UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

Le vaccinazioni negli atleti viaggiatori

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Available vaccines for travelers (otherwise not routinely used)

- Yellow fever
- Japanese encephalitis
- Dengue fever
- Tick-borne encephalitis
- Typhoid fever
- Hepatitis A
- Cholera
- Rabies

Olympic games 2021: Tokyo



Table 1. **Incidence and characteristics of selected notifiable (non-sentinel) vaccine-preventable diseases (VPDs), Japan, 2006–2016**

Disease (*n* cases; period reviewed)	Period incidence[a]	Annual incidence range[b]	% Male (*n*)	Predominant age groups in years: % (*n*)	Case reporting	Vaccination schedule[f]
Rubella (18 117; 2008–2015)	1.78	0.07–11.3	75 (13 660)	20–44: 69 (12 440)	Clinical or laboratory	Routine
IPD (5229; 2013[c]–2015)	1.50	1.05–1.9	60 (3134)	<5: 19 (1017); ≥60: 62 (3227)	Clinical and laboratory	Routine (PCV7 and PPSV23)
Measles (13 805; 2008–2016)	1.20	0.03–8.6	57 (7812)	20–39: 58 (95)[d]	Clinical or laboratory	Routine
Viral hepatitis[e] (2454; 2006–2015)	0.19	0.17–0.22	74 (1808)	20–44: 64 (1559)	Clinical and laboratory	Routine (hepatitis B)
Hepatitis A (2245; 2006–2015)	0.18	0.10–0.34	58 (1313)	25–64: 72 (1744)	Laboratory	Voluntary
IHD (560; 2013[c]–2015)	0.16	0.11–0.20	60 (338)	≥70: 52 (293)	Clinical and laboratory	Routine
Tetanus (1158; 2006–2015)	0.09	0.07–0.10	56 (653)	≥55: 85 (984)	Clinical	Routine
Typhoid (330; 2008–2015)	0.03	0.02–0.05	59 (195)	20–39: 59 (194)	Laboratory	Not approved
IMD (94; 2013–2015)	0.03	0.02–0.03	64 (60)	≥50: 59 (55)	Clinical and laboratory	Voluntary (MCV4)
Japanese encephalitis (51; 2006–2015)	0.004	0.002–0.008	63 (32)	≥60: 61 (31)	Clinical and laboratory	Routine

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Case report

The 2014 autochthonous dengue fever outbreak in Tokyo: A case series study and assessment of the causes and preventive measures

Mayuko Kori [a,*], Nobuyasu Awano [a], Minoru Inomata [a], Naoyuki Kuse [a], Mari Tone [a], Hanako Yoshimura [a], Tatsunori Jo [a], Kohei Takada [a], Atsuko Tanaka [b], Momoko Mawatari [b], Akihiro Ueda [b], Takehiro Izumo [a]

RAPID COMMUNICATIONS

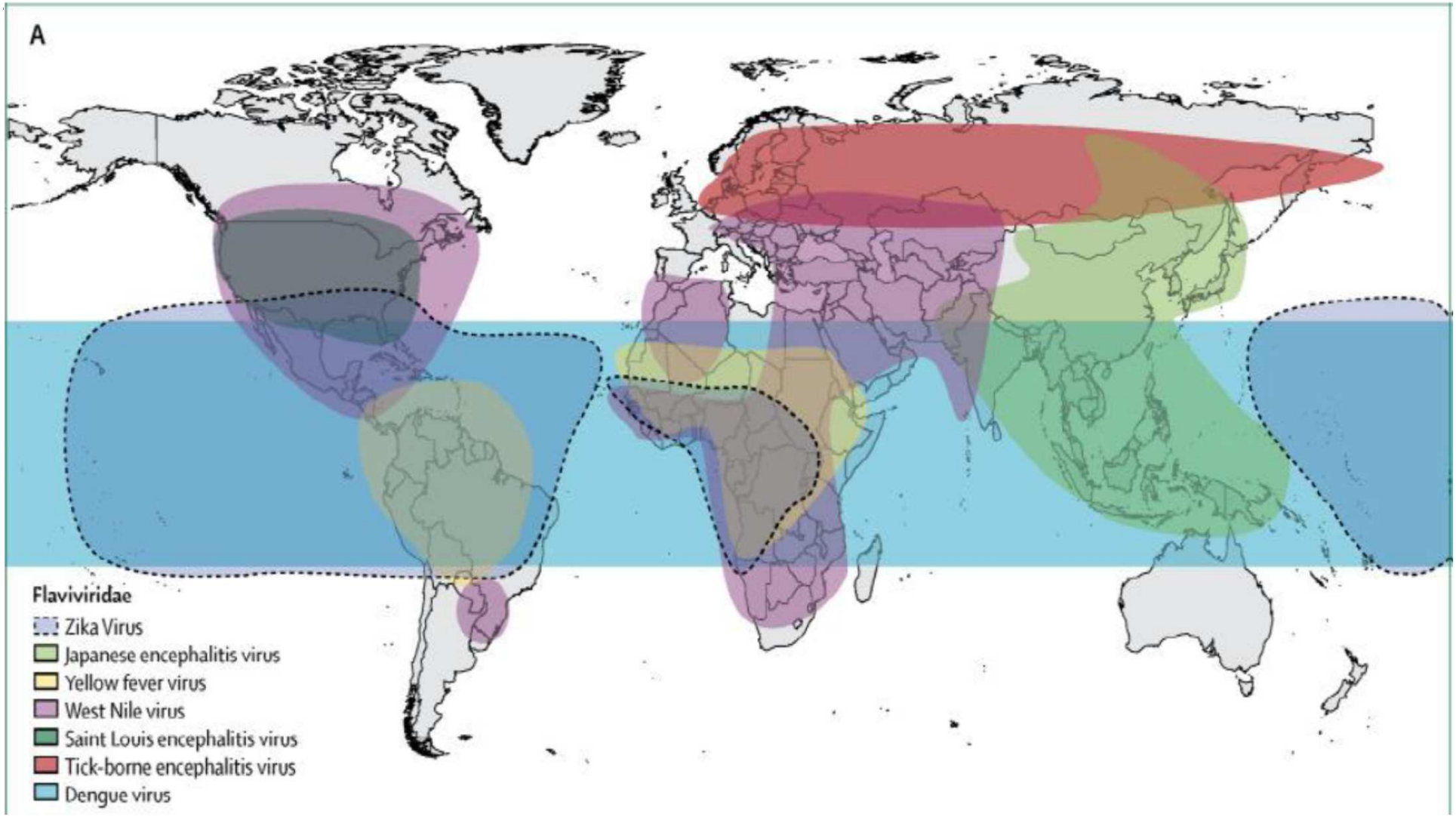
A case of Japanese encephalitis in a 20 year-old Spanish sportsman, February 2013

P Doti[1], P Castro[1], M J Martínez[2,3], Y Zboromyrska[2], E Aldasoro[3], A Inciarte[1], A Requena[3], J Milisenda[1], S Fernández[1], J M Nicolás[1], J Muñoz (jose.munoz@cresib.cat)[3]

