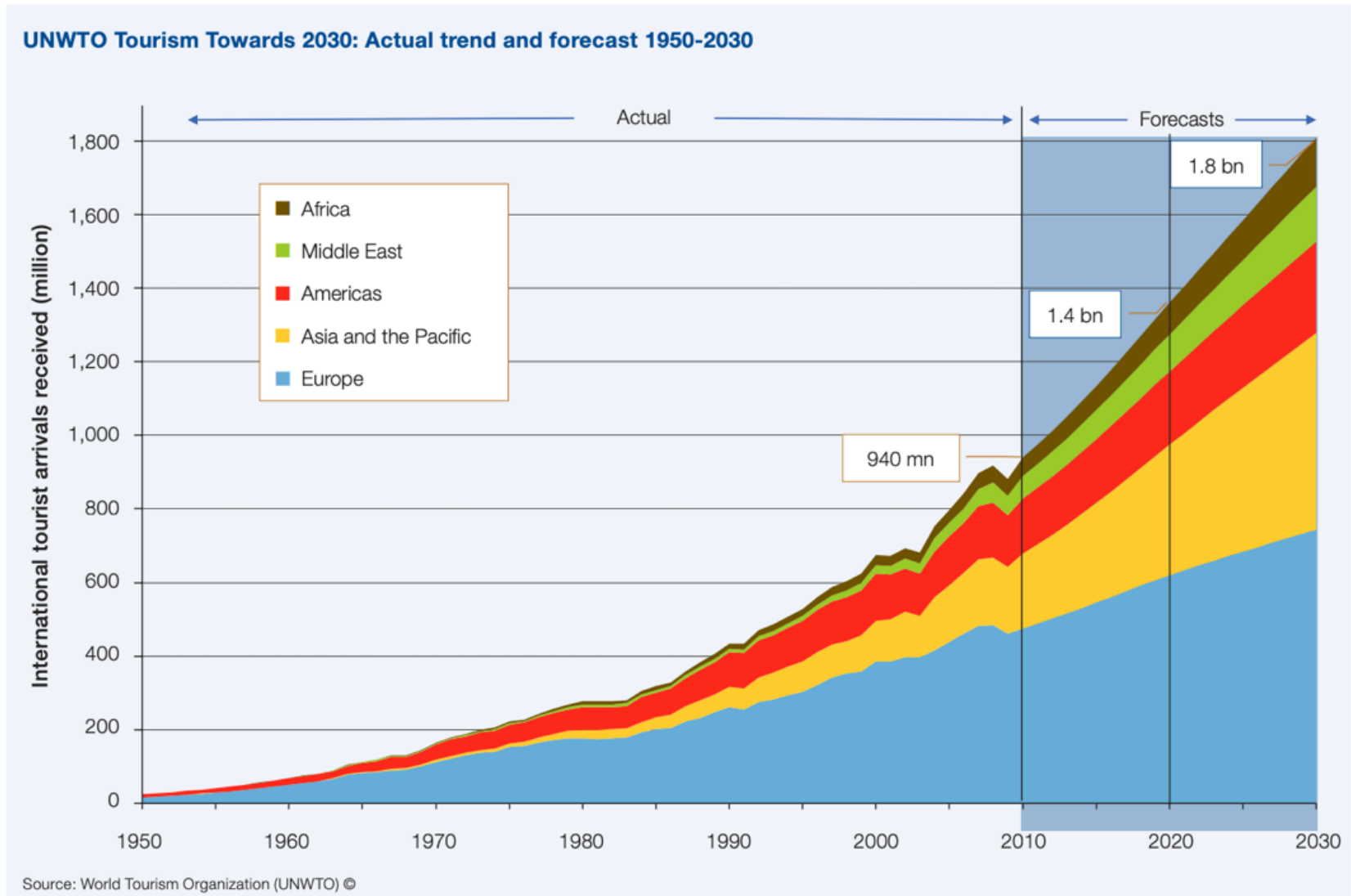


APPROACH TO FEVER IN THE RETURNING TRAVELER

Emily Vandamme – ASO Urgentiegeneeskunde - UZ Gent

- **Approach to Fever in the Returning Traveler.** Thwaites GE, Day NP. N Engl J Med 2017;376:548-560.
- **Fever in the returning traveller.** Fink Doug, Wani Robert Serafino. *BMJ* 2018;360 :j5773

Scope of the problem



Scope of the problem

Where have you been? The potential to overlook imported disease in the acute setting

Simon M. Smith *European Journal of Emergency Medicine* 2005, 12:230–233

A travel history was recorded in only 2% of all patients attending the accident and emergency department (5.3% of those with a potential of having imported disease).

Between 15-70% of travelers to tropical settings experience ill health

HOW COMMON IS FEVER IN THE RETURNING TRAVELER?

ORIGINAL RESEARCH

Annals of Internal Medicine

GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011

Karin Leder, MBBS, MPH, PhD; Joseph Torresi, MBBS, PhD; Michael D. Libman, MD; Jakob P. Cramer, MD, MSc;

23,3%

Table 1. Characteristics of Ill Returned Travelers

Variable	Total	Gastrointestinal Diagnoses	Febrile Illness	Dermatologic Diagnoses	Respiratory or Pharyngeal Diagnoses	Neurologic Diagnoses	GU, STI, and Gynecologic Diagnoses
Travelers, n (%)	42 173	14 346 (34.0)	9817 (23.3)	8227 (19.5)	4613 (10.9)	724 (1.7)	1209 (2.9)
Diagnoses, n*	49 379	14 837	10 092	9669	4851	738	1260
Men, %†	49.9	44.5	58.9	47.8	51.7	50.6	37.2
Median age (range), y‡	34 (0–95)	32 (0–92)	35 (0–91)	35 (0–95)	36 (0–93)	38 (0–88)	37 (0–88)
Travel reason, %§							
Tourism	55.7	59.3	45.1	68.2	53.6	55.4	51.9
Business	13.6	14.2	14.2	9.5	17.0	12.8	13.9
Visiting friends/relatives	15.5	8.8	28.1	10.2	16.5	13.5	18.5
Missionary	11.6	13.9	8.7	8.4	9.2	13.5	13.1
Student	2.6	3.4	2.0	2.5	2.9	4.0	1.9
Region, % 							
Australia and New Zealand	0.5	0.2	0.2	0.7	1.8	0.7	0.6
Southeast Asia	16.3	13.8	18.1	22.0	17.4	10.1	17.3
South-Central Asia	13.6	19.1	13.2	9.1	10.6	7.6	11.1
Northeast Asia	2.7	2.2	1.2	2.9	5.8	3.2	2.4
Europe	4.7	3.5	2.1	4.7	10.1	9.3	7.4
Latin America and Caribbean	19.2	20.4	14.3	27.3	14.2	23.6	15.6
Middle East and North Africa	6.1	8.7	2.5	5.6	5.2	6.5	6.1
North America	1.5	0.5	0.4	1.6	5.3	2.9	2.1
Oceania	0.8	0.7	1.0	1.2	0.9	1.4	0.5
Sub-Saharan Africa	26.7	22.5	42.6	19.5	20.6	22.3	26.9

GU = genitourinary; STI = sexually transmitted infection.

* Some travelers had >1 diagnosis. Other diagnoses (adverse events to medication or vaccine, injury or musculoskeletal problems, ophthalmologic or oral conditions, and psychological problems) are not shown (7932 diagnoses).

† Data were missing in 36 cases (0.09%).

‡ Data were missing in 143 cases (0.3%).

§ Data were missing in 22 cases (0.05%), and alternate reason (military or medical tourism) accounted for 1%.

|| Region of illness acquisition not ascertainable in 3299 cases (7.8%).

APPROACH?

