Acute unspecified fever in returning travellers

Jose Muñoz
Hospital Clinic Barcelona

Martes, 13 de junio
Aticco Bogatell, Barcelona

- 36 year-old man

- AUFI
- Neurological impairment, hypotension
- CRP x20, AKI
- Thrombocytopenia, hemoconcentration

- Negative malaria test
- Blood cultures

- Ceftriaxone

What are the most likely diagnoses?

What diagnostic tests should we perform?

Should we have prescribed different empirical antibiotics?

Should we consider any public health related issue?

Imported Febrile illnesses

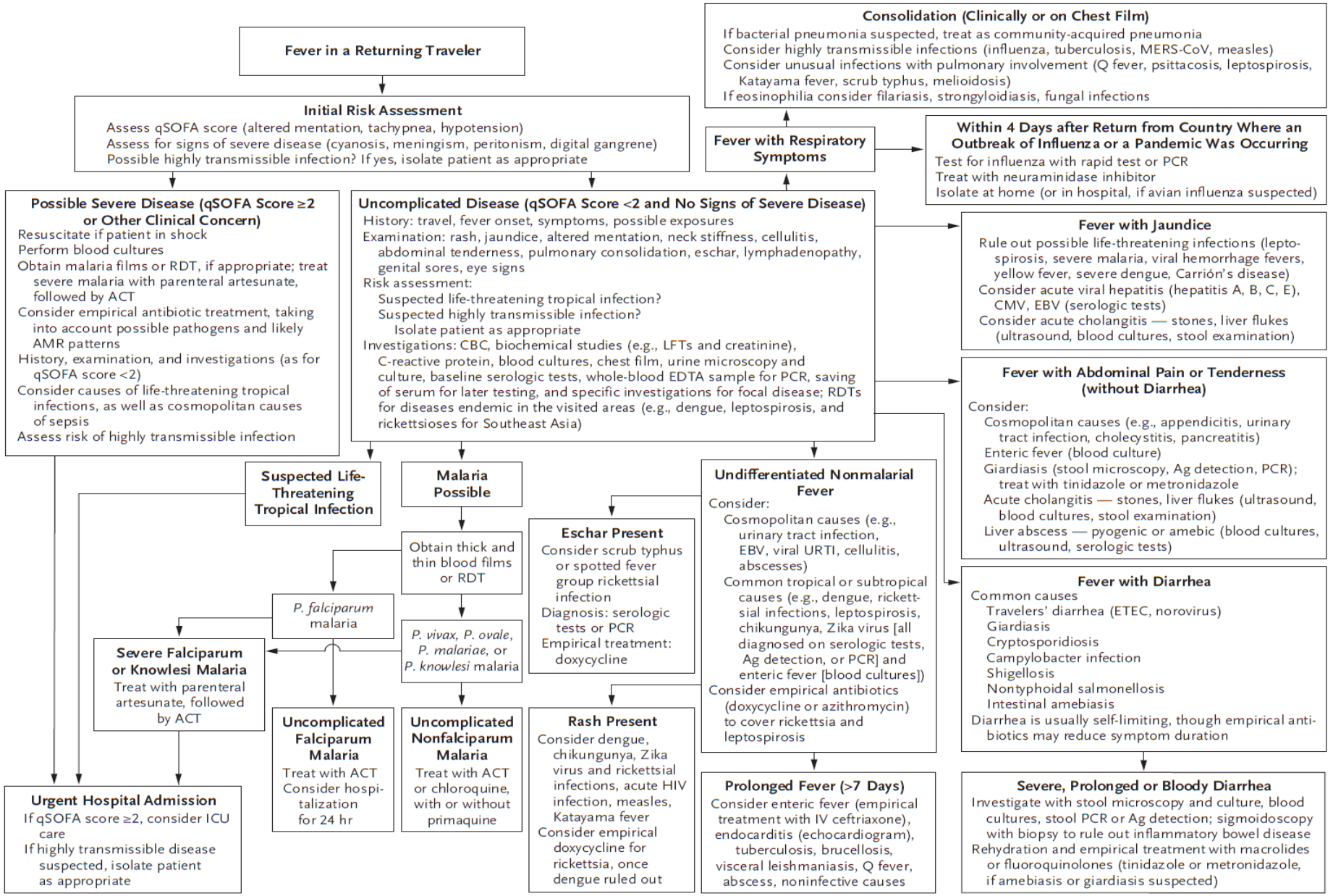
- Main cause of hospitalization in returned travelers

- There is a myriad of causes. Challenging etiological diagnosis.

- Lack of sensitive and specific diagnostic tests (for some microorganisms).

- Need for empirical antibiotics.

- An important proportion of cases remain undiagnosed.



Thwaites, et al. *N Engl J Med* 2017; 376:548-560

JTM Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Journal of Travel Medicine, 2020, 1–12
doi: 10.1093/jtm/taaa207
Advance Access Publication Date: 4 November 2020
Original Article