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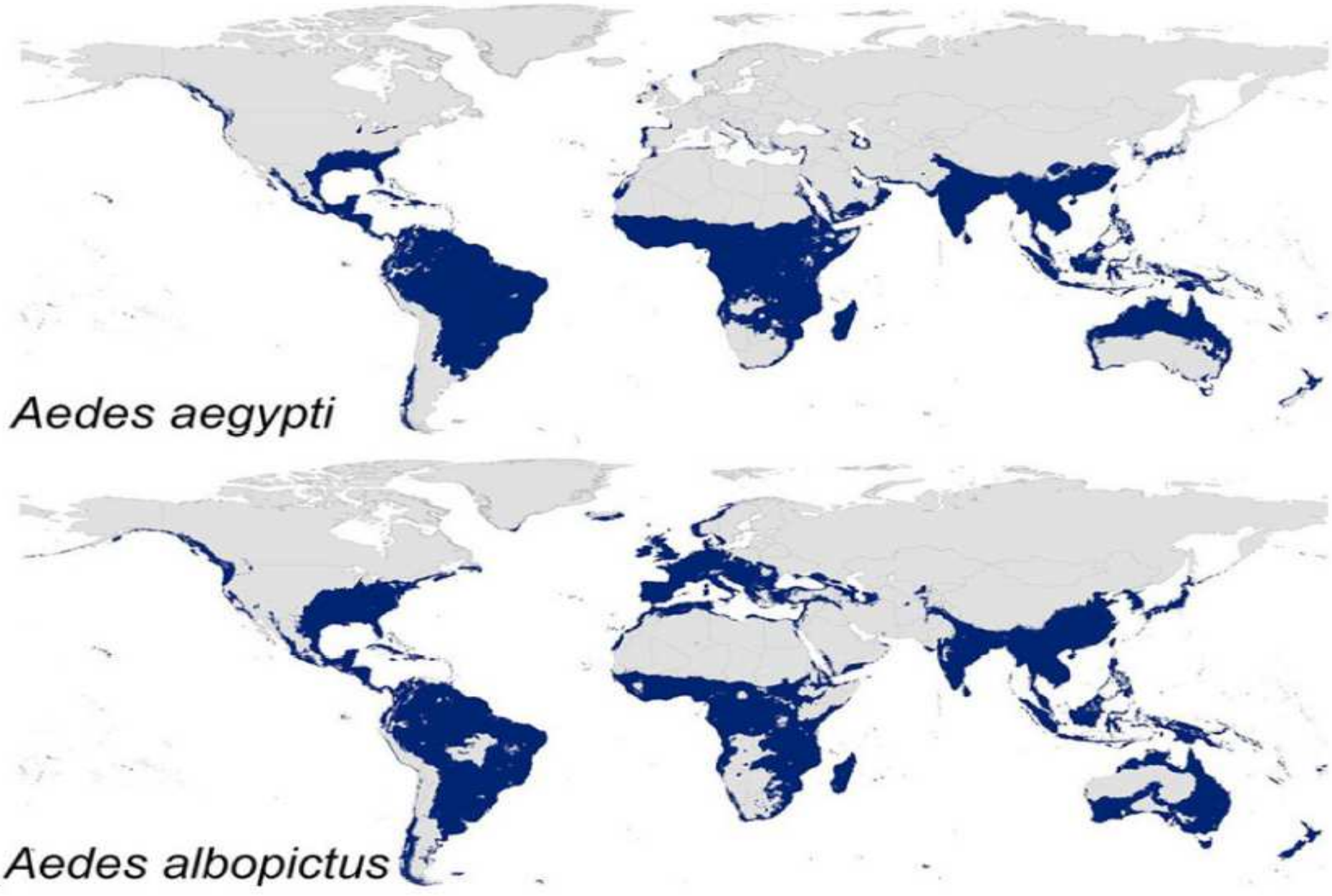
Flavivirus Risk Map



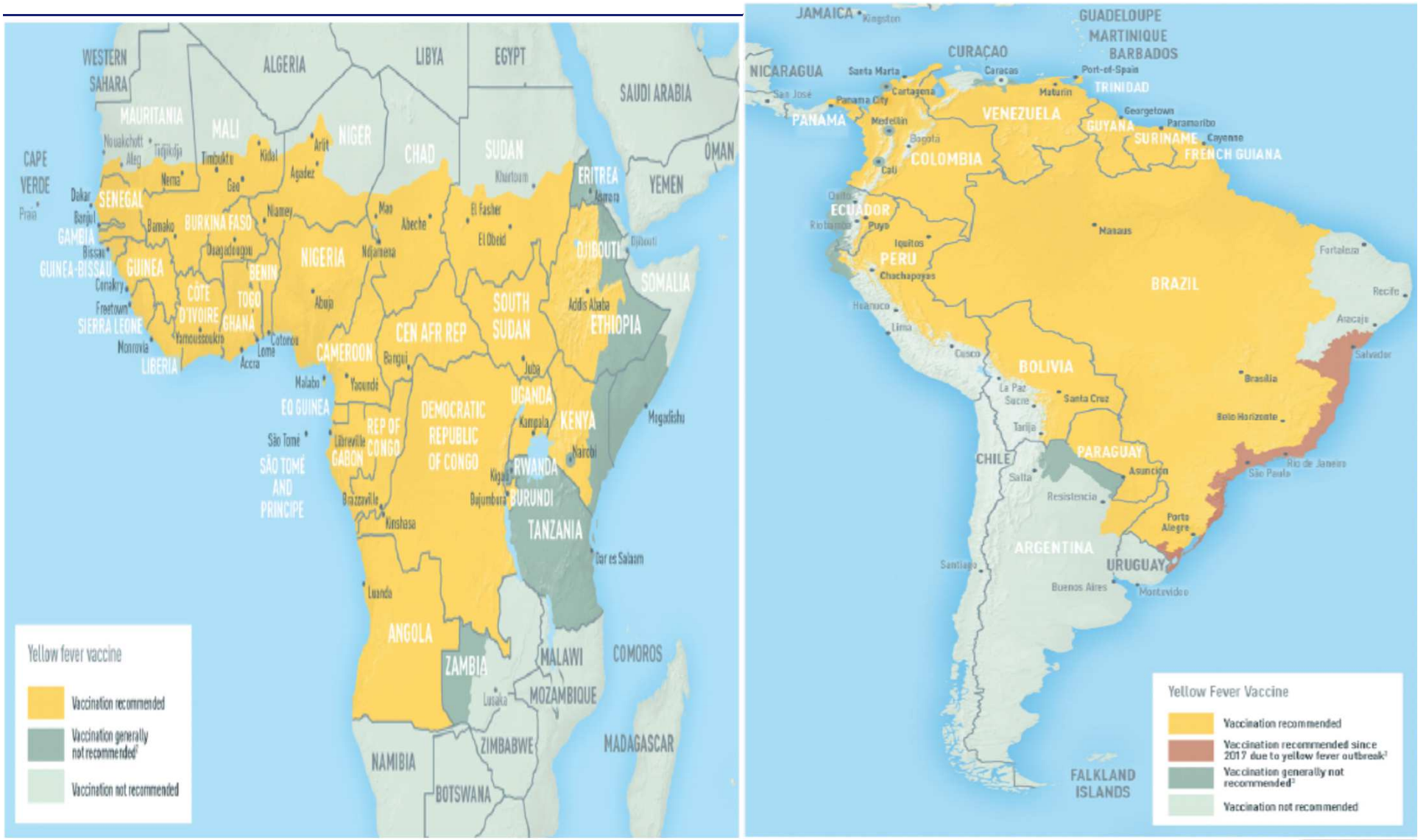
Dengue & Yellow Fever

Table 1. *Aedes*-borne arboviral incubation periods and the asymptomatic fraction of infections