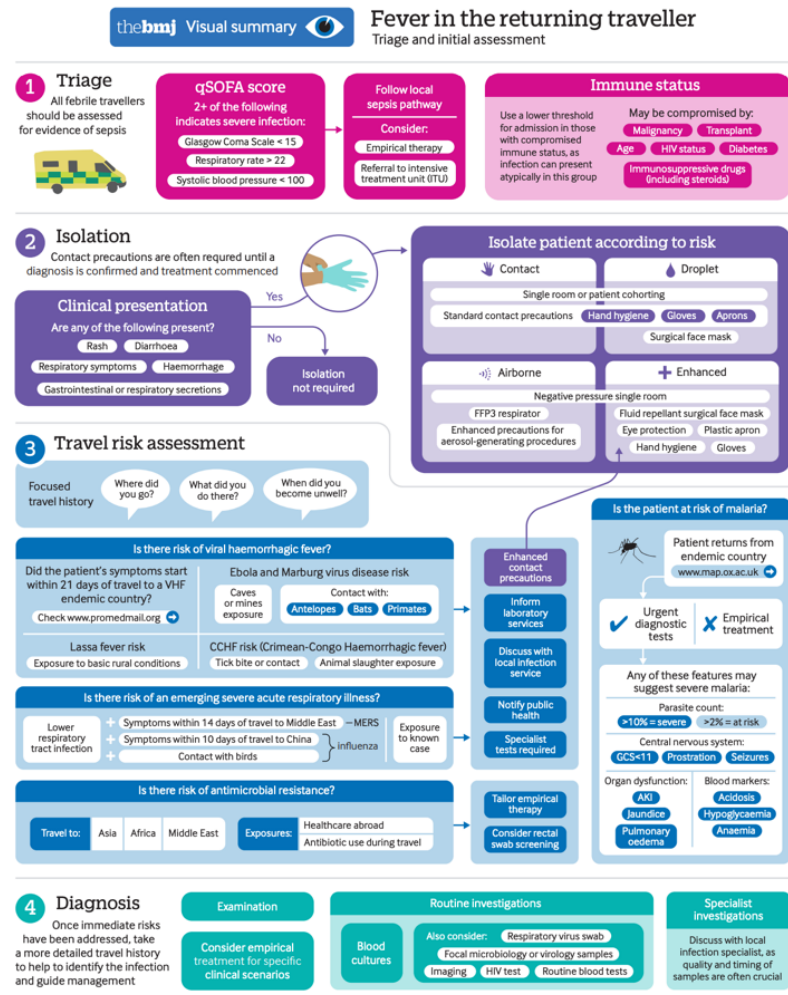
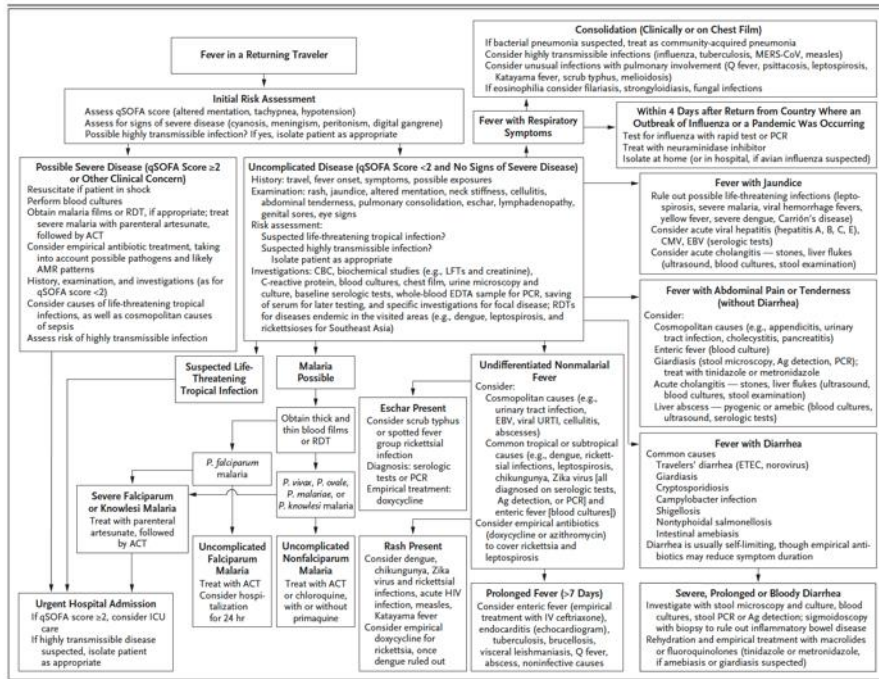


STEPWISE RISK BASED APPROACH

CLINICAL APPROACH: RISK BASED APPROACH

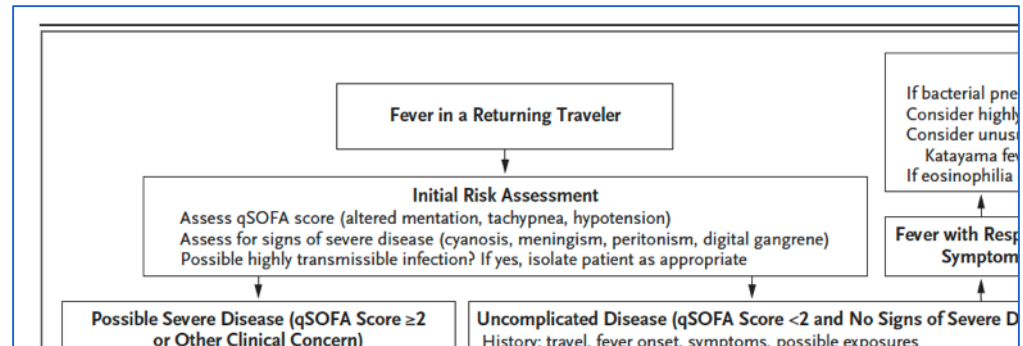
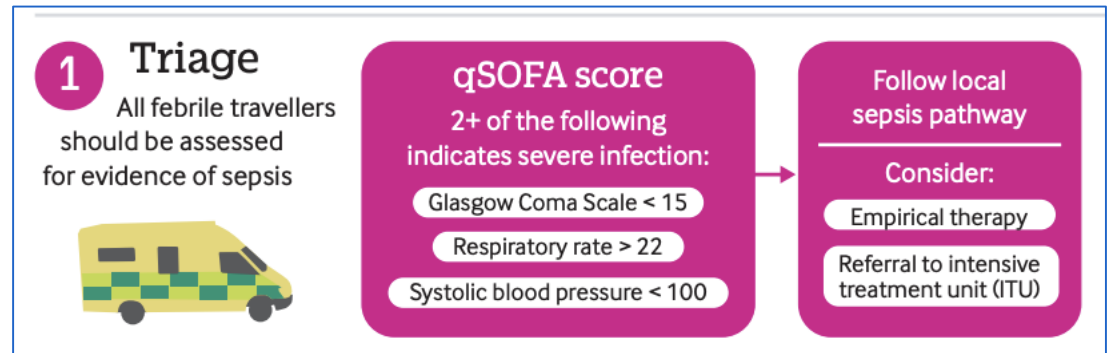
NEJM

BJM



STEP 1: TRIAGE – INITIAL RISK ASSESSMENT

- ABCDE
- Sepsis?



STEP 2: RECOGNIZE HIGHLY TRANSMISSIBLE CAUSES OF FEVER - ASSESS NEED FOR ISOLATION

2 Isolation

Contact precautions are often required until a diagnosis is confirmed and treatment commenced



Clinical presentation

Are any of the following present?

Rash

Diarrhoea

Respiratory symptoms

Haemorrhage

Gastrointestinal or respiratory secretions

Yes

No

Isolation not required

Isolate patient according to risk

Contact

Droplet

Single room or patient cohorting

Standard contact precautions

Hand hygiene

Gloves

Aprons

Surgical face mask

Airborne

Enhanced

Negative pressure single room

FFP3 respirator

Enhanced precautions for aerosol-generating procedures

Fluid repellent surgical face mask

Eye protection

Plastic apron

Hand hygiene

Gloves

STEP 2: RECOGNIZE HIGHLY TRANSMISSIBLE CAUSES OF FEVER - ASSESS NEED FOR ISOLATION

Assess risk for:

- **Viral haemorrhagic fevers**
 - Ebola, CCHF, Marburg, Lassa fever
 - <21 days endemic country?
- **Severe respiratory illness**
 - MERS-CoV: Middle East (camels or hospitals)
 - Avian influenza: Asia (chickens)
- **Risk of antimicrobial resistance**
 - ESBL
 - CPE

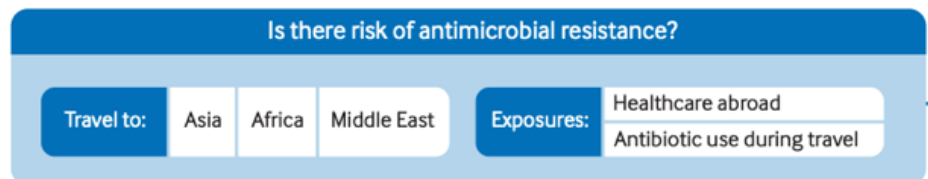
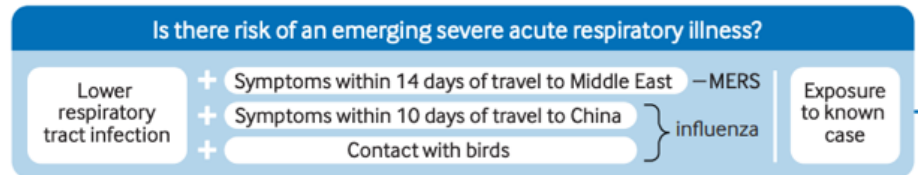
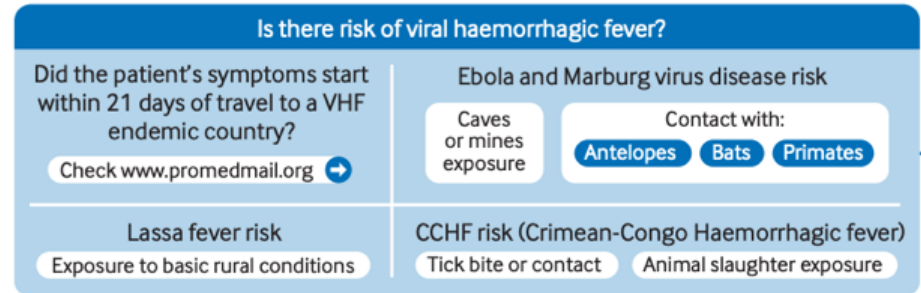