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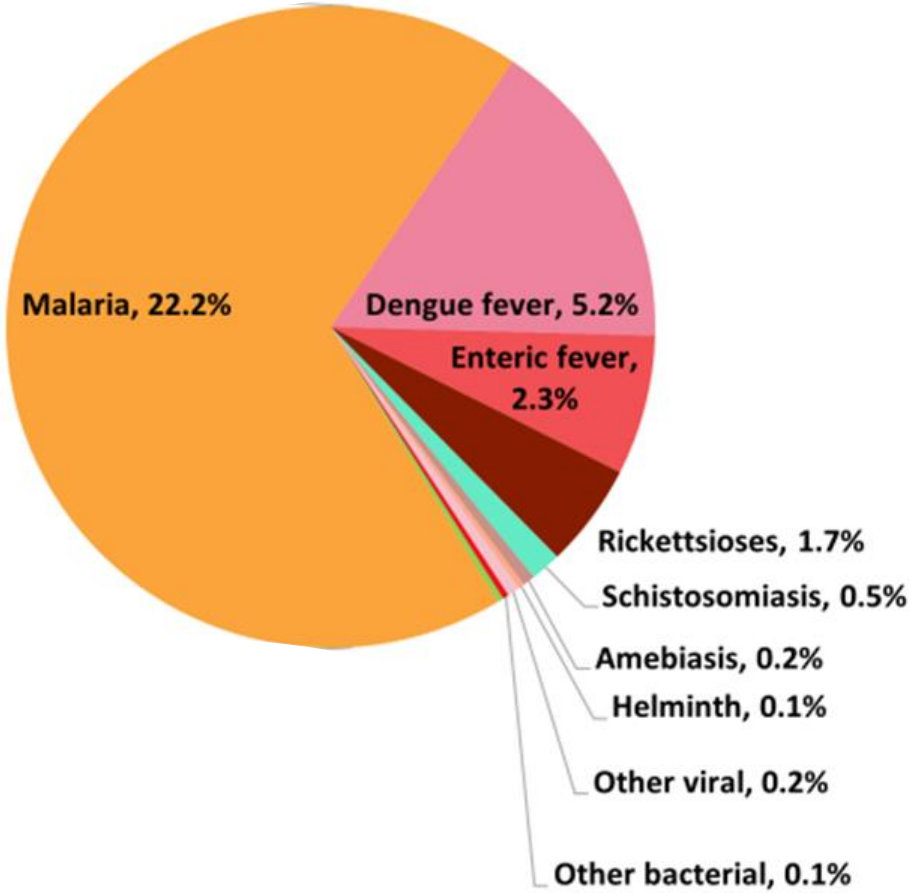

14,047 reports identified (2000-2020)

30 studies included:

- 26 case-series (>100 cases)
- 4 case-control studies (predictors)

18,755 febrile travelers

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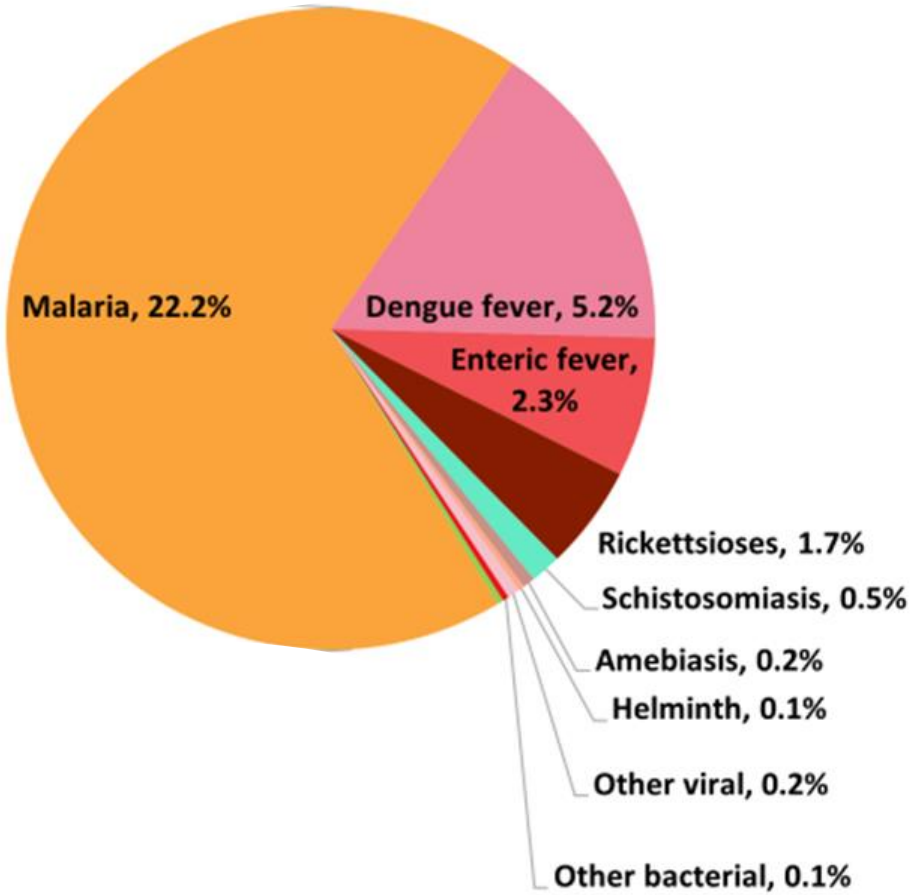
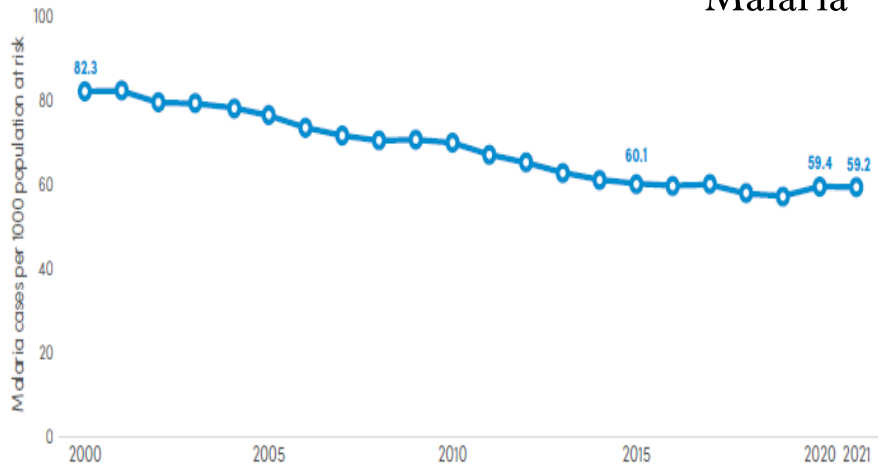
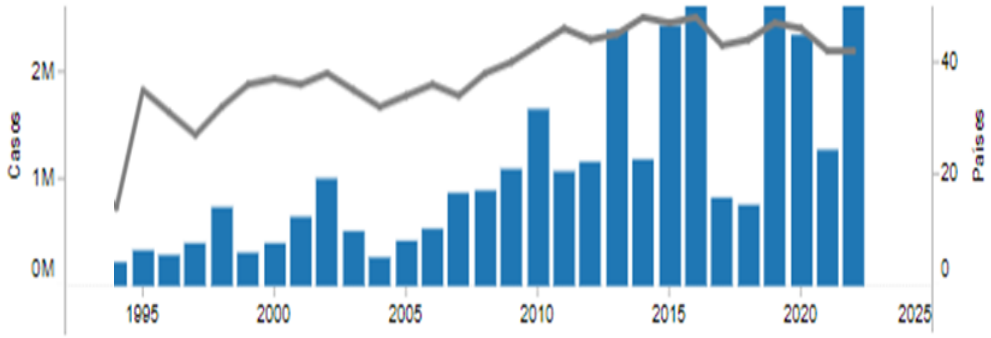