Aedes-Borne Arboviruses	Virus Type	Transmitted By	Symptoms	Supportive Treatment	Coinfection with Other Arboviruses	Intrinsic Incubation Period (Days)	Extrinsic Incubation Period (Days)	Asymptomatic Proportion in Infected Humans (%)
Dengue	*Flavivirus* [14]	*Ae. Aegypti* *Ae. albopictus* [5,6]	Sudden high grade fever, Headache, Nausea, Arthralgia, Eye and Muscle pain [65]	DENV vaccine and drug administration [66]	Yes (e.g., DENV and ZIKV) [67]	Median: 5.3 [68] Mean: 5.9 [42]	Mean: 15 (at 25 °C) 6.5 (at 30 °C) [42]	75 [69]
Zika	*Flavivirus* [70]	*Ae. aegypti* *Ae. albopictus* Human (via blood transfusion) [45,46,51]	Fever, Conjunctivitis, Muscle pain, Headache, Joint pain, Rash and Microcephaly [71,72]	Fluid intake and drug administration (such as acetaminophen) [73]	Yes (e.g., ZIKV and CHIKV) [74]	Median: 6.8 [75] 6.2 [76]	Median: 5.1 (at 30 °C) 9.6 (at 26 °C) 24.2 (at 21 °C) [77]	80 [78]
Chikungunya	*Alphavirus* [79]	*Ae. aegypti* *Ae. albopictus* [80]	High fever, Joint pain, Myalgia, Arthritis, Conjunctivitis, and Dermatologic manifestations [81,82]	Plenty of rest, Fluid intake and Acetaminophen [52,80]	Yes (e.g., CHIKV and DENV) [83]	Median: 3.0 [68]	Median: 2 [84]	Approx. 18 to 28 [85]
Yellow Fever	*Flavivirus* [56]	*Ae. aegypti* *Ae. Albopictus* [86]	Headache, Nausea, Vomiting, Fever, Dizziness and Joint pain [87,88]	YFV vaccine and Ribavirin [89,90]	Yes (e.g., YFV and CHIKV) [91]	Median: 4.3 [92] 4.4 [68]	Median: 10 (at 25 °C) [92]	55 [93]


Aedes aegypti
Aedes albopictus

Yellow fever maps of risk: Africa & Latin America



Yellow fever vaccine

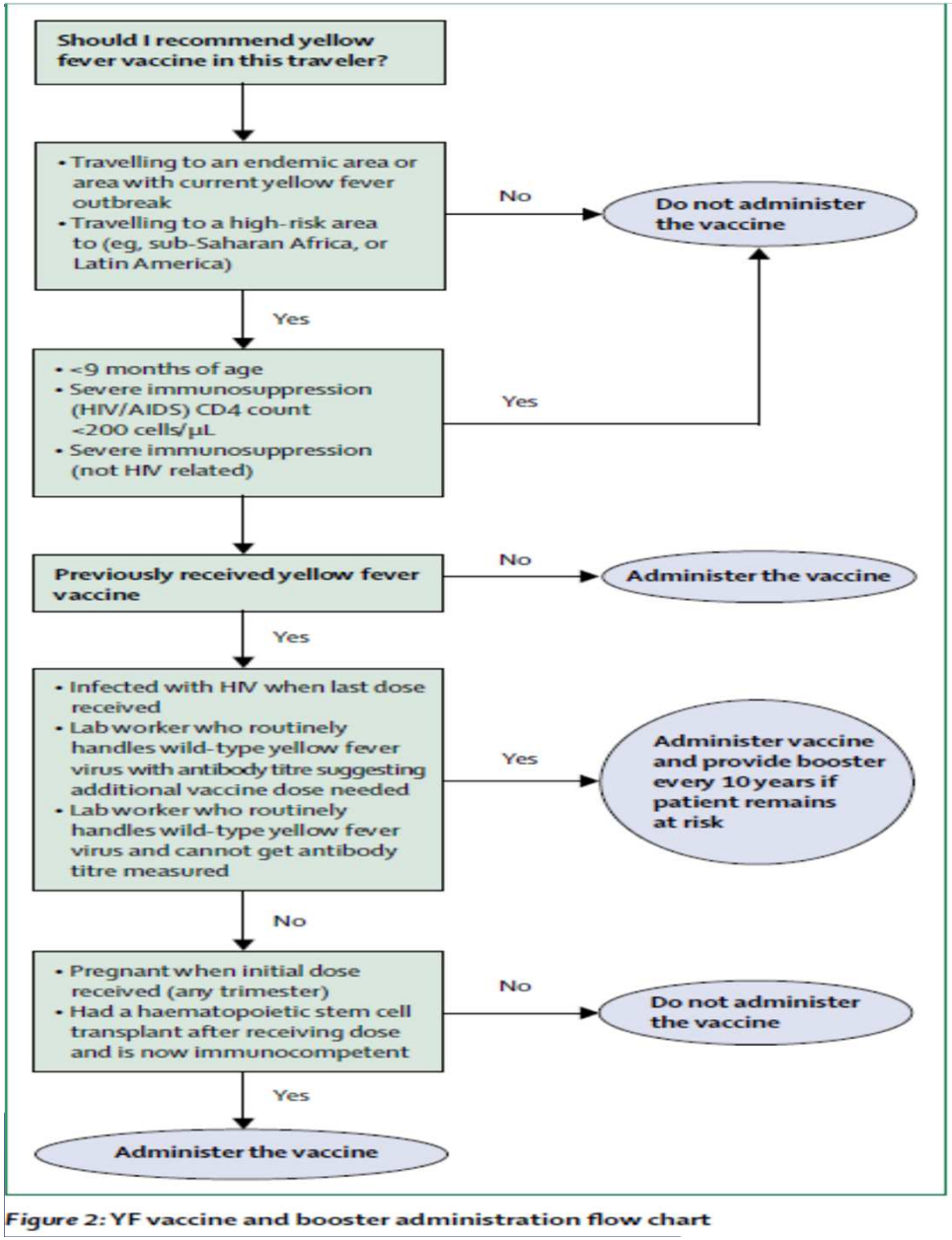


Figure 2: YF vaccine and booster administration flow chart

17D vaccine developed by Theiler & Smith

Virus-attenuated vaccine

Widely held to be one of the safest vaccine in use

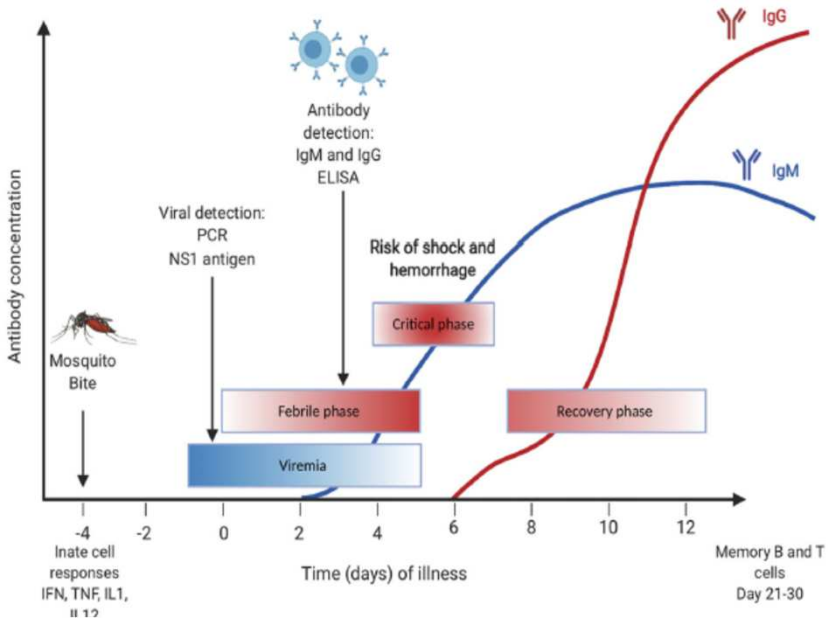
YF vaccine-associated viscerotropic adverse events (YELV-AVD)