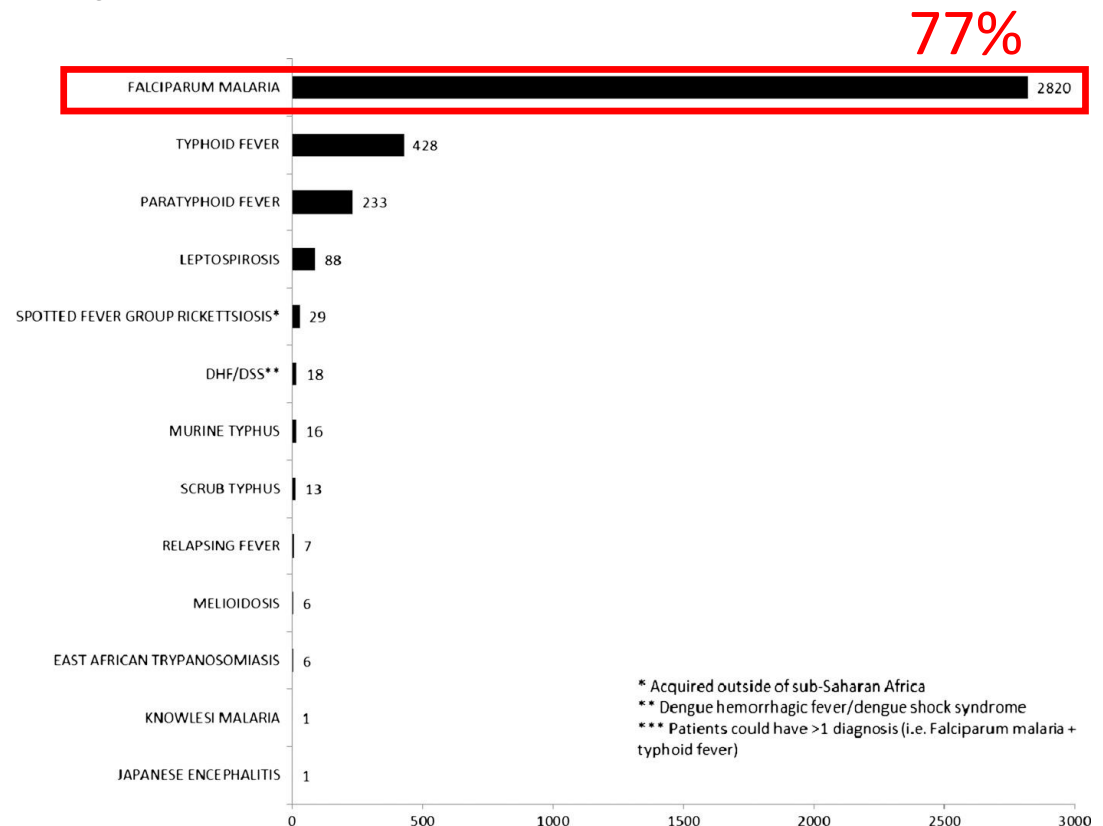
Table 3. Serious Transmissible Infections in Febrile Returning Travelers.

Infection	Geographic Regions Affected	Mode of Transmission	Incubation Period	Immediate Precautions for Suspected Infection*
Viral hemorrhagic fevers				
Ebola virus disease	Guinea, Sierra Leone, Liberia, Ivory Coast, Sudan, Uganda, Kenya, Democratic Republic of Congo, Republic of the Congo, Gabon, Angola, Zimbabwe	Direct contact with blood, secretions, organs, or other body fluids of infected persons; contact with objects (e.g., needles or clothing) contaminated with infected secretions	2–21 days	Isolate patient and use strict barrier nursing techniques; hospital workers have frequently been infected in Ebola outbreaks
Marburg hemorrhagic fever	Ivory Coast, Sudan, Uganda, Kenya, Democratic Republic of Congo, Republic of the Congo, Gabon, Angola, Zimbabwe	Initial infection through exposure in mines or caves inhabited by rousettus bats; person-to-person transmission requires direct contact with blood or other body fluids from an infected person (feces, vomit, urine, saliva, or respiratory secretions)	3–10 days	Isolate patient and use strict barrier nursing techniques
Lassa fever	Guinea, Sierra Leone, Liberia, Nigeria	Initial infection through direct or indirect contact with infected rodent excreta on surfaces or in food or water; person-to-person transmission occurs through contact with infected body fluids (e.g., blood, saliva, urine, or semen)	5–21 days	Isolate patient and use strict barrier nursing techniques
Crimean–Congo hemorrhagic fever	Broad area of endemicity: Africa, Middle East, Asia, Eastern Europe; outbreaks in Russia, Turkey, Iran, Kazakhstan, Mauritania, Kosovo, Albania, Pakistan	Tickborne transmission, but possible transmission to humans through direct contact with body fluids of infected humans or animals	1–9 days for tick bite, 5–13 days for direct contact	Isolate patient and use strict barrier nursing techniques
Severe acute respiratory infections				
Influenza A	Global distribution; outbreaks of avian influenza in Southeast Asia and China	Direct or airborne transmission	1–4 days	Isolate patient and use strict barrier nursing techniques; staff should wear FFP3 or N95 masks
MERS-CoV	Arabian Peninsula, particularly Saudi Arabia	Direct contact with respiratory secretions or airborne transmission of large droplets	2–14 days	Isolate patient and use strict barrier nursing techniques; staff should wear FFP3 or N95 masks
Pneumonic plague	Remote areas of Africa, Asia, and South America	Inhalation of infective droplets or hematogenous spread to lungs in septicemic or bubonic plague	1–3 days, if acquired through inhalation	Isolate patient and use strict barrier nursing techniques; staff should wear FFP3 or N95 masks; prophylactic oral ciprofloxacin or doxycycline should be administered if a health care worker is exposed
Other serious infections				
Measles	Global distribution with regional outbreaks	Direct or airborne transmission	7–21 days	Isolate patient; check status of vaccinations and previous infections in contacts in hospital (staff and other patients)
Chickenpox	Global distribution	Direct or airborne transmission	10–21 days	Isolate patient; check status of vaccinations and previous infections in contacts in hospital (staff and other patients)
Pulmonary tuberculosis	Global distribution; common in Africa and Asia	Airborne transmission	Months to years	Isolate patient; for suspected case of multidrug-resistant tuberculosis, isolate patient in negative-pressure room, if available

* Strict barrier nursing techniques include the use of masks, gloves, and gowns. FFP3 denotes filtering facepiece, class 3.

STEP 3: RECOGNIZING LIFE-THREATENING CAUSES OF FEVER

- Among 82,825 cases of illness in travelers 4% involved acute and potentially life-threatening tropical diseases
- Fever was a symptom in 91%
- Falciparum malaria 77%
- Enteric fever 18%
- Thirteen patients (0.4%) died:
 - 10 falciparum malaria
 - 2 melioidosis
 - 1 severe dengue



Life-Threatening Tropical Infections Characterized by Fever

Table 1. Life-Threatening Tropical Infections Characterized by Fever.*

Disease (pathogen)	Incubation Period	Geographic Regions Affected	Vector or Exposure	Diagnostic Test	Treatment
Viral infections					
Avian influenza (H5N1 influenza A virus)	2–8 days	East and Southeast Asia	Poultry	RT-PCR	Oseltamivir, peramivir, or zanamivir
MERS-CoV	2–14 days	Arabian peninsula	Contact with infected humans or camels	RT-PCR	Supportive
Ebola virus disease, Lassa fever, and Marburg hemorrhagic fever	<22 days	Africa	Contact with infected humans or animals	RT-PCR	Supportive; also consider ribavirin for Lassa fever
Crimean–Congo hemorrhagic fever	1–9 days for tick bite, 3–13 days for infective contact	Southern Europe, Middle East, Africa, northwestern China	Ixodid (hard) ticks; contact with infected humans or animals	RT-PCR	Supportive
Yellow fever	3–8 days	South America, Africa	Aedes mosquitoes; haemagogus and sabethes mosquitoes in the jungle cycle	RT-PCR, IgM ELISA	Supportive