Buss i, et al. *J Travel Med*. 2020 Dec 23;27(8):taaa207

Malaria



Dengue



World malaria report 2022. Geneva: World Health Organization; 2021

https://www3.paho.org/data/index.php/es/temas/indicadores-dengue.html

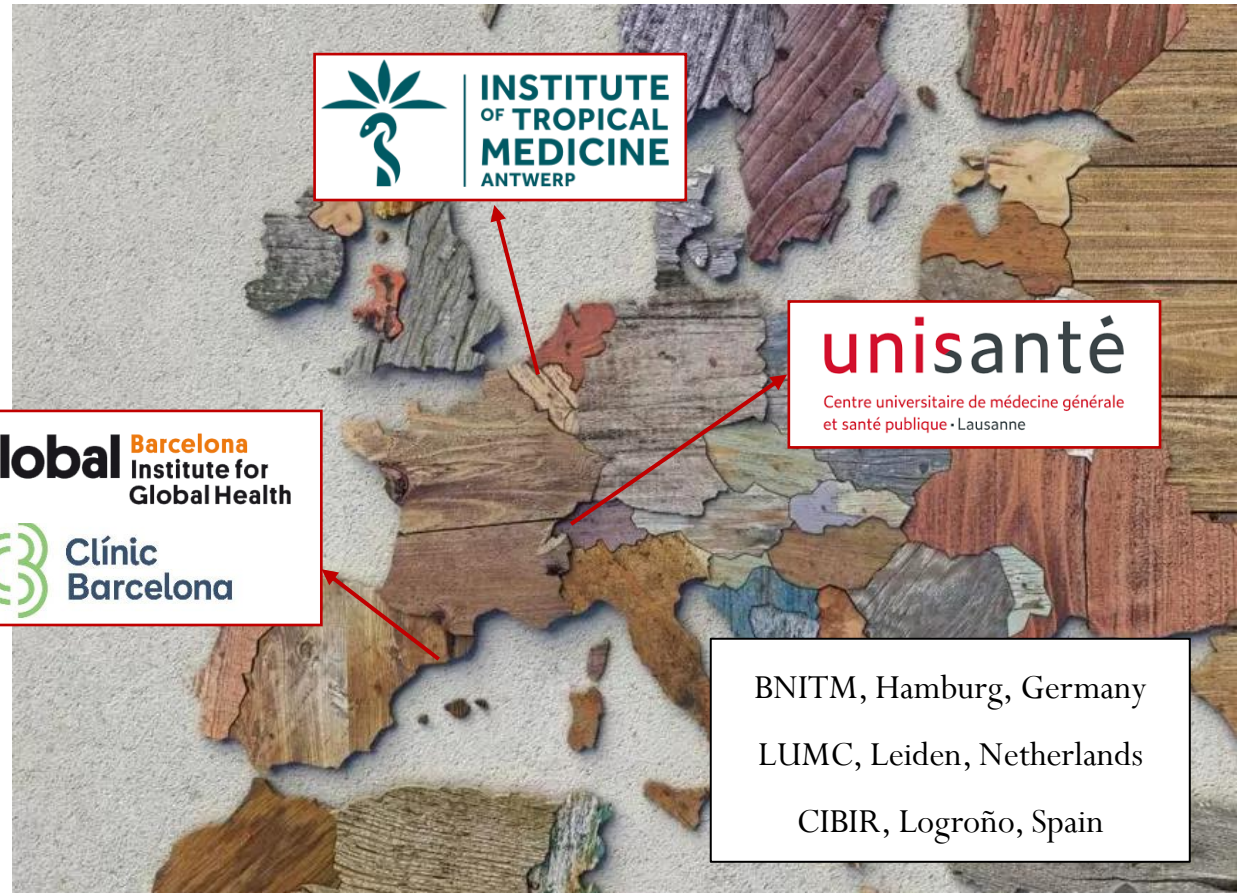
Evaluating **F**easible tools for etiological diagnosis of **F**ever to **O**rientate management in the **R**eturning **T**raveller (EFFORT)