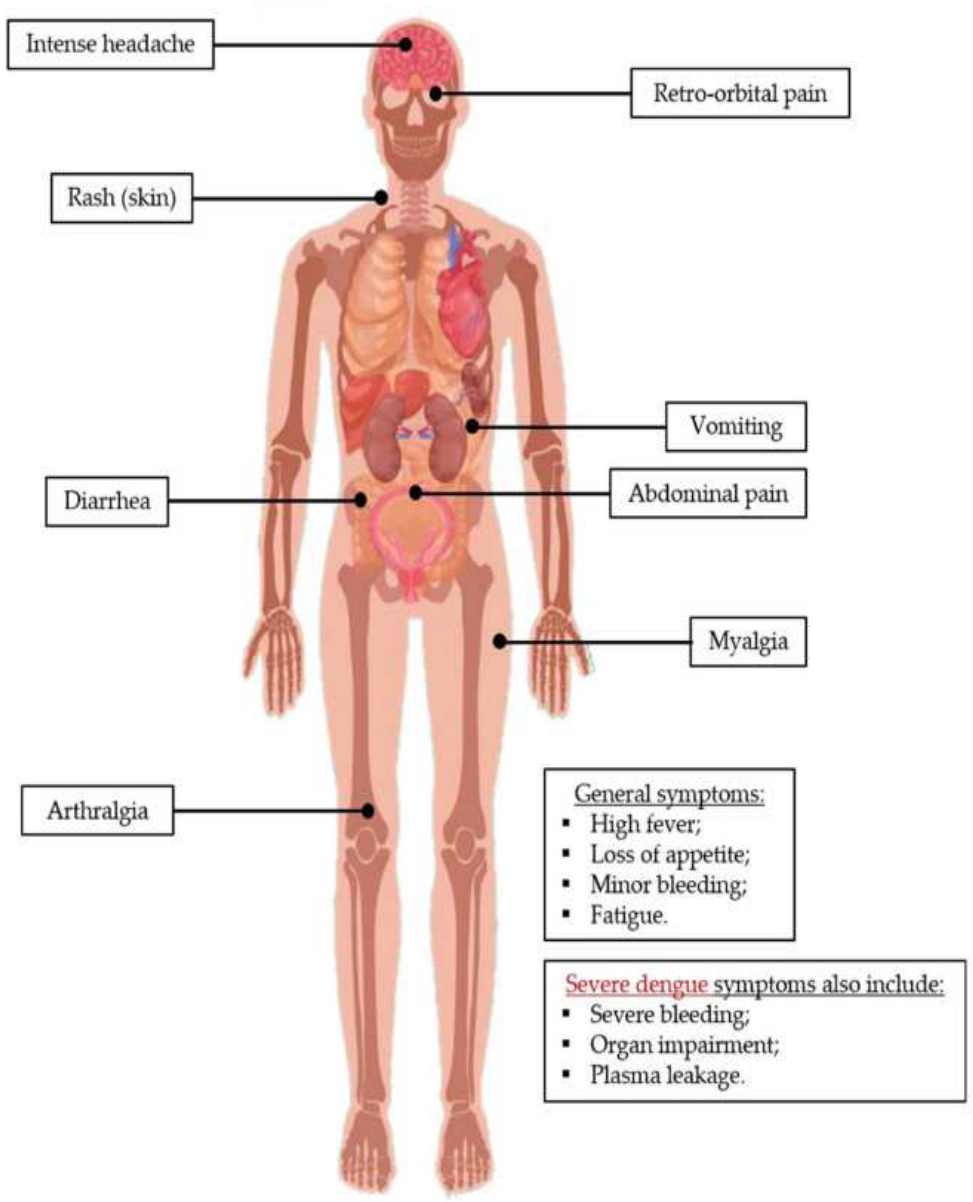
YF vaccine-associated neurotropic disease (YEL-AND)

Form 11 July 2016 the certificate of vaccination against YF is valid for the life of the person vaccinated