Severe dengue	4–7 days	Widespread, particularly South and Southeast Asia, South and Central America, Caribbean, Africa	Aedes mosquitoes	Leptospirosis	2–29 days	Widespread, particularly South and Southeast Asia and South America	Contact with urine from infected animals (many domestic and wild animals, including rodents)	IgM and IgG ELISAs, PCR	Doxycycline or azithromycin (for mild infection); parenteral penicillin, doxycycline, or third-generation cephalosporin (for severe infection)
Japanese encephalitis	5–15 days	Asia, western Pacific	Culex mosquitoes	Louseborne relapsing fever (<i>Borrelia recurrentis</i>)	4–14 days	Ethiopia, Eritrea, and Sudan	Human body lice (<i>P. humanus</i>)	Microscopic examination of blood smear, IgM and IgG ELISAs, PCR	Doxycycline (Jarisch–Herxheimer reactions are common and may require ICU admission)
Rift Valley fever	2–6 days	Africa, Arabian peninsula	Mosquitoes (species v. gion); exposure to l from infected anim	Melioidosis (<i>Burkholderia pseudomallei</i>)	1–21 days (but can be months or years)	South and Southeast Asia, northern Australia; isolated reports from Africa and South America	Contact with contaminated soil or surface water	Bacterial culture	Ceftazidime or a carbapenem, followed by prolonged oral therapy with cotrimoxazole
Rabies (rabies virus and other lyssaviruses)	20–60 days (usually longer than 4 weeks but can be shorter; occasionally months or years)	Widespread	Animal bite	Murine or endemic typhus (<i>R. typhi</i>)	7–14 days	Widespread, particularly Southeast Asia	Rodent fleas	IgM and IgG ELISAs, PCR	Doxycycline or chloramphenicol
Bacterial infections									
Anthrax (<i>Bacillus anthracis</i>)	1 day for cutaneous anthrax, 1–7 days for pulmonary anthrax	Enzootic in Africa and Asia	Contact with infected animal products	Oroya fever, or Carrion's disease (<i>Bartonella bacilliformis</i> , <i>B. rochalimae</i> , and <i>B. ancashensis</i>)	10–210 days	South America, particularly Peru	Phlebotomine sandflies	Bacterial culture	Ciprofloxacin plus ceftriaxone, chloramphenicol
Enteric fever (<i>Salmonella enterica</i> serovar Typhi and <i>S. enterica</i> serovar Paratyphi A and C)	6–30 days	South and Southeast Asia	Fecal–oral transmissio	Scrub typhus (<i>Orientia tsutsugamushi</i>)	6–20 days	Asia and northern Australia	Larval mites (chiggers)	IgM and IgG ELISAs, PCR	Doxycycline, azithromycin
Epidemic typhus (<i>Rickettsia prowazekii</i>)	7–14 days	Central Africa; Asia; Central, North, and South America; usually outbreak-associated	Human body lice (<i>Pediculus humanus</i>), flying s ectoparasites, poss ticks	Spotted fever group rickettsioses	2–14 days	Widespread	Mostly ticks	IgM and IgG ELISAs, PCR	Doxycycline
				Plague (<i>Yersinia pestis</i>)	2–6 days for bubonic plague, 1–3 days for pneumonic plague	Remote areas of Africa, Asia, and South America	Rodent fleas	Bacterial culture	Aminoglycosides (streptomycin or gentamicin), tetracyclines, or fluoroquinolones
Protozoal infections									
				East African sleeping sickness (<i>Trypanosoma brucei rhodesiense</i>)	7–21 days	Eastern and southern Africa	Tsetse flies	Microscopic examination of blood, lymph node fluid, or chancre-tissue biopsy specimen	Suramin (for early stage), eformithine plus nifurtimox (for late stage), melarsoprol (for late stage)
				Falciparum malaria (<i>Plasmodium falciparum</i>)	7–30 days (can be longer)	Africa, Asia, South America; highest risk of infection in sub-Saharan Africa	Anopheles mosquitoes	Microscopic examination of thick and thin blood smears; rapid diagnostic tests (antigen detection)	Parenteral artesunate (for severe malaria), ACT (for uncomplicated malaria)
				Knowlesi malaria (<i>P. knowlesi</i>)	10–14 days	Southeast Asia, particularly Borneo	Anopheles mosquitoes	Microscopic examination of thick and thin blood smears	Same as treatment for falciparum malaria

* The listed diseases are those with an incubation period of less than 4 weeks and at least a 5% risk of death within 4 weeks after symptom onset in the absence of treatment. Only diseases largely confined to tropical or subtropical regions are included. Data are from Jensenius et al.¹¹ ACT denotes artemisinin-based combination therapy, ELISA enzyme-linked immunosorbent assay, ICU intensive care unit, MERS-CoV Middle East respiratory syndrome coronavirus, RFFIT rapid fluorescent focus inhibition test, and RT-PCR real-time polymerase chain reaction.

- Exclude malaria!
- Think cosmopolitan → *it is not always a zebra..*

Etiology and Outcome of Fever After a Stay in the Tropics

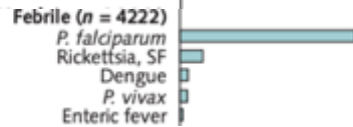
Emmanuel Bottieau, MD; Jan Clerinx, MD; Ward Schrooten, MD, PhD; [et al](#)
Arch Intern Med. 2006;166(15):1642-1648. doi:10.1001/archinte.166.15.1642

Table 2. Diagnosis of Imported Fever

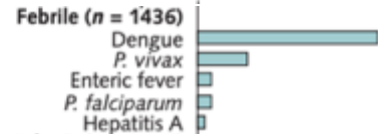
Condition	Cases, No. (%) (N = 1842)
Tropical diseases	722 (39.2)
<i>Plasmodium falciparum</i> malaria	408 (22.1)
Nonfalciparum malaria	103 (5.6)
<i>Plasmodium vivax</i>	50 (2.7)
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Rickettsial infections	60 (3.3)
<i>Rickettsia conorii/africae</i> (African tick bite fever/Mediterranean spotted fever)	53 (2.9)
<i>Rickettsia typhi</i> (murine typhus)	4 (0.2)
<i>Orienta tsutsugamushi</i> (scrub typhus)	3 (0.2)
Dengue fever	56 (3.0)
Acute schistosomiasis (Katayama fever)	33 (1.8)
Enteric fever	15 (0.8)
<i>Salmonella typhi</i>	8 (0.4)
<i>Salmonella paratyphi A</i>	7 (0.4)
Invasive amebiasis	10 (0.5)
Protozoan enteritis*	10 (0.5)
Other tropical diseases†	27 (1.5)
Cosmopolitan infections	631 (34.2)
Respiratory tract infection‡	134 (19.5)
Bacterial enteritis§	115 (6.2)
Infectious mononucleosis-like syndromes	72 (3.9)
Skin/soft tissue infection	67 (3.6)
Genitourinary infection¶	63 (3.4)
Tuberculosis	30 (1.6)
Bacteremia#	18 (0.1)
Q fever	13 (0.7)
Hepatitis A	11 (0.6)
AIDS-related opportunistic infections (other than tuberculosis)	10 (0.5)
Leptospirosis	6 (0.3)
Other infections (≤5 cases for each diagnosis)	32 (1.7)
Unknown causes	449 (24.4)
No focus of infection	166 (8.1)
Symptoms of enteritis	151 (8.2)
Symptoms of upper respiratory tract infection	130 (7.1)
Noninfectious causes	40 (2.2)

Where did you travel?

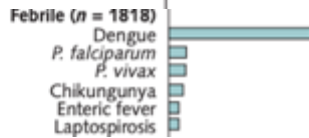
Sub-Saharan Africa (n = 11 251)



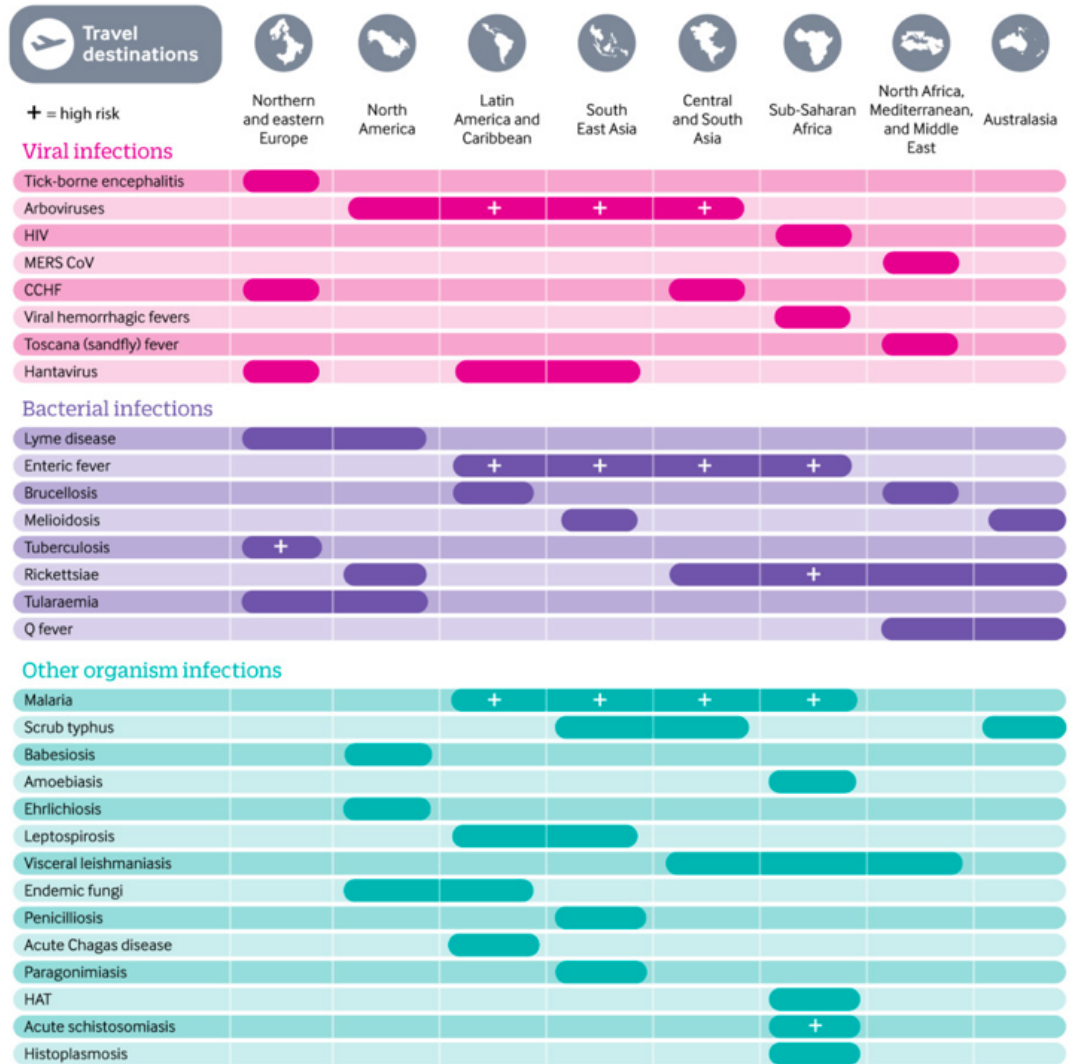
Latin America and Caribbean (n = 8099)