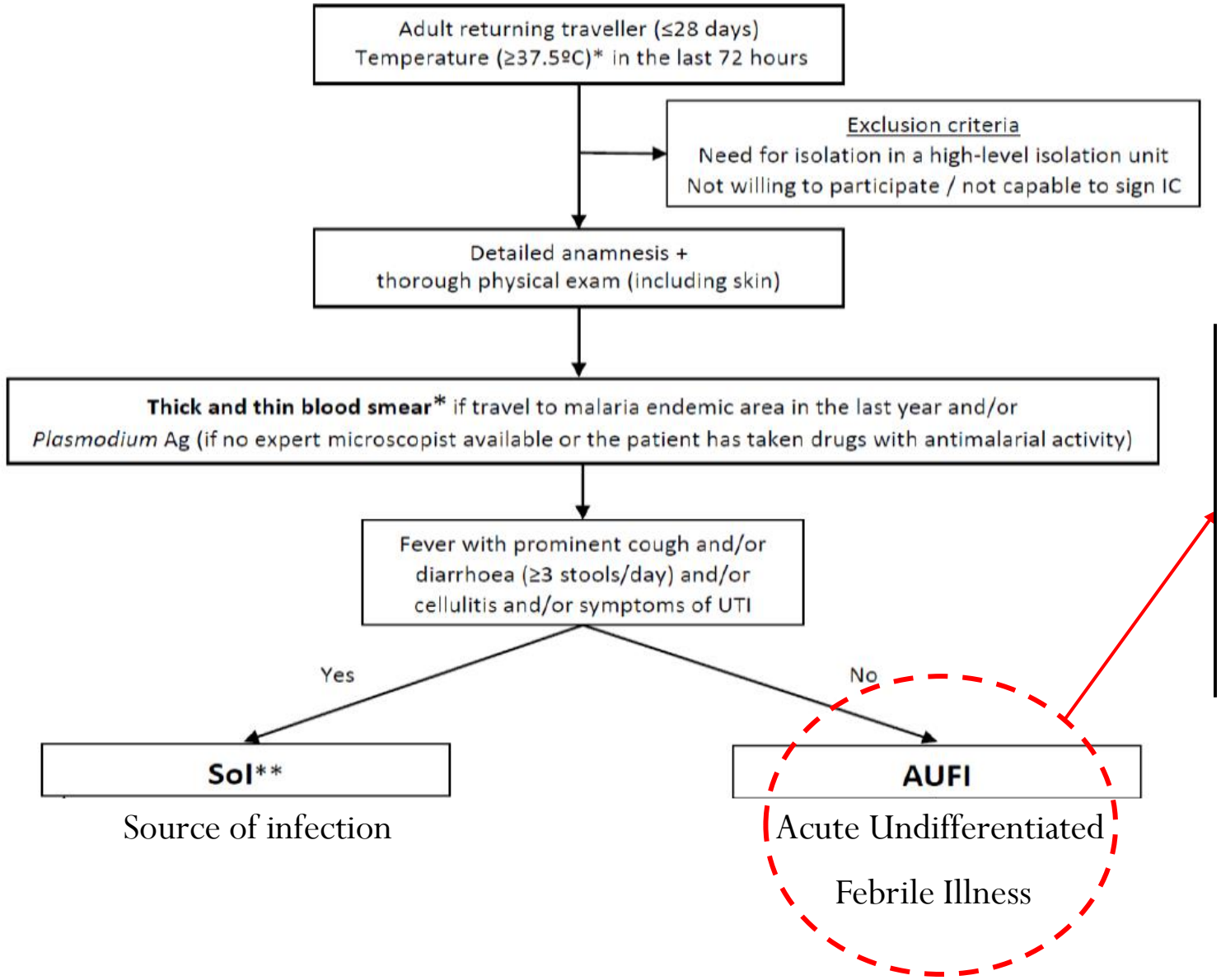
EFFOR

Prospective multi-center cohort study

500 undifferentiated fevers

Nov 2017 – Nov 2019





1- Blood smear / malaria RDT

2- PCR / serology DENV, CHIKV, ZIKV (<14d)

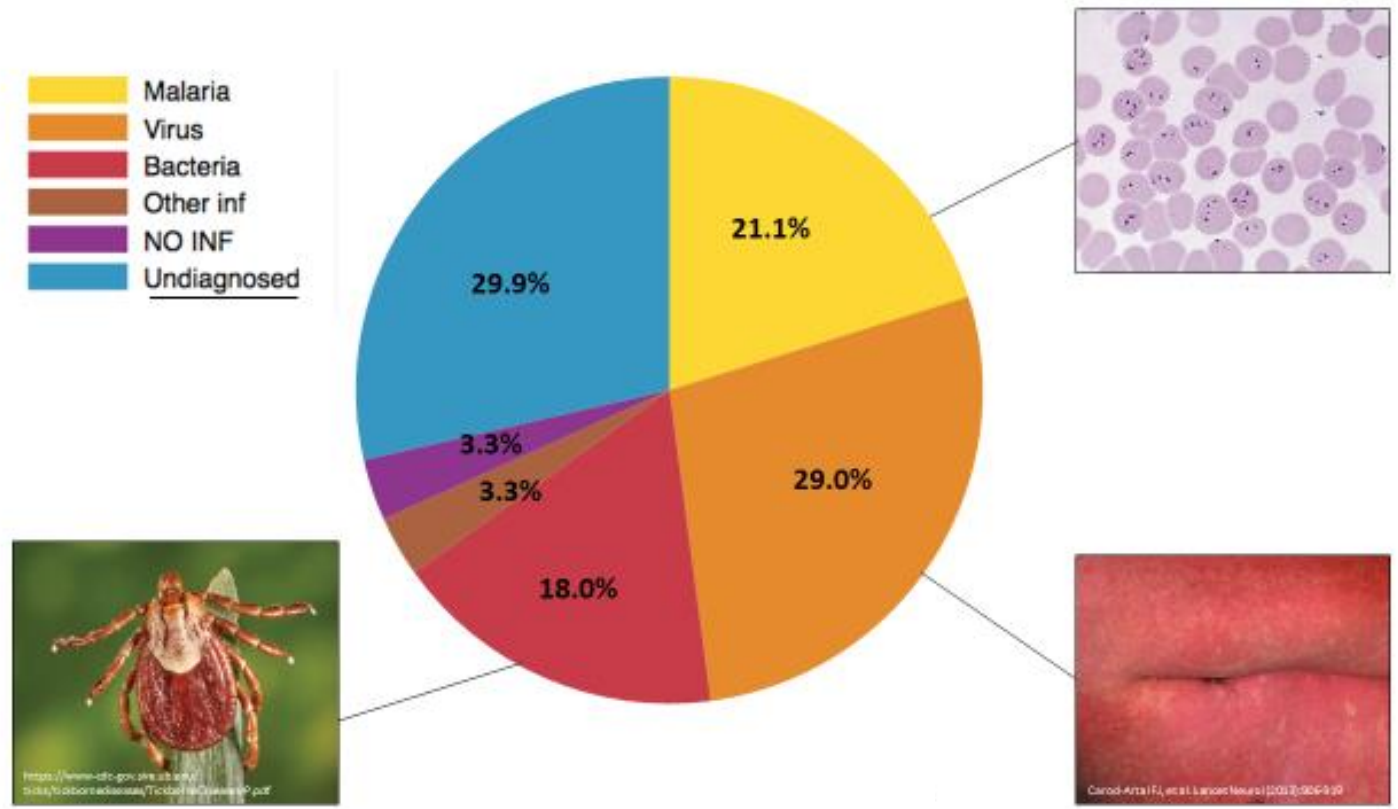
3- PCR /serology *Leptospira* spp. (water exposure)