Dengue fever

390 million infections worldwide with 96 million of clinical cases every year





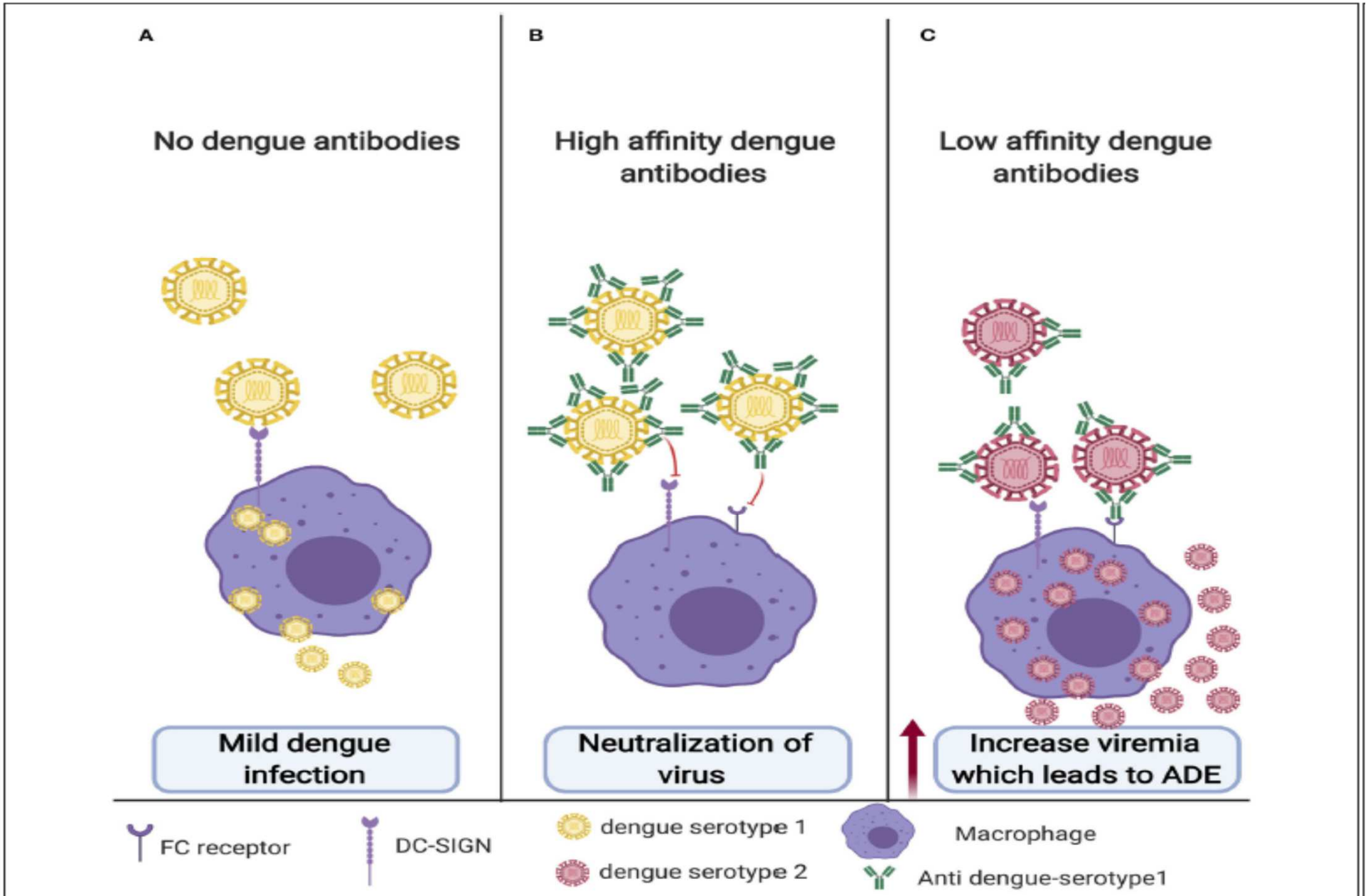


FIGURE 4 | Antibody dependent enhancement (ADE): **(A)** Primary infection with no previous vaccination. DENV will enter macrophage through its cognate receptor; however, most of the time, it will result in mild disease, and sometime this could even be symptomatic or with mild flu-like symptoms. **(B)** DENV in the presence of neutralizing antibodies for the same serotype. DENV will not be able to enter the cells and establish infection. **(C)** Cross-reactive antibodies from previous unsuccessful dengue vaccine or dengue infection with different serotypes will bind but not neutralize the virus. This low-affinity binding will facilitate the entry of the virus to the macrophage through FC receptor resulting in increased viremia leading to ADE.

Dengvaxia

First licensed dengue vaccine

CYD-TDV, a tetravalent live attenuated with a yellow fever 17D backbone, is the first dengue vaccine to be licensed, under 'Dengvaxia'. Despite being first licensed in 2015 in Mexico followed by 20 other dengue endemic countries based on results from Phase 3 trials conducted in more than 30 000 children and adolescents aged 2–16, it was only introduced in two subnational public health programs in the Philippines and Brazil. The Phase 3 trials

post-hoc retrospective analyses of the long-term safety data revealed an excess risk of severe dengue in those who were seronegative at baseline. Serostatus refers to

Table 1

Comparison of the 3 leading tetravalent live-attenuated dengue vaccine candidates

	CYD-TDV (Dengvaxia) (Sanofi Pasteur)	TAK-003 (Takeda)	TV003/TV005)/ NIH)
Licensure	December 2015	Not yet	Not yet
Phase 3	Completed 5 year observation time	Stage 1 and 2 completed and published	Recruitment closed, Phase 3 trial results not yet published
Study sites of Phase 3 trial	10 countries in Asia and Latin America	8 countries in Asia and Latin America	Brazil
Age range of Phase 3 study	participants	2–16	4–16
2–59			
Doses	3 (6 months apart), but label change is imminent for 2 doses only	2 doses (3 months apart)	1 dose
Backbone	Yellow fever	DENV 2	Full-genome for DENV 1, 3 and 4. Backbone for DENV 2 is DENV 4
Dengue non-structural proteins	Not present in the vaccine construct	DENV 2	DENV 1, 3 and 4

Japanese encephalitis Map



Japanese encephalitis vaccines

JEV belongs to the family Flaviviridae

Only a single serotype has been identified; based on phylogenetic analysis of the envelope gene of JEV, 5 genotypes have been described

There has existed since the 1940s, a series of efforts to develop multiple vaccines against JEV, which may be broadly categorised into three types: (1) inactivated JE vaccines, (A) inactivated virus grown in mouse brain (MB-JEV) and (B) inactivated virus grown in primary hamster kidney or Vero cells; (2) live-attenuated JE virus vaccines and (3) live yellow fever virus (YFV)-JEV chimeric recombinant vaccine.

Inactivated JE vaccines

The BIKEN vaccine prepared from either the Nakayama or Beijing-1 strains of JEV grown in suckling mouse brains (MB-JEV) was licensed for human use by the Ministry of Health and Welfare, Japan, in 1954 and is credited with having brought down the incidence of JE encephalitis dramatically in Japan and Taiwan. The disadvantages of MB-JEV has been the requirement for multiple doses as would be expected for a killed vaccine,

prompted the discontinuation of its manufacture, and it ceased to be used once all vaccine lots were exhausted in 2011. However, MB-JEV manufactured in a Thai facility using technology transferred from the BIKEN Foundation continued to be used as part of the Thai National Immunization program.

Inactivated JE vaccines

time, the latter has found favour for veterinary use. The attenuated strain SA-14-14-2 of JEV grown in Vero cells and formalin inactivated was developed as a vaccine (IC51) by Intercell AG under licence of VaccGen International LLC and sold under the brand name IXIARO in Europe and Americas and as JESPECT in Australia and New Zealand.

Inactivated JE vaccines

Features and properties of Japanese encephalitis vaccine (inactivated, adsorbed) [IXIARO®]	
Indication	
For immunization against Japanese encephalitis virus in adults	
Vaccine composition	
Vaccine comprises formalin-inactivated Japanese encephalitis strain SA_{14}-14-2 adsorbed to an aluminium hydroxide (0.1%) adjuvant	
Dosage and administration (in clinical trials in healthy adult volunteers)	
Dose	Two doses of 6µg (in 0.5 mL)
Route of administration	Intramuscular injection into deltoid muscle
Frequency of administration	Vaccination at 0 and 28 days
Most common adverse events (>10%)	
Systemic	Headache, myalgia, influenza-like illness, fatigue
Injection site	Tenderness, pain

Tick-bite encephalitis

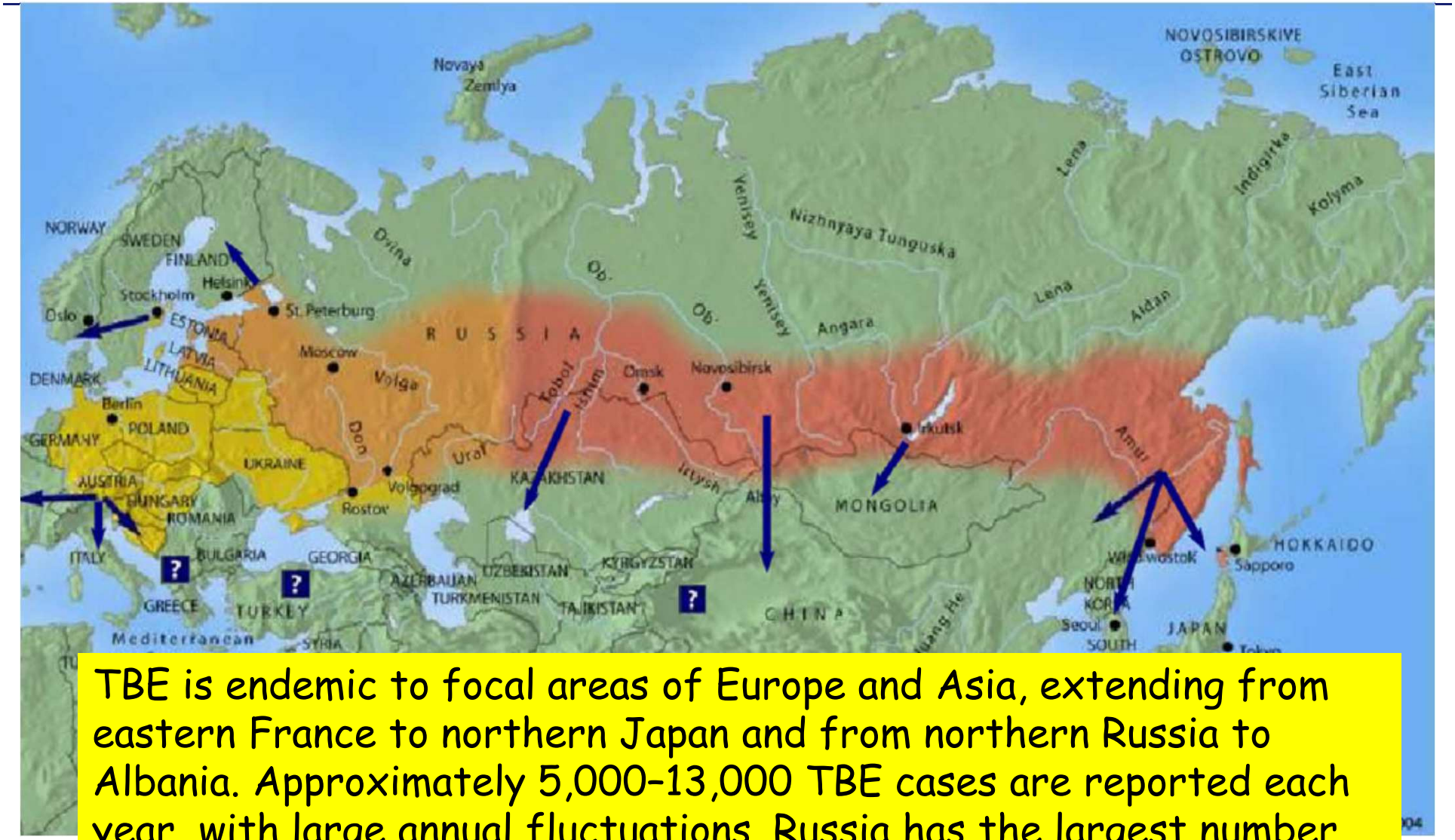
The overall risk of acquiring TBE for an unvaccinated visitor to a highly endemic area during the TBE virus transmission season has been estimated at 1 case per 10,000 person-months of exposure. Most TBE virus infections result from tick bites acquired in forested areas through activities such as camping; hiking; fishing; bicycling; collecting mushrooms, berries, or flowers; and outdoor occupations such as forestry or military training.