Southeast Asia (n = 6890)



ORIGINAL RESEARCH | *Annals of Internal Medicine*
GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011



MERS CoV = Middle East respiratory syndrome coronavirus CCHF = Crimean Congo haemorrhagic fever HAT = Human African trypanosomiasis

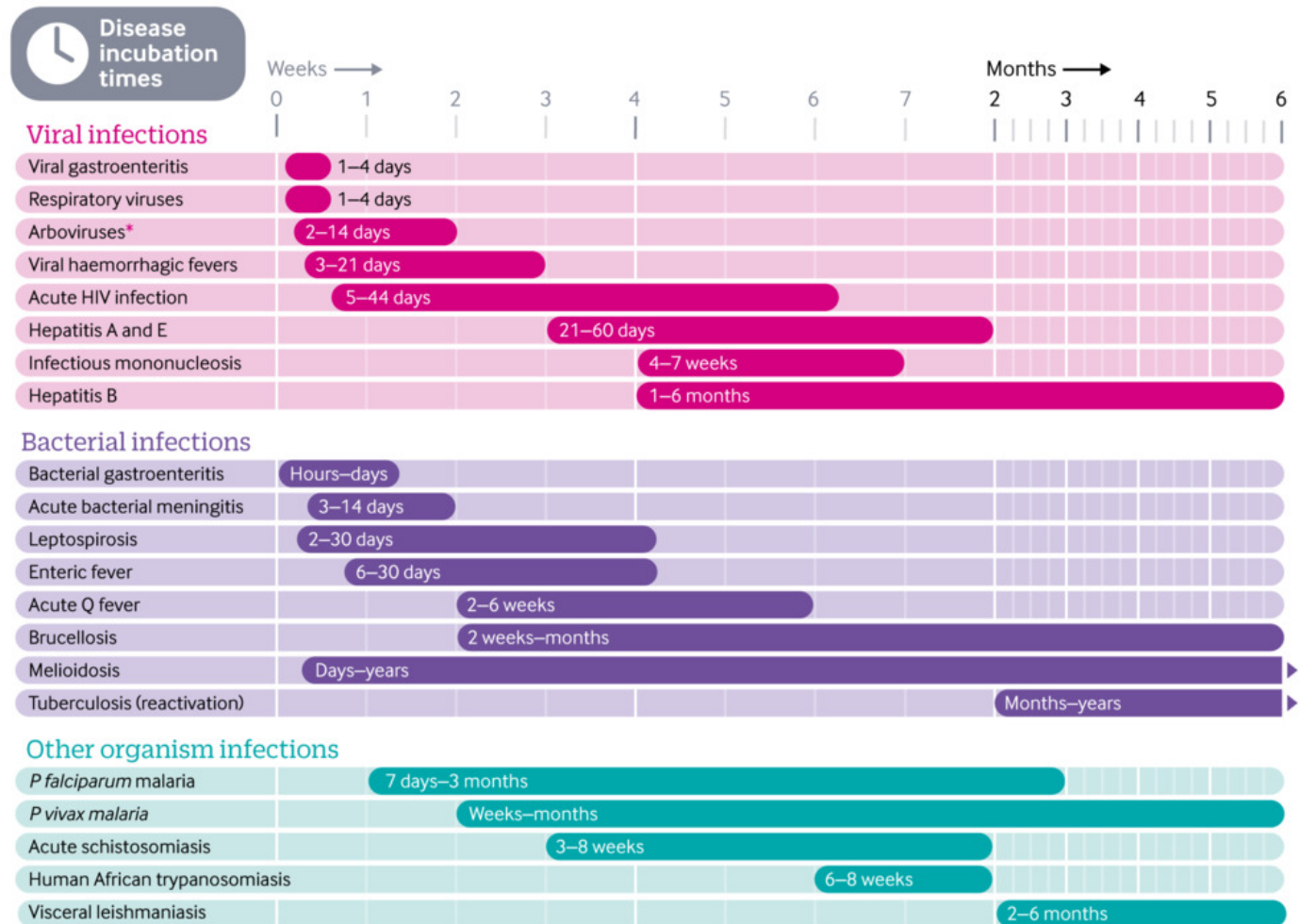
Useful sites: [CDC: https://wwwnc.cdc.gov/travel/destinations/list/](https://wwwnc.cdc.gov/travel/destinations/list/)
[ITG: http://reisgeneeskunde.be](http://reisgeneeskunde.be)

Outbreak? <http://www.who.int/csr/don/en/>

When did you travel?

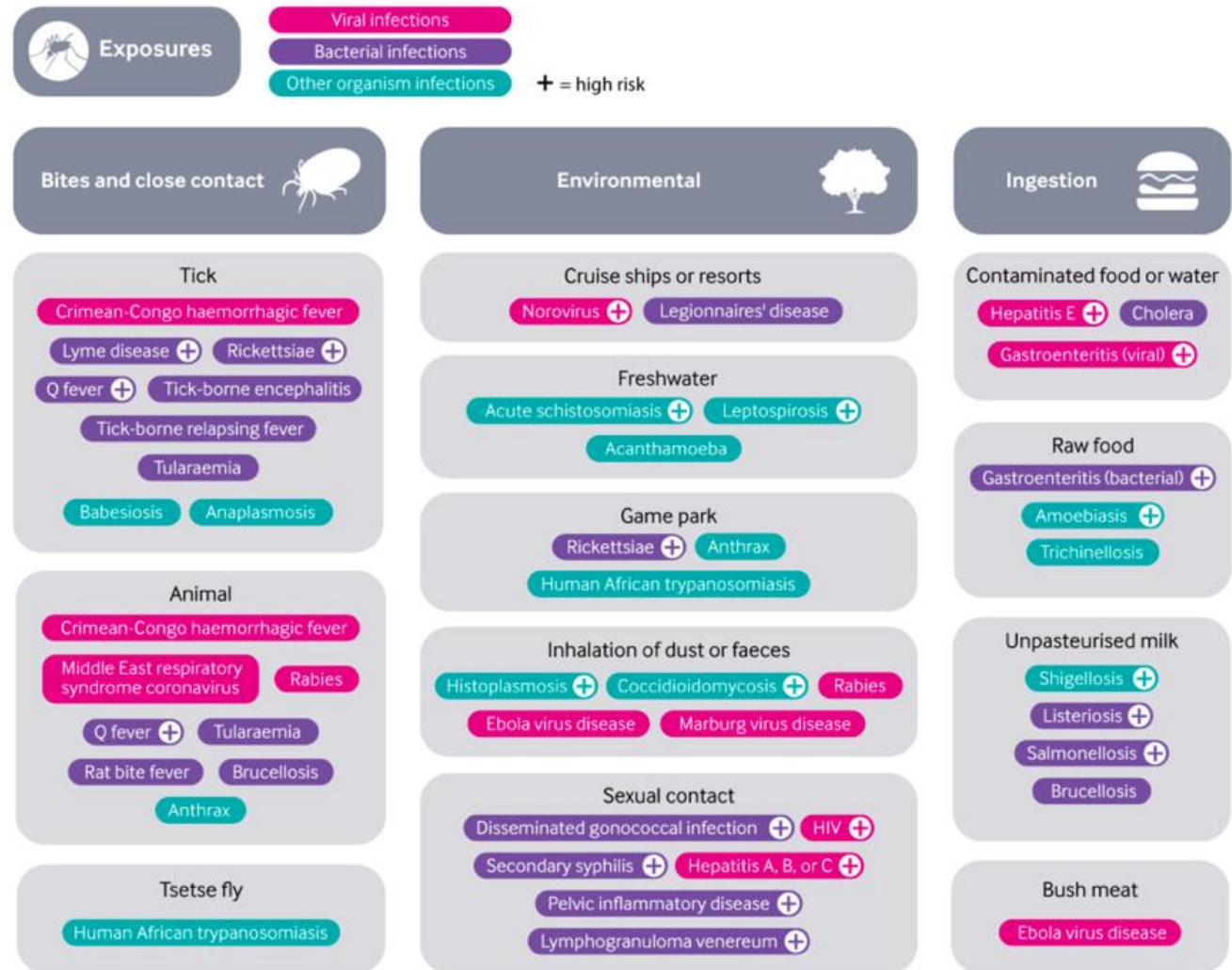
Incubation Times !