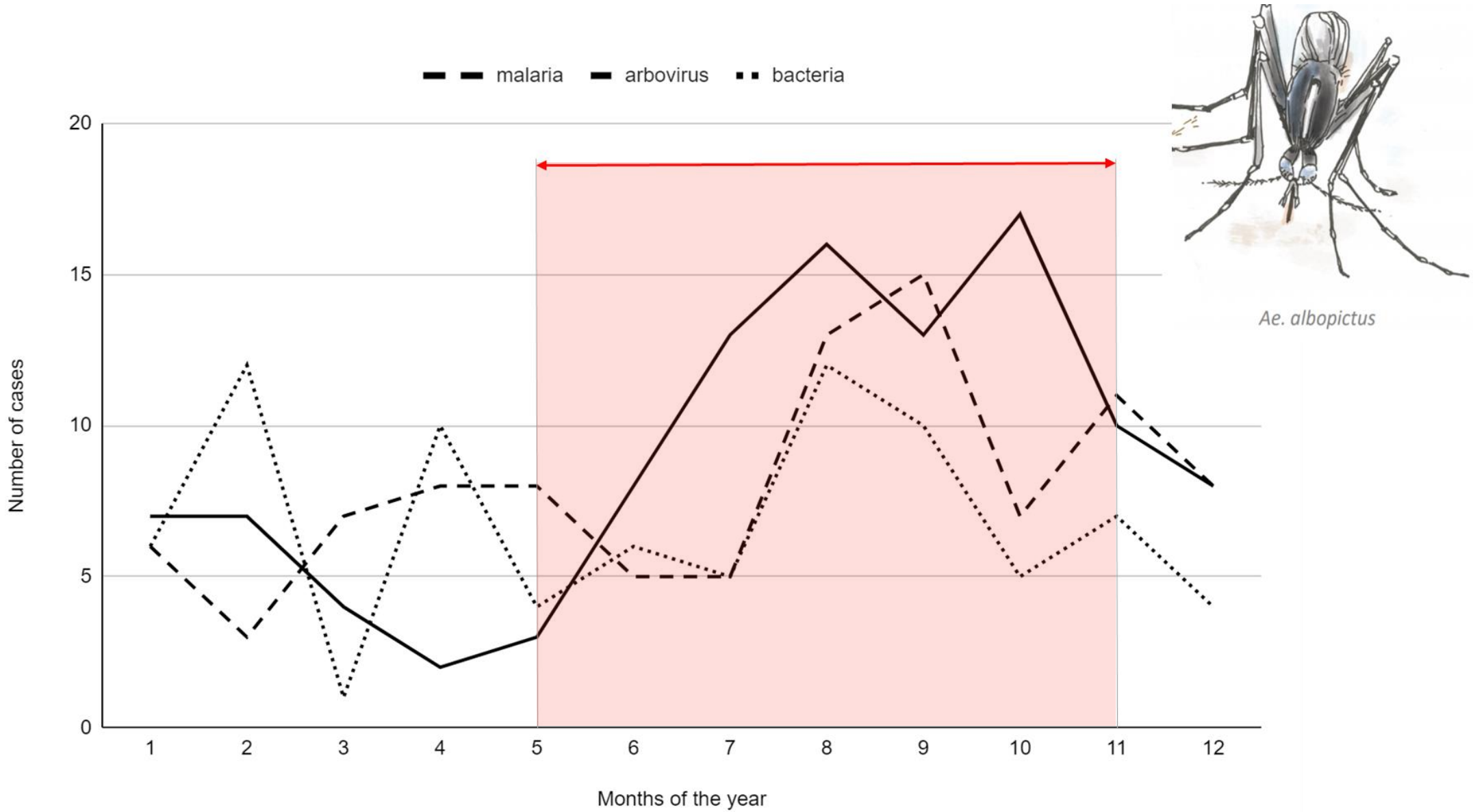
4- Blood cultures

5- HIV (p24 Ag + anti-HIV) (exposure)

