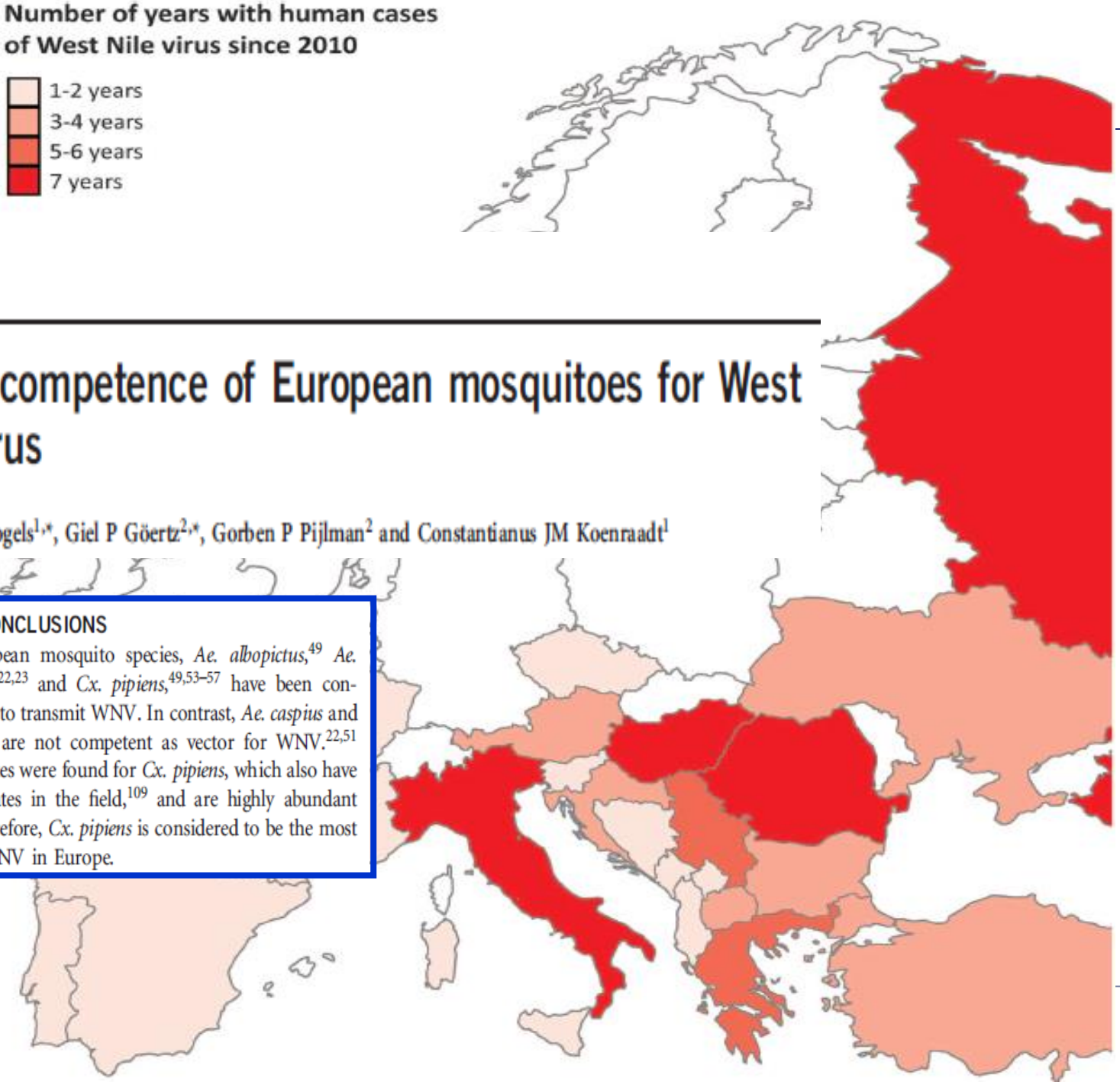
West Nile virus transmission: results from the integrated surveillance system in Italy, 2008 to 2015

C Rizzo [1], C Napoli [1], G Venturi [1], S Pupella [2], L Lombardini [3], P Calistri [4], F Monaco [4], R Cagarelli [5], P Angelini [5], R Bellini [6], M Tamba [7], A Piatti [8], F Russo [9], G Palù [10], M Chiari [11], A Lavazza [11], A Bella [1], the Italian WNV surveillance working group [12]