- Malaria: 7 days – ...
- Arboviruses: 7-14 dagen
- Enteric fever: 6-30 dagen
- VHF: 3-21 dagen



* e.g. chikungunya, dengue, Zika, Japanese encephalitis, yellow fever

What risk factors were you exposed to?



- Pre-travel preparation
- High-risk foods
- Animal/insect exposure and bites
- Fresh water activities
- Blood and body fluid exposures
- Sick contacts
- Health of fellow travelers

Table 2. Obtaining a History of the Returning Traveler with Fever.*

History	Implications or Associated Diseases
Day-by-day itinerary	Provides geographic disease associations
Vaccinations and malaria prophylaxis	Narrow the differential diagnosis but do not rule out vaccine-preventable diseases or malaria
Other drugs taken while or since traveling	Partial treatment of infection may delay or alter disease presentation (e.g., malaria)
Immune status (diabetes, glucocorticoid treatment, renal failure, splenectomy, diseases associated with immune deficit)	Melioidosis, listeriosis, tuberculosis, fungal infections, CMV infection
Consumption of unclean water, unpasteurized milk, or improperly cooked or raw food	Travelers' diarrhea, giardiasis, nontyphoidal salmonellosis, enteric fever, shigellosis, campylobacter infection, hepatitis A and E, amebic dysentery, brucellosis, listeriosis
Exposure to fresh water (rafting, kayaking, swimming in rivers or lakes, floods)	Leptospirosis, acute schistosomiasis
Skin contact with soil (e.g., walking barefoot)	Strongyloidiasis, melioidosis
Tattoos, piercings, intravenous drug use, or medical procedures (e.g., injections and blood-product transfusions)	Hepatitis B or C virus infection, acute HIV infection, CMV infection, malaria, babesiosis
Sexual contact, specifically unprotected sex with a new partner, commercial sex workers, or multiple partners	Primary herpesvirus infection; acute HIV infection; hepatitis A, B, or C virus infection; syphilis; gonorrhea; Zika virus infection; viral hemorrhagic fevers
Visits with relatives or friends while abroad (Was anyone ill?)	Tuberculosis, other infections transmitted by exposure to ill persons
Insect bites	
Mosquitoes	Malaria, dengue fever, chikungunya, Zika virus infection, Japanese encephalitis, yellow fever, Rift Valley fever, West Nile virus infection, filarial fever
Ticks	Rickettsioses, Q fever, tickborne relapsing fever, Lyme disease, tickborne encephalitis, babesiosis, Crimean–Congo hemorrhagic fever, tularemia
Mites	Scrub typhus, rickettsialpox (<i>R. akari</i>)
Fleas	Murine typhus, plague
Lice	Louseborne relapsing fever (<i>B. recurrentis</i>), epidemic typhus (<i>R. prowazekii</i>), trench fever (<i>Bartonella quintana</i>)
Flies	Leishmaniasis, African sleeping sickness, bartonellosis, phlebotomus (sandfly) fever
Triatomine bugs	Chagas' disease
Animal bites	Rabies, cat-scratch fever (<i>B. henselae</i>), rat-bite fever (<i>Spirillum minus</i> or <i>Streptobacillus moniliformis</i> infection), simian herpesvirus B infection
Close contact with animals	Toxoplasmosis, anthrax, Q fever, hantavirus infection, Nipah virus, Hendra virus, plague, psittacosis, diseases from animal ectoparasites
Close contact with wild or pet birds	Psittacosis, avian influenza

* CMV denotes cytomegalovirus, and HIV human immunodeficiency virus.

STEP 4: DIAGNOSIS: EXAMINATION

- Many imported infections have a non-specific febrile presentation

Physical Finding	Likely Infection or Disease
Rash	Dengue Fever, typhus, syphilis, gonorrhea, Ebola fever, brucellosis, Chikungunya, HIV seroconversion
Jaundice	Hepatitis, Malaria, Yellow Fever, Leptospirosis
Lymphadenopathy	Rickettsial infections, brucellosis, HIV, Lassa fever, Leishmaniasis, EBV, CMV, Toxoplasmosis, Trypanosomiasis
Hepatomegaly	Amebiasis, Malaria, Typhoid, Hepatitis, Leptospirosis
Splenomegaly	Malaria, Trypanosomiasis, Typhoid, Brucellosis, Kala-azar, Typhus, Dengue Fever, Schistosomiasis
Eschar	Typhus, Borreliosis, Crimean Congo hemorrhagic fever, anthrax
Hemorrhage	Lassa, Marburg or Ebola viruses, Crimean-Congo hemorrhagic fever, meningococemia, epidemic louse-borne typhus



FIGURE 45.—Typical eschar seen in scrub typhus indicates site of infection by the tracheal mite. The lesion, generally up to 1 cm in diameter, consists of a central rough black scab surrounded by a slightly elevated, dull red areola. It is neither painful nor pruritic. (Courtesy, Carlton Bailey, M.D.)

Figure: Dengue skin rash “white isles in a red sea” (Photograph Dr. R. Huits, ITM)

STEP 4: DIAGNOSIS: INVESTIGATIONS

4 Diagnosis

Once immediate risks have been addressed, take a more detailed travel history to help to identify the infection and guide management

Examination

Consider empirical treatment for specific clinical scenarios

Routine investigations

Blood cultures

Also consider: Respiratory virus swab
Focal microbiology or virology samples
Imaging HIV test Routine blood tests

- CBC & diff (anemia, lymphopenia, thrombocytopenia)
- Serum inflammatory markers, kidney function, liver function
- Blood cultures
- **Malaria testing in all patients** with geographical risk, regardless of reported adherence to anti-malarial prophylaxis
- Save serum for serology
- Urine, Feces culture
- Chest X-ray
- US Liver

THE BIG FIVE



THE BIG FIVE WITH FEVER

1. Malaria
2. Dengue
3. Enteric Fever
4. Rickettsial infection
5. Acute schistosomiasis



Table 2. Diagnosis of Imported Fever

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<i>Salmonella paratyphi A</i>	7 (0.4)
Invasive amebiasis	10 (0.5)
Protozoan enteritis*	10 (0.5)
Other tropical diseases†	27 (1.5)
Cosmopolitan infections	631 (34.2)

P. Falciparum malaria was the only tropical disease leading to admission to the ICU (n=30) and to death (n=5; fatality rate of 1.2%).

Etiology and Outcome of Fever After a Stay in the Tropics

Emmanuel Bottieau, MD; Jan Clerinx, MD; Ward Schrooten, MD, PhD; et al
Arch Intern Med. 2006;166(15):1642-1648.