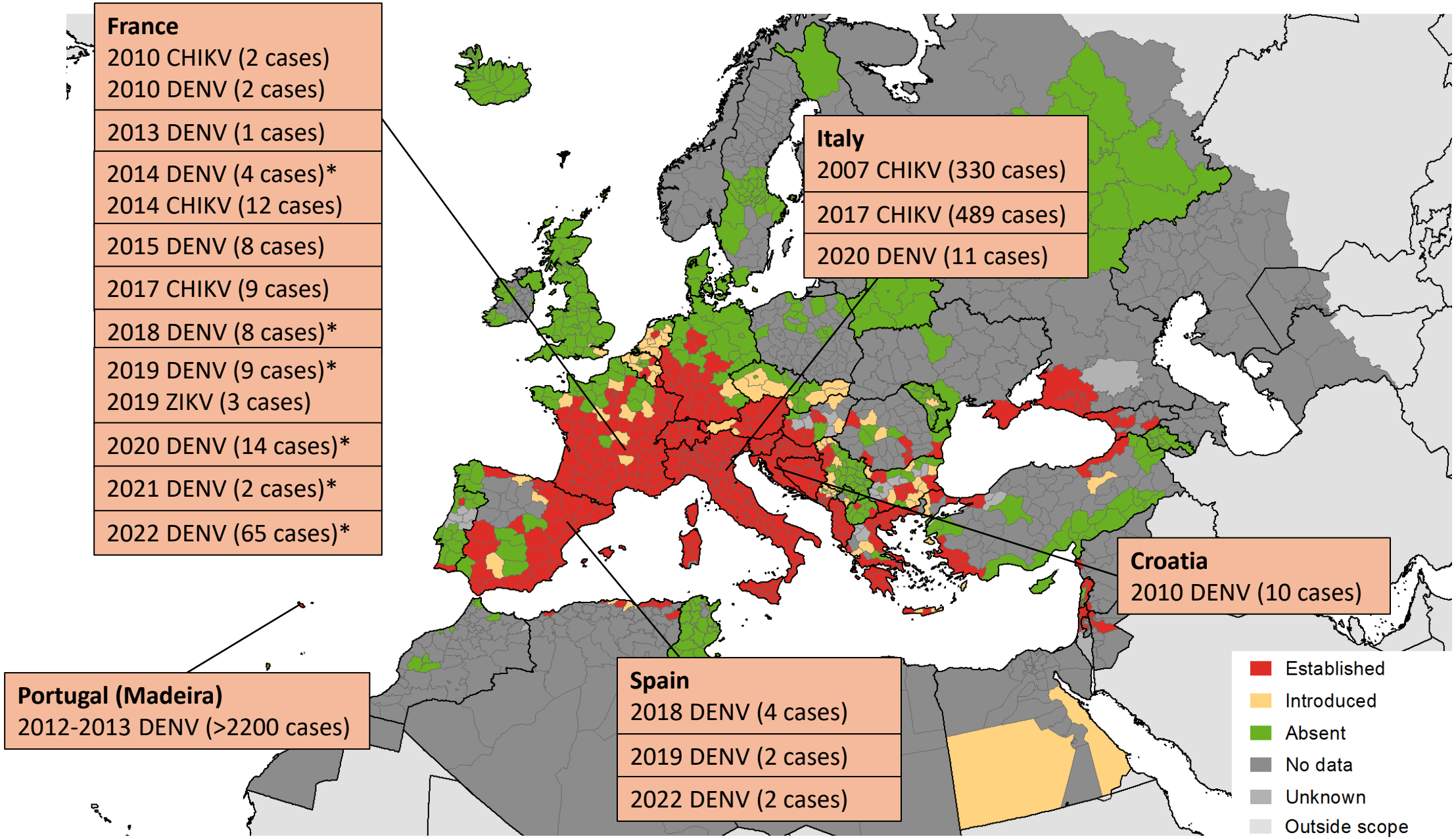
6- *Rickettsia* spp. serology (exposure)

Acute undifferentiated febrile illness (AUFI)	$N = 455$
• Malaria	96 (21.1)
• Viral infections	132 (29.0)
Arbovirus	108 (23.7)
Dengue virus	92 (20.2)
Chikungunya	9 (2.0)
Zika virus	6 (1.3)
West-Nile virus	1 (0.2)
Tick-borne encephalitis	1 (0.2)
Other viral infections	24 (5.3)
HIV	5 (1.1)
CMV	7 (1.5)
EBV	2 (0.4)
HAV	2 (0.4)
Hantavirus	1 (0.2)
Other viruses*	7 (1.5)
• Bacterial infections	82 (18.0)
Rickettsia	46 (10.1)
Leptospira	21 (4.6)
Enteric fever	6 (1.3)
Q fever	6 (1.3)
Syphilis	5 (1.1)
Other bacteria*2	7 (1.5)
• Other infections	15 (3.3)
Mycobacteria	3 (0.7)
Helminths	9 (2.0)
Acute schistosomiasis	7 (1.5)
Other helminths*3	2 (0.4)
Histoplasmosis	3 (0.7)
• Undiagnosed AUFI	136 (29.9)
• Non-infectious diseases*4	15 (3.3)





Ae. albopictus



* >1 outbreak

Barzon L. *J Clin Virol 2018;*107:38-47

https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea

https://www.ecdc.europa.eu/en/publications-data/aedes-invasive-mosquitoes-current-known-distribution-march-2022

The use of dengue RDT

Table 1
Probabilistic cost analysis of dengue rapid-diagnostic tests (RDT) in travelers with undifferentiated non-malarial fevers (UNMF).

Test	RDT targets	RDT sensitivity (%) (95% CI)	RDT specificity (%) (95% CI)	RDT price (€)	Savings per patient[a] (€) (95% CI)	Reference
A	NS1	82.7 (74.4–93.0)	99.6 (98.8–100)	3.77	342.63 (334.64–350.61)	[6]
B	NS1	95.8 (78.9–99.9)	97.9 (94.6–99.4)	7.60	389.31 (381.25–397.38)	[7]
C	NS1, IgM, IgG	68.1 (55.7–78.5)	100 (90.6–100)	10.00	289.08 (281.23–296.93)	[8]