The risk is negligible for people who remain in urban or unforested areas and who do not consume unpasteurized dairy products.

TBE virus transmission

TBE virus is transmitted to humans through the bite of an infected tick of the *Ixodes* species, primarily *I. ricinus* (European subtype) or *I. persulcatus* (Siberian and Far Eastern subtypes). The virus is maintained in discrete areas of deciduous forests. Ticks act as both vector and virus reservoir, and small rodents are the primary amplifying host. TBE can also be acquired by ingesting unpasteurized dairy products (such as milk and cheese) from infected goats, sheep, or cows.

The "TBE-belt"



TBE is endemic to focal areas of Europe and Asia, extending from eastern France to northern Japan and from northern Russia to Albania. Approximately 5,000–13,000 TBE cases are reported each year, with large annual fluctuations. Russia has the largest number of reported cases.

TBE-vaccines

Two inactivated cell culture-derived TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (also marketed as TicoVac) (Pfizer, France) and Encepur (GSK, Germany). Two inactivated TBE vaccines are available in Russia: TBE-Moscow (Chumakov Institute) and EnceVir (Microgen). SenTaiBao (Changchun Institute of Biological Products in China) also manufactures an inactivated TBE vaccine. Immunogenicity studies suggest that the European and Russian vaccines provide cross-protection against all 3 TBE virus subtypes.

TBE-immunization

Table 2 Registered schedules for TBE immunization

	Primary immunization			First booster	Subsequent boosters[a]
	Dose 1	Dose 2	Dose 3	Dose 4	Doses 5+
Conventional schedules					
FSME-Immun	Day 0	Day 21[b]	5–12 Months after 2nd dose[c]	After 3 years	Every 5 years for people aged <60 years Every 3 years for people aged ≥60 years
Encepur	Day 0	1–3 Months after first dose	9–12 Months after 2nd dose	After 3 years	Every 5 years for people aged <60 years Every 3 years for people aged ≥60 years
Accelerated conventional schedule					
FSME-Immun	Day 0	Day 14	5–12 Months after 2nd dose[c]	After 3 years	Every 5 years for people aged <60 years Every 3 years for people aged ≥60 years
Encepur	Day 0	Day 14	5–12 Months after 2nd dose[c]	After 3 years	Every 5 years for people aged <60 years Every 3 years for people aged ≥60 years
Rapid schedule					
Encepur	Day 0	Day 7	Day 21	After 12–18 months	Every 5 years for people aged <60 years Every 3 years for people aged ≥60 years

Adapted from Ref. 54.

[a] According to recommendations of the Austrian Immunization Board.

[b] For FSME-Immun Junior: 1–3 months after first dose.

[c] For FSME-Immun Junior: 9–12 months after second dose.

Banzoff A et al. Travel Med Infect Dis 2008; 6:331-41

Cholera cases

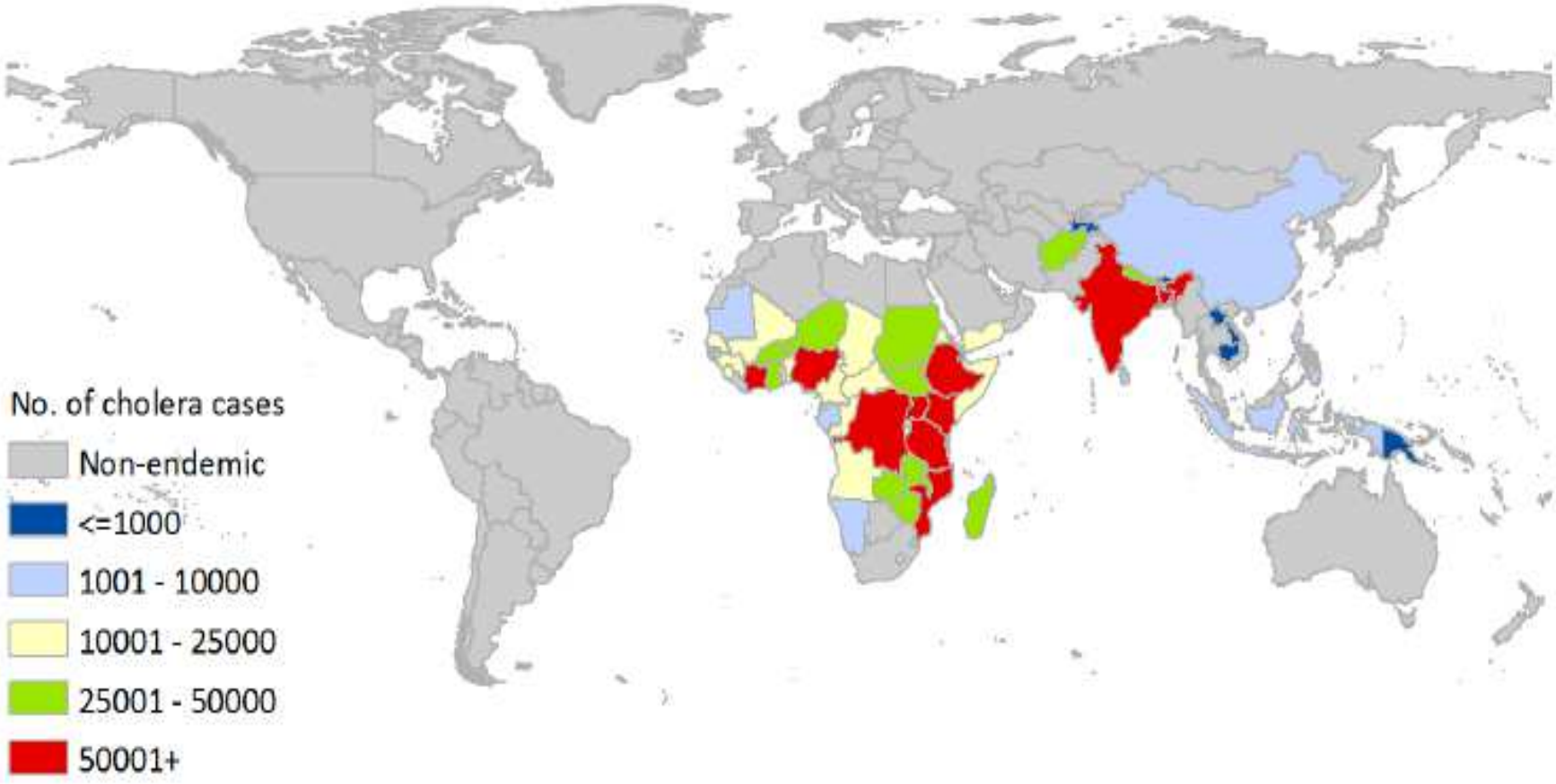


Fig 2. Annual number of cholera cases in endemic countries.