A. Veterinary cases

B. Human cases





REVIEW

Vector competence of European mosquitoes for West Nile virus

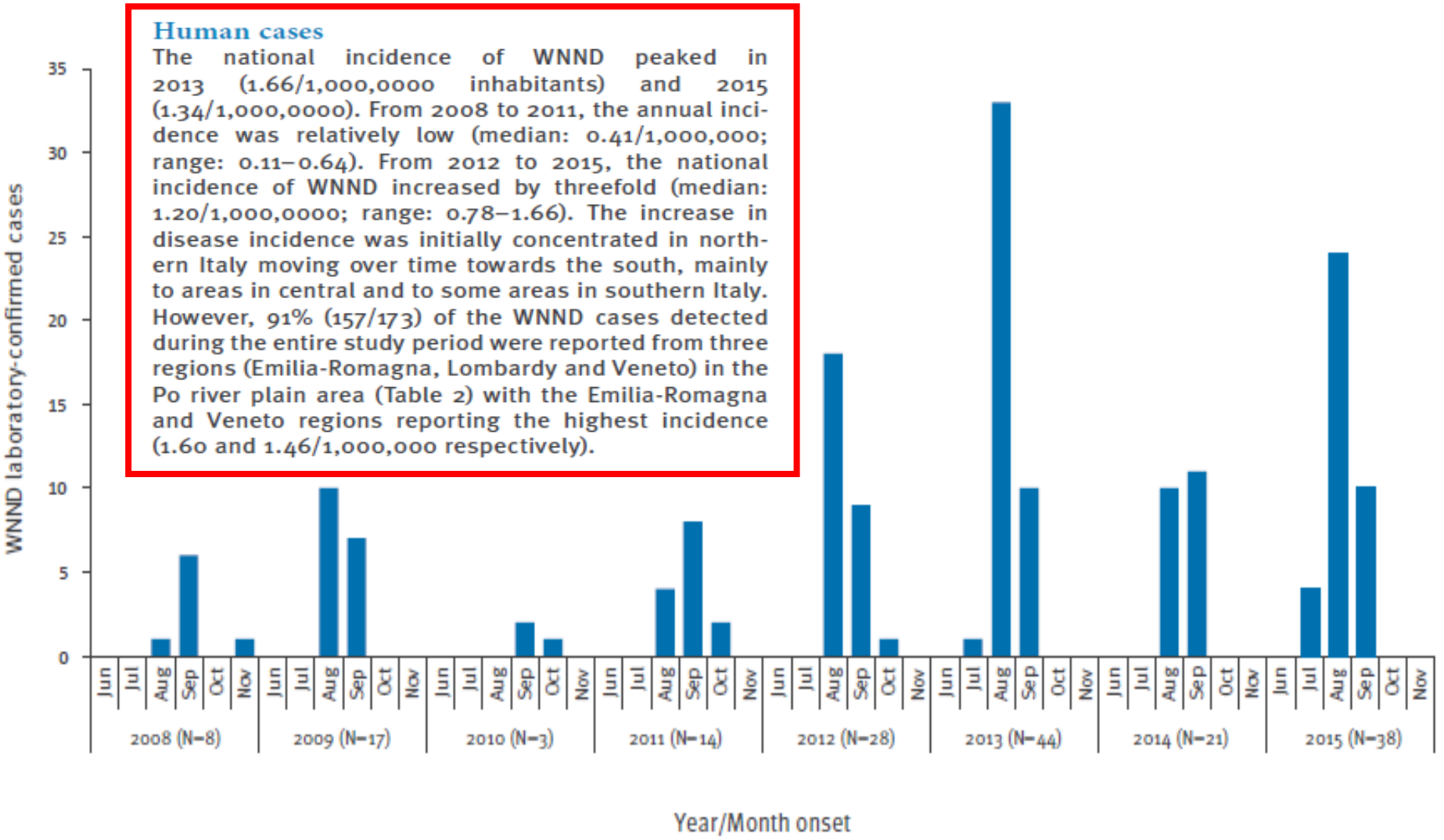
Chantal BF Vogels[1,*], Giel P Göertz[2,*], Gorben P Pijlman[2] and Constantianus JM Koenraadt[1]

DISCUSSION AND CONCLUSIONS

Until now, four European mosquito species, *Ae. albopictus*,[49] *Ae. detritus*,[50] *Cx. modestus*[22,23] and *Cx. pipiens*,[49,53–57] have been confirmed to be competent to transmit WNV. In contrast, *Ae. caspius* and *Ae. japonicus japonicus* are not competent as vector for WNV.[22,51] Highest transmission rates were found for *Cx. pipiens*, which also have high WNV infection rates in the field,[109] and are highly abundant during summer.[110] Therefore, *Cx. pipiens* is considered to be the most important vector for WNV in Europe.

FIGURE 3

Human West Nile neuroinvasive disease cases by month of symptom onset and year, Italy 2008–2015 (n=173)



WNND: West Nile neuroinvasive diseases.

The median age of cases was 73 years (range: 10–90 years) during the entire surveillance period, varying from a minimum of 67 years (range: 41–68 years) in 2010 to 77 years (range: 42–89 years) in 2013. Most of the reported cases (69%, 120/173) were male. All WNND cases were hospitalised: 82 presented as encephalitis, 44 as meningo-encephalitis, 31 as meningitis, seven as polyradiculoneuritis, one as facial paralysis and eight as other neurological symptoms: meningeal symptoms (n=2), extrapyramidal syndrome (n=1), confusion (n=1), headache (n=1), ataxic paraparesis (n=1), neuropathy of lower limbs (n=1), symptoms were not specified for one case. Eighteen of the 173 WNND cases died (2009: n=3; 2011: n=5; 2012: n=1; 2013: n=7; 2014 and 2015: n=1 each), corresponding to an overall case fatality rate of 10%. The median age of WNND fatal cases was 82 years (range: 34–89 years), 14 of 18 were male. All fatal cases were reported to have chronic conditions before symptom onset and 10 presented with encephalitis, six with meningo-encephalitis and two with meningitis.

In 2015, a total of 316,614 WNV NAT screening tests were conducted in blood donors in the affected provinces and 13 asymptomatic donors, six in Emilia Romagna and seven in Lombardy were identified. No

From 2008 to 2010, only circulation of lineage 1 was reported. The complexity of the epidemiological scenario increased in 2011 with the detection of the novel lineage 2 which overcame lineage 1 from 2013 to 2015 and was responsible for both human and animal cases [12]. It is not clear why there was more WNV activity