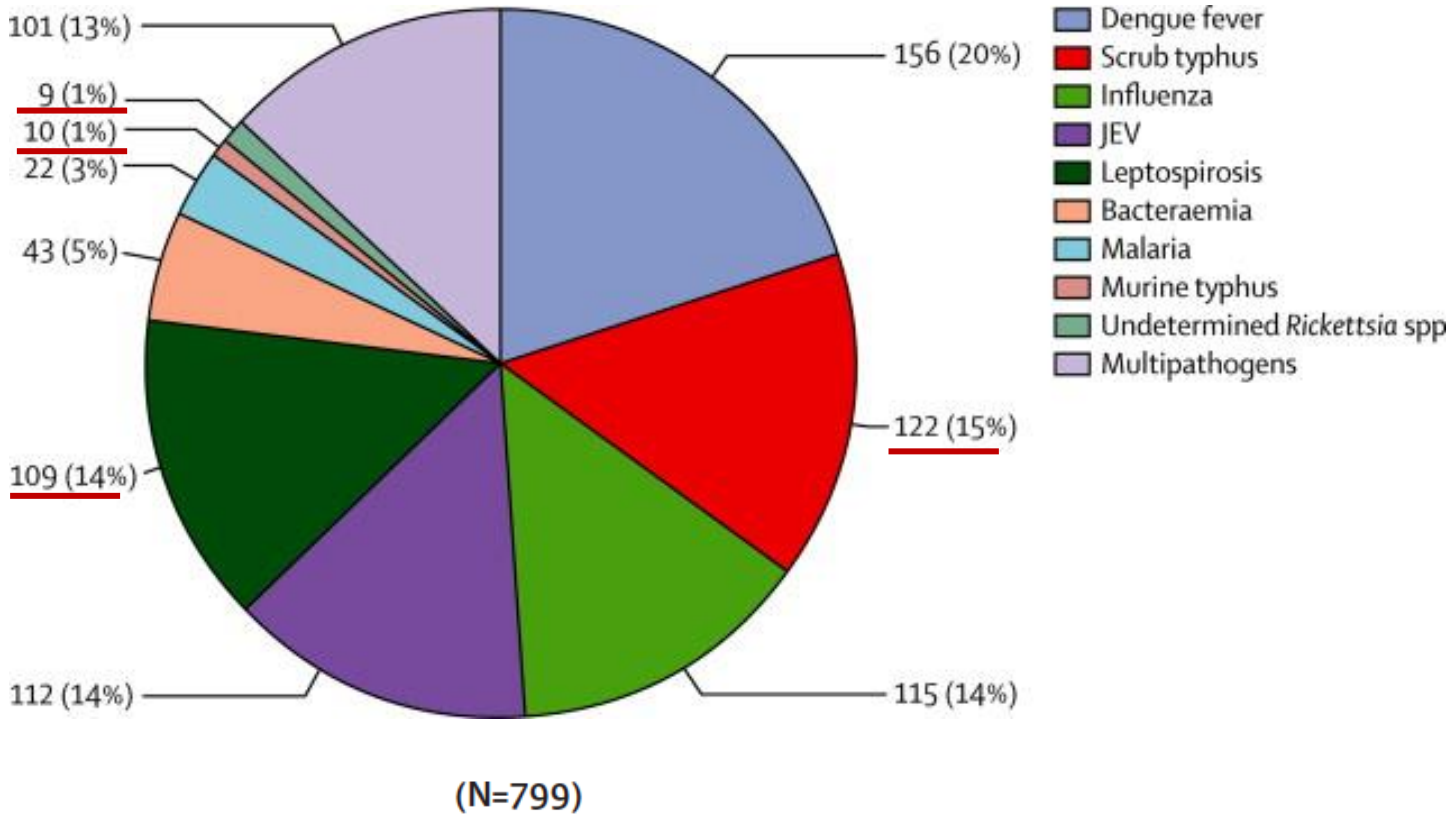
[a] Estimated savings per patient with UNMF tested.

Hospitalizations: ↓ 53.6% (95%CI: 33.9 – 72.5)
Savings 289.08–389.31 USD
Empirical antibiotic: ↓ 46.4% (95%CI: 27.5 – 66.1)
Increase Case Detection Rate

D. Camprubí-Ferrer, F. Ramponi, L. Balerdi-Sarasola et al., Rapid diagnostic tests for dengue would reduce hospitalizations, healthcare costs and antibiotic prescriptions in Spain: A cost-effectiveness analysis, Enferm Infecc Microbiol Clin., https://doi.org/10.1016/j.eimc.2022.12.009

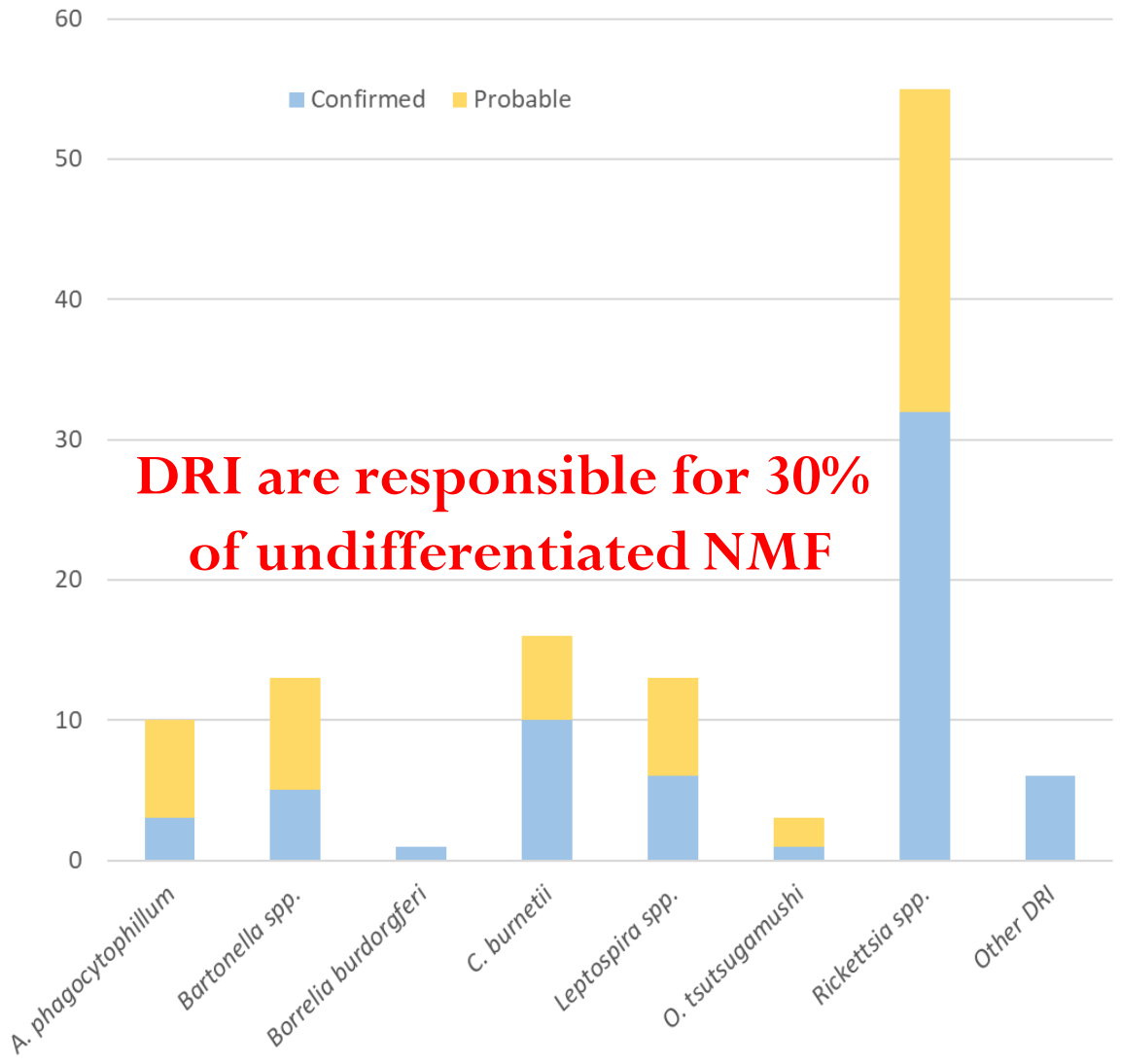
Causes of non-malarial fever in Laos: a prospective study