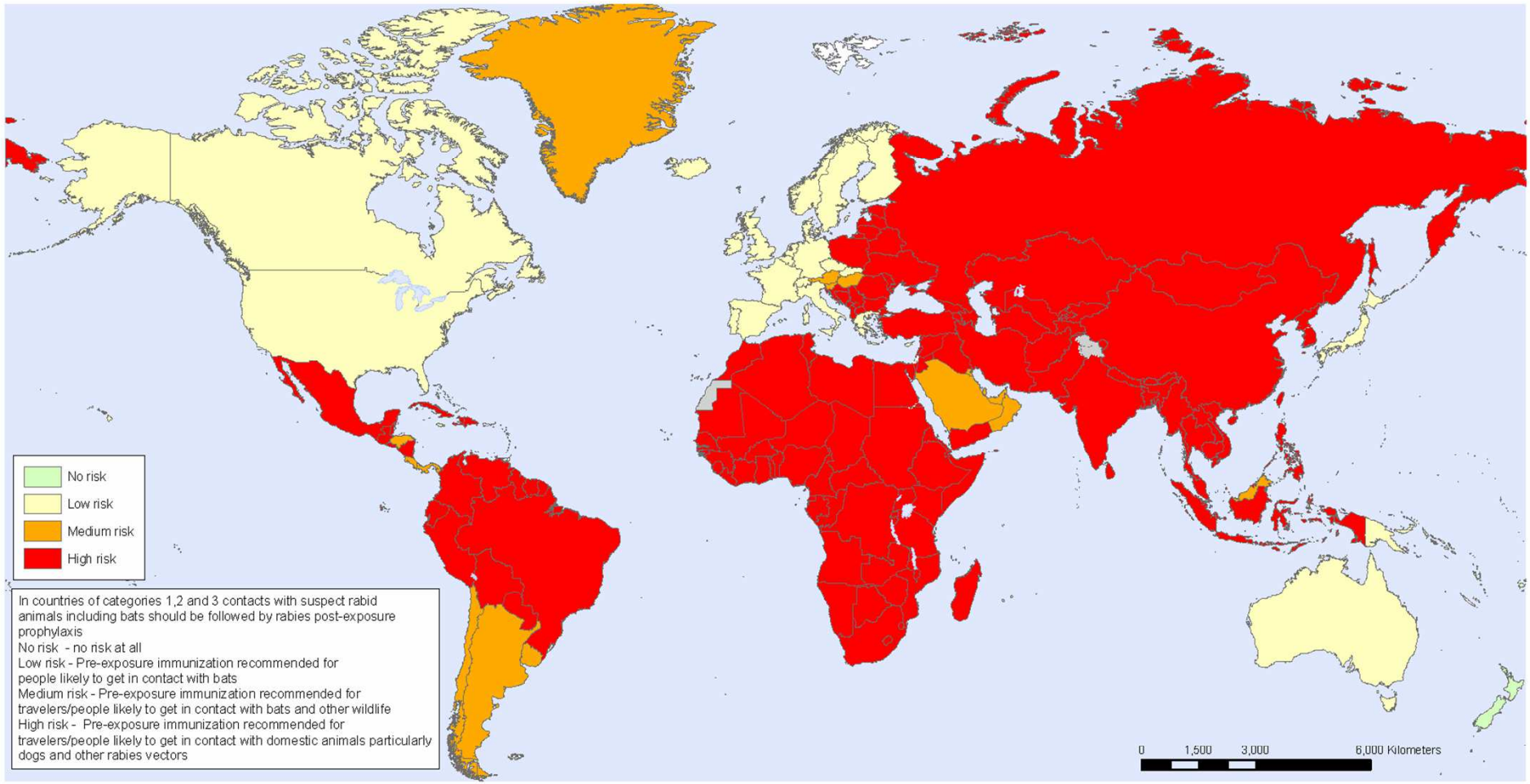
Subunità B ricombinante della tossina colerica

Table 1. Licensed Oral Cholera Vaccines

Variable	WC-rBS	WC-only	Modified WC-only	CVD 103-HgR
Trade name	Dukoral	ORC-Vax	Shanchol or mORC-Vax	Orochol or Mutacol
Live or killed	Killed	Killed	Killed	Live
Target	O1 classical and El Tor	O1 classical and El-Tor; possibly O139 (no clinical evaluation to date)	O1 classical and El-Tor; possibly O139 (no clinical evaluation to date)	O1 classical and El Tor
Regimen	2 doses given 7–42 days apart (3 doses for children 2–5 years of age)	2 doses given at least 14 days apart	2 doses given 14 days apart	1 dose
Duration of protection	2 years (6 months for children 2–5 years of age)	≥3 years	≥3 years	≥ 6 months (established only in North American volunteers)
Booster dose requirements	Every 2 years (every 6 months for children, 2–5 years of age)	Every 2 years	Every 3 years (may be longer after further evaluation of Kolkata trial)	Unknown
Age range for vaccination	>2 years	≥1 year	Shanchol: ≥1 year; mORC-Vax: ≥2 years	>2 years
Requirement for oral buffer	Yes	No	No	Yes
Storage temperature	2–8°C	2–8°C	2–8°C	2–8°C
Shelf life	3 years	2 years	2 years	2 years
International acceptance	WHO prequalified	Not prequalified by WHO	Pending WHO prequalification	Not prequalified by WHO
Price to the public sector per dose	~$5.25	$0.75	Shanchol: $1.85 or less depending on volume mORC-Vax: ~$0.75	Vaccine not currently available

NOTE. WC, whole cell. Adapted from [18]. WHO, World Health Organization.

Rabies, countries or areas at risk



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: WHO Rabnet/CDC
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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Table 1 Rabies vaccines which have met the WHO criteria for immunogenicity.

Vaccine	IM dose[a]	Trade name, manufacturer, country of origin
HDCV Human Diploid Cell Vaccine	1 ml	Imovax rabies, Sanofi Pasteur France
PCEC Purified Chick Embryo Cell vaccine	1 ml	Rabipur/RabAvert, Novartis/Germany Rabipur Chiron, India
PVRV Purified vero cell Rabies Vaccine	0.5 ml	Verorab Sanofi Pasteur, France
PDEV Purified Duck Embryo Vaccine	1 ml	Vaxirab Zydus Cadila, India[b]

[a] volume per ampoule.
[b] previously in Switzerland.

Table 4 Suggested pre-exposure rabies immunisation schedule for travellers.