THE BIG FIVE WITH FEVER

potentially life-threatening

1. Malaria
2. Enteric Fever
3. Rickettsial infection
4. Leptospirosis
5. Dengue



Table 2

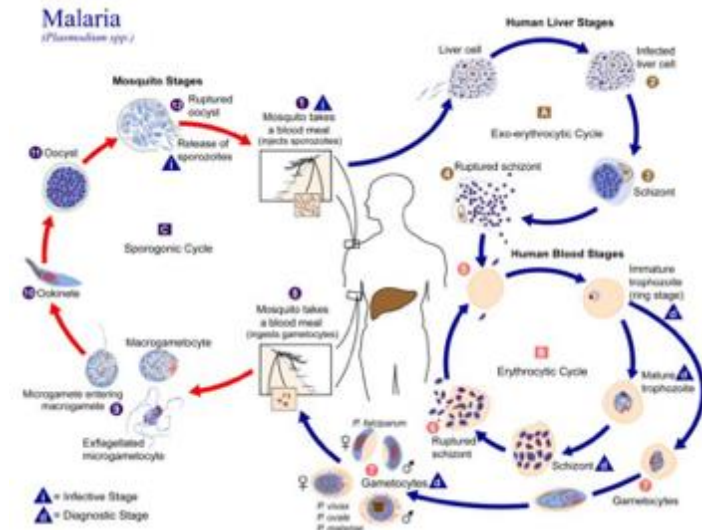
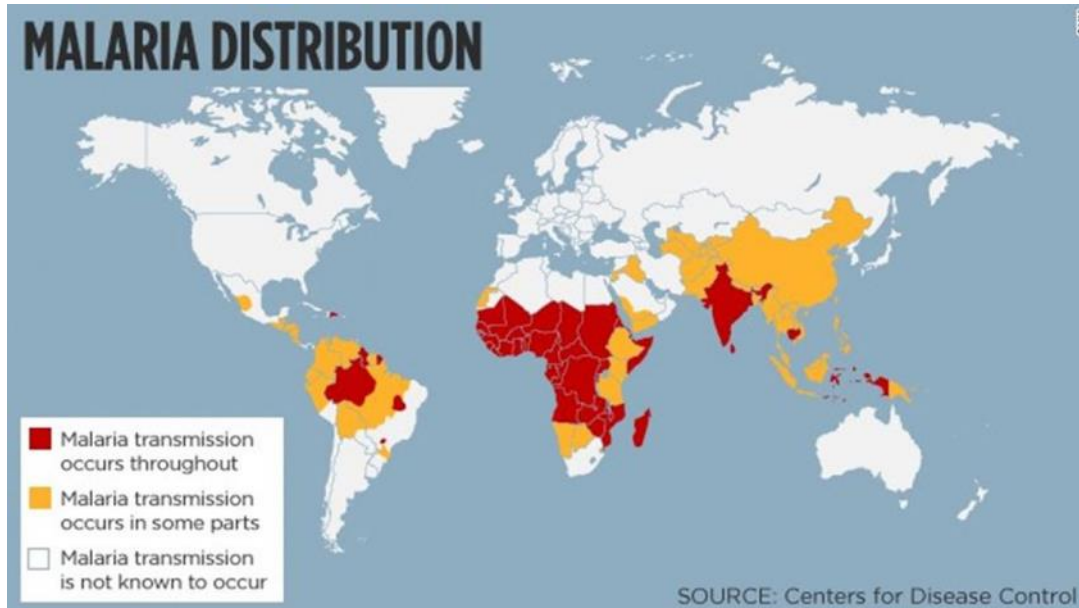
Causes of acute and potentially life-threatening tropical diseases in 3655 travellers – based on data from the GeoSentinel Multicentre Study 1996–2011*

Diseases	Number of patients (%)
Malaria	2821 (76.9%)
<i>Plasmodium falciparum</i> malaria	2820 (76.9%)
<i>Plasmodium knowlesi</i> malaria	1 (0.03%)
Enteric fever	661 (18.0%)
Typhoid	428 (11.7%)
Paratyphoid	233 (6.4%)
Rickettsial disease	58 (1.6%)
Spotted fever group of rickettsiosis	29 (0.79%)
Murine typhus	16 (0.44%)
Scrub typhus	13 (0.35%)
Leptospirosis	88 (2.4%)
Dengue hemorrhagic fever/dengue shock syndrome	18 (0.49%)
Relapsing fever	7 (0.19%)
Melioidosis	6 (0.16%)
East African Trypanosomiasis	6 (0.16%)
Japanese encephalitis	1 (0.03%)

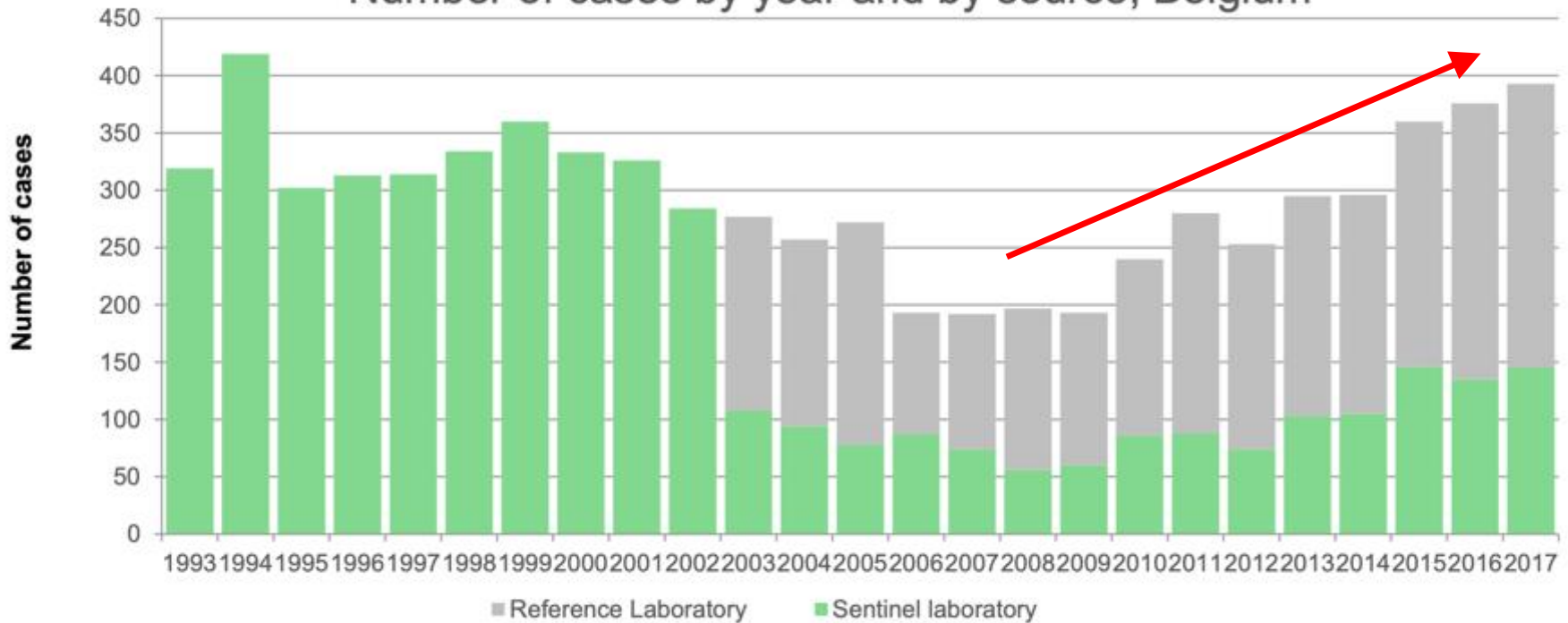
* Based on data from Jensenius M, et al., *Am J Trop Med Hyg* 2013; 88:397–404.

1. MALARIA

- = Moeraskoorts, Paludisme
- Protozoal infection
- Plasmodium
 - 5 species: P. Falciparum (60%), P. Vivax, P. Ovale, P. Malariae , P. Knowlesi
- Transmission: female *Anopheles* mosquito
- Malaria map CDC: https://www.cdc.gov/malaria/travelers/about_maps.html



Number of cases by year and by source, Belgium



Majority of infections (84 % in 2015-2016) imported from Africa: RDC, Ghana, Cameroun, Guinee Conakry, Ivory Coast and Nigeria

MALARIA: Incubation

- Falciparum malaria most likely < 3 months of return
- Other malaria species may present >1 year after return

Table 4. Prevalence of Tropical Diseases According to Period Between Return or Arrival From Endemic Countries and Fever Onset*

Tropical Disease	Before and Within the First Month of Return or Arrival (n = 1434)	Within the Second Month of Return or Arrival (n = 137)	Within the Third Month of Return or Arrival (n = 66)	Within 4-12 Months of Return or Arrival (n = 205)	Total, No. (N = 1842)
<i>Plasmodium falciparum</i> malaria	373 (26)	20 (15)	7 (11)	8 (4)	408
Nonfalciparum malaria	28 (2)	23 (17)	16 (24)	36 (18)	103

Etiology and Outcome of Fever After a Stay in the Tropics Emmanuel Bottieau, MD; Jan Clerinx, MD; Ward Schrooten, MD, PhD; et al Arch Intern Med. 2006;166(15):1642-1648.

MALARIA: History

- Travel history
- Malaria prophylaxis?
- **Appropriate prophylaxis with full adherence does not exclude malaria!**



Visiting friends or relatives

Table 3. Prevalence of the Main Diagnoses According to Category of Travelers*

Main Diagnosis	Western Travelers (n = 1098)	Expatriates (n = 266)	VFR Travelers (n = 249)	Foreign Visitors or Migrants (n = 229)
<i>Plasmodium falciparum</i> malaria	159 (14)	100 (38)	90 (36)	59 (26)
Nonfalciparum malaria	59 (5)	19 (7)	7 (3)	18 (8)

Etiology and Outcome of Fever After a Stay in the Tropics Emmanuel Bottieau, MD; Jan Clerinx, MD; Ward Schrooten, MD, PhD; et al Arch Intern Med. 2006;166(15):1642-1648.

MALARIA: Symptoms

- Symptoms of malaria are often non-specific:
 - Fever/sweats/chills
 - Malaise
 - Myalgia
 - Headache
 - Diarrhea
 - Cough

	Total (n=387)
<hr/>	
Clinical features	
Headache and/or myalgia, no. (%)	345 (89)
Fever $\geq 39^{\circ}\text{C}$, no. (%)	201 (52)
Vomiting, no. (%)	132 (34)
Diarrhea, no. (%)	116 (30)
Splenomegaly, no. (%)	82 (21)
Jaundice, no. (%)	52 (13)



Flu like symptoms



Selective ambulatory management of imported falciparum malaria: a 5-year prospective study

Eur J Clin Microbiol Infect Dis (2006) 26:181–188

SEVERE MALARIA

=> Opname IZ

a. Cerebrale malaria onafhankelijk van parasitemie (encefalopathie: verminderd bwz, delirium en/of epileptische aanvallen)
of

b. Een van de volgende symptomen/tekenen

- Nierfunctiestoornissen (oligurie <0,5 ml/kg/u of creat >2 mg/dL)
- Acidose (pH<7,35 of stijging van lactaat)
- Hypoglycemia (<40 mg/dL)
- Pulmonair oedeem op RX-thorax of SpO2 <92%
- Hemoglobine <8 g/dL
- Shock (BP <90/60 mmHg)
- Hemoglobinurie (zonder G6PD-deficiëntie)
- INR >1,5 of aPTT > 60 sec
- Thrombocyten < 80.000

EN

- Met parasitemie boven 5%

***P. falciparum is the species most likely to cause severe Malaria and death.
Any cases of suspected Malaria should be considered to be P. falciparum until proven otherwise.***

Severe malaria in Europe: an 8-year multi-centre observational study (2006-2014).

- Total cases (n): 185
- Mortality (n): 3

Table 1 Number of study centres and reported cases per country (n = 185)

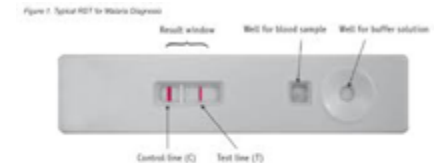
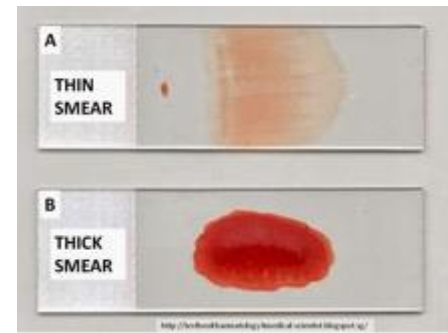
Country	Number of centres	Number of reported cases	% of total number of cases
Austria	2	7	4
Belgium	1	19	10
Denmark	2	14	7
France	2	52	28
Germany	7	15	8
Italy	5	50	27
Netherlands	1	4	2
Norway	1	7	4
Portugal	1	1	1
Spain	2	12	6
Switzerland	3	3	2
UK	1	1	1

MALARIA: Diagnosis

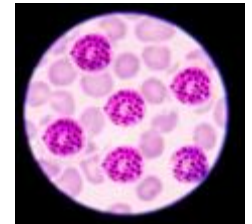
- Thick and thin blood films gold standard for detection and speciation
- Antigen Rapid Diagnostic Test (RDT)
- Negative blood films/RDT but ongoing clinical suspicion: repeat!

UZ GENT:

- **LAMP-test**
 - DNA Plasmodium, geen onderscheid tussen de species
 - **Negatieve test sluit malaria uit**
 - Aanwezigheid koorts niet nodig
- **Malaria-sneltest (RDT)** na een positieve LAMP-test
 - P. Falciparum onderscheiden
- **MO: Dikdruppel en bloeduitstrijkje**
 - Definitieve speciesidentificatie + correcte inschatting parasitemie



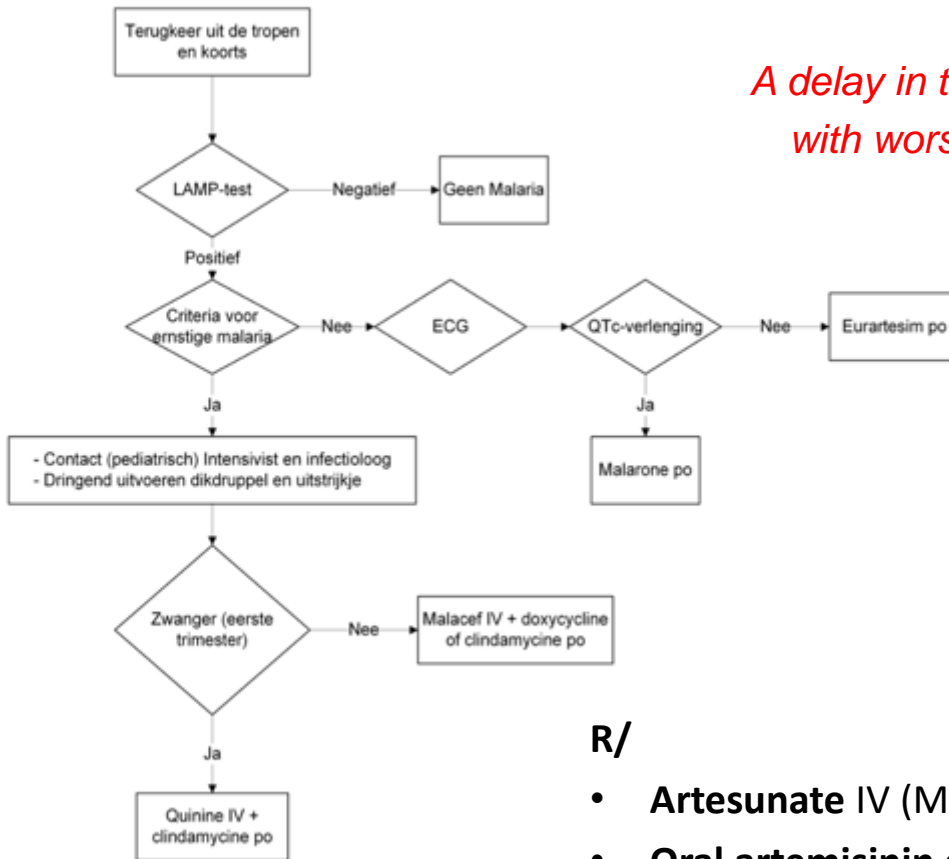
Source: Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva: WHO, 2011.



MALARIA: Treatment

Richtlijn Diagnostiek en behandeling van malaria –UZ Gent - Prof. Dr. S. Callens

*A delay in treating *P. falciparum* > 6 hours is associated with worse outcomes. Do not delay treatment while awaiting lab confirmation.*



R/

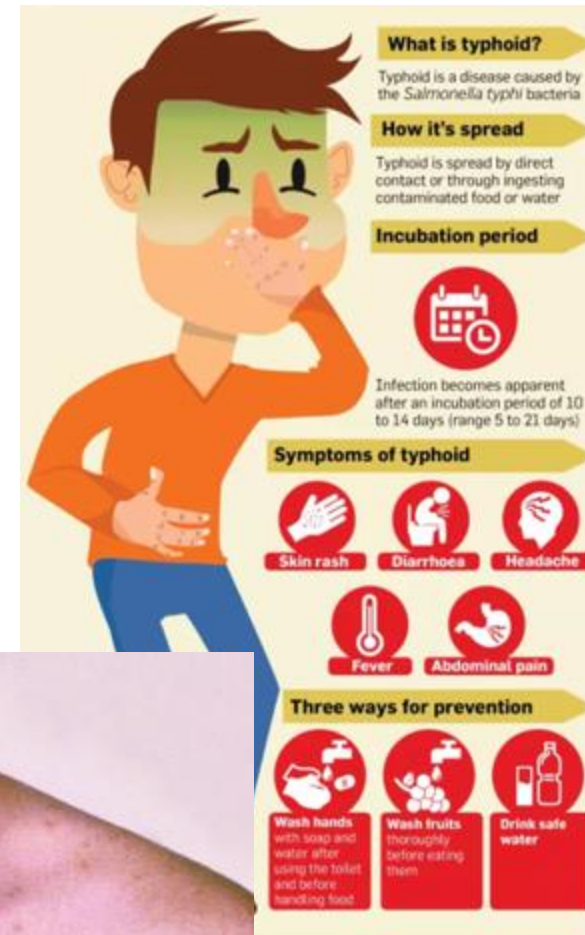
- **Artesunate IV (Malacef):** severe/complicated cases
- **Oral artemisinin combination therapy (ACT)** for non-severe cases

2. ENTERIC FEVER (TYPHOID FEVER, BUIKTYFUS)

- Salmonella Typhi and Paratyphi
- Feco-oral
- Incubation: 1 to 3 weeks
- Highest incidence: South Asia, Southeast Asia and southern Africa
- Symptoms: Abdominal pain, fever, chills, headache, cough, constipation (some diarrhea)
- Examination: rose spots (5-30%)
- Diagnosis: blood (40-80%), urine, faeces cultures (best bone marrow)
- R/ AB (Ciprofloxacin, Ceftriaxone, Azithromycin)

!! Vaccination:

- Maximal protection against Typhoid is 75%



3. RICKETTSIAL DISEASES (SPOTTED AND TYPHUS FEVER)

- Transmission: arthropod ticks (bites, body fluid, feces)
 - Asia: Scrub Typhus: **potential fatal**
 - Africa: African tick typhus: less