31% DRI
Doxycycline Responding Illness



Mayxay M. *Lancet Glob Health* 2013;*1*:e46-54

	Total DRI ($n = 106$)
Rickettsia spp.	55 (51·9)
• SFG *Rickettsia*	39 (36·8)
• TG *Rickettsia*	3 (2·8)
• *Rickettsia* (unspecified)	13 (12·3)
Coxiella burnetii	16 (15·1)
Bartonella spp.	15 (14·2)
• *Bartonella henselae*	6 (5·7)
• *Bartonella quintana*	1 (0·9)
• *Bartonella* (unspecified)	8 (7·5)
Leptospira spp.	13 (12·3)
Anaplasma phagocytophilum	10 (9·5)
Treponema pallidum	5 (4·7)
Orientia tsutsugamushi	3 (2·8)
Borrelia burgdorferi	1 (0·9)
Chlamydia trachomatis	1 (0·9)



Camprubí-Ferrer D, Oteo JA, Bottieau E, Genton B, Balerdi-Sarasola L, Portillo A, Cobuccio L, Van Den Broucke S, Santibáñez S, Cadar D, Rodriguez-Valero N, Almuedo-Riera A, Subirà C, d'Acremont V, Martinez MJ, Roldán M, Navero-Castillejos J, Van Esbroeck M, Muñoz J. Doxycycline responding illnesses in returning travellers with undifferentiated non-malaria fever: a European multicentre prospective cohort study. J Travel Med. 2023 Feb 18;30(1):taac094.

	Doxycycline	Azithromycin	Ceftriaxone	Penicillin	Quinolones
Anaplasmosis (*A. phagocytophillum*)	Appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
Bartonellosis (*B. henselae, B. quintana*)	Appropriate	Appropriate	Not appropriate	Not appropriate	Appropriate
Tick-borne relapsing fever and **Lyme borreliosis** (*B. recurrentis, B. miyamotoi, B. burdorgferi*)	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Melioidosis *(Burkholderia pseudomallei)*	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
Infection by ***Chlamydia*** spp.	Appropriate	Appropriate	Not appropriate	Not appropriate	Appropriate
Enteric fever (*Salmonella typhi and paratyphi*)	Not appropriate	Appropriate	Appropriate $^{\alpha}$	Not appropriate	Not appropriate$^{\beta}$
Q fever (*Coxiella burnetii*)	Appropriate	Not appropriate	Not appropriate	Not appropriate	Appropriate
Leptospirosis	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Scrub typhus (*Orientia tsutsugamushi*)	Appropriate	Appropriate $^{\alpha}$	Not appropriate	Not appropriate	Not appropriate$^{\beta}$
Spotted fever group rickettsiosis	Appropriate	Appropriate $^{\alpha}$	Not appropriate	Not appropriate	Not appropriate$^{\beta}$
Typhus group rickettsiosis	Appropriate	Appropriate $^{\alpha}$	Not appropriate	Not appropriate	Not appropriate$^{\beta}$

*Appropriateness (based on the available literature and expert opinion of the authors) used for the rough estimation of the therapeutic appropriateness of the most common antibiotics.
$^{\alpha}$ Although considered appropriate for the study, resistant strains have been reported.
$^{\beta}$ Empirical treatment with quinolones not appropriate due to the increasing report of resistances.

Combinations of antibiotics

	Treated inappropriately
Doxy + Ceftri	4 (3%)
Ceftri + Azithro	23 (18%)

p<0·001

	Duration of fever*
Undiagnosed*[2] appropriately treated	0.5 (0-2) days
Undiagnosed not appropriately treated	3 (1-6) days

*After ATB initiation
*[2] By routine diagnostic methods

P=0·003

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TAKE HOME MESSAGES

- Travelers with AUFI more severe disease than those with focal signs / symptoms.
- >40% of cases were diagnosed with malaria and dengue, which can be diagnosed by RDT.
- Arbovirus most common and 75% diagnosed during *Aedes* spp. highest activity months.
- Around 30% of AUFI patients undiagnosed.
- DRI are responsible for 30% of undifferentiated NMF but are seldom recognized.
- Empirical treatment with doxycycline should be considered in any returning traveler with acute undifferentiated fever and a negative test for malaria and dengue, particularly when presenting severe illness.