Situation	Action
Unvaccinated people at risk	Primary 3 dose pre-exp course IM or ID days 0, 7, 28 (advance towards day 21 if no time)
If risk of exposure will continue	Booster dose after 1—2 years, IM or ID
Travellers with access to vaccine if exposed to rabies	No further boosters
Travellers to remote areas, uncertain access to vaccine	Serology test. No booster if >0.5 IU/ml neutralising antibody Otherwise: repeat booster dose before departure if last dose was >3—5 years previously
All vaccinees	Keep a record of treatment as it may affect management in the future. Ensure urgent booster injection(s) if exposed to rabies.

Table 2 Comparison of selected rabies vaccine regimens.

Vaccine Regimen & Route	Days of Injection Superscript: Number of sites injected						Visits to Clinic	Total Vaccine Used
Pre-exposure								
IM	0		7			28	3	3
ID 0.1 ml[a]	0		7			28	3	<1–3[b]
Post-exposure (+RIG day 0)								
IM 5 dose	0	3	7	14		28	5	5
IM 2-1-1	0^2		7		21		3	4
IM 4 dose (CDC)	0	3	7	14			4	4
2-site ID	0^2	3^2	7^2			28^2	4	<2–4[b]
4-site ID[c]	0^4		7^2			28	3	<2–3[b]
Post-exposure if previous vaccine course								
IM	0	3					2	2
ID[d]	0^4						1	1 (or <1)[d]

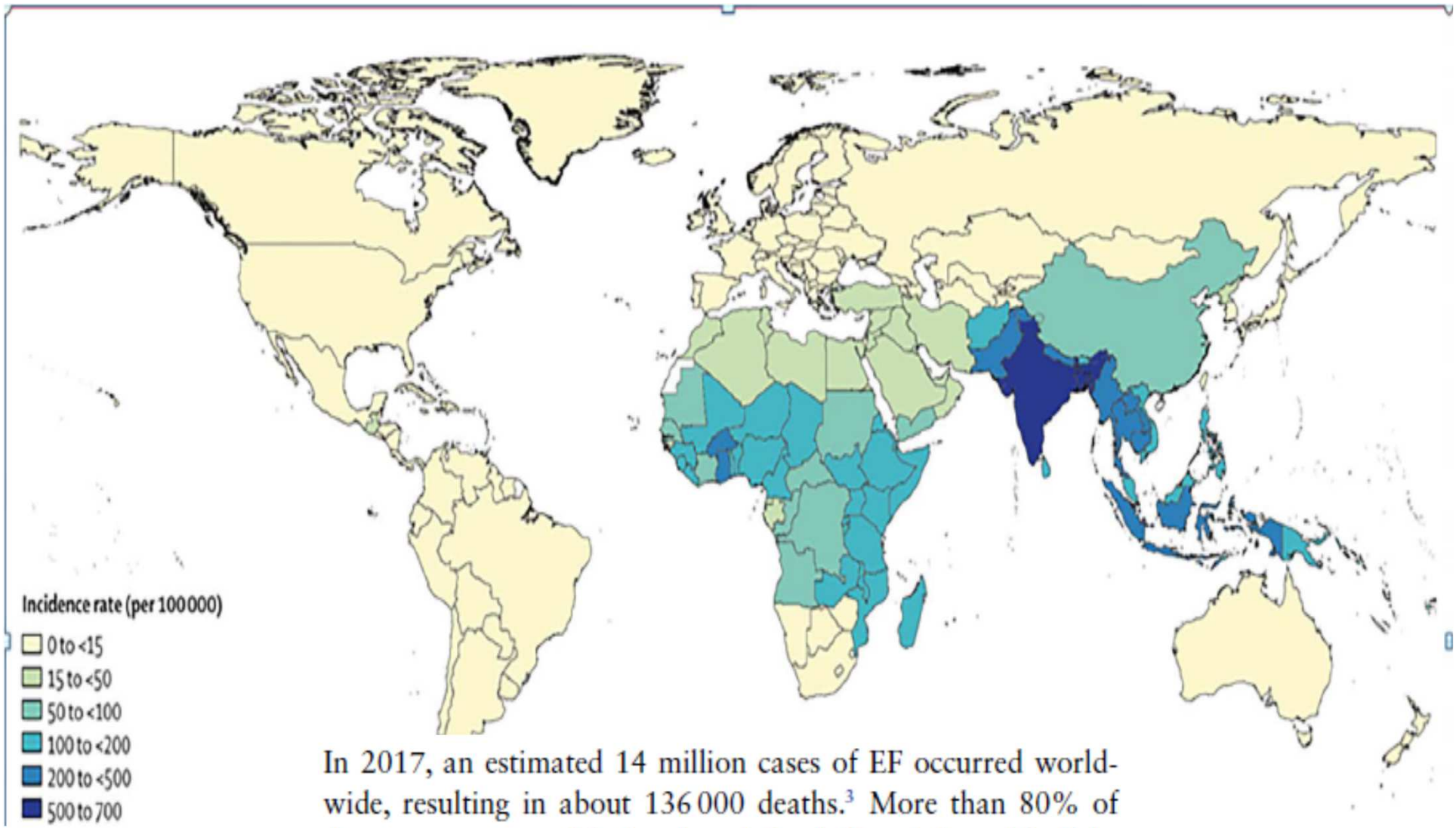
[a] ID doses are all 0.1 ml per site of injection.

[b] Maximum used if ampoules not shared.

[c] ID doses are 0.1 ml/site for PVRV vaccine (0.5 ml/ampoule) or the equivalent dose 0.2 ml/site for PCECV vaccine (1.0 ml/ampoule).

[d] 0.1 ml/site, whole ampoule used for 0.5 ml vaccines. 1 ml ampoules share between two, alternatively use whole dose to avoid wastage.

Typhoid fever



In 2017, an estimated 14 million cases of EF occurred worldwide, resulting in about 136 000 deaths.[3] More than 80% of these cases occurred in South and South East Asia and in Sub-Saharan Africa (Figure 1). Supplementary Table 1, available at

Table 1: Typhoid vaccines [74,75,77-103]

Brand and manufacturer	• Vivotif® Emergent BioSolutions	• TYPHIM Vi® Sanofi Pasteur
Formulation	• Enteric-coated capsules [74]	• Liquid [75]
Type	• Live attenuated Ty21a strain of *S.* Typhi [74]	• Purified Vi capsular polysaccharide from the Ty2 *S.* Typhi strain [75]
Route of administration	• Oral [74]	• Injectable • Intramuscular [75]
Recommended dose / regimen	• Three dose regimen, taken on alternate days [74] • Four dose regimen in USA and Canada [79]* • Entire vaccination schedule to be completed at least one week prior to travel to endemic area [74]	• One dose [75] • Optimum antibody protection may be reached 2 weeks after administration [75]

Journal Pre-proof

COVID-19 vaccination in athletes: ready, set, go...

A logical concern in the context of COVID-19 vaccination relates to the impact of vaccine-related side effects. Detail on COVID-19 vaccination tolerability in the general population is still emerging (ie, the post-licensing data is still awaited) and will likely differ based on type and formulation of vaccine. In the meantime, preliminary trial data provides reassurance regarding an overall low serious adverse event rate, and that severe systemic effects were reported in only

A broad range

efficacy. While the susceptibility of elite athletes to upper respiratory infection has been long recognised, the uptake of vaccination historically has often been suboptimal, given concerns over side effects, timing to competition, and efficacy. It will therefore be important for clinicians to discuss these issues and to plan to carefully monitor symptoms post vaccination. It might also be appropriate to consider a temporary reduction in training load in the first 48–72 h post vaccine injection, particularly after the second dose. Other general considerations are likely to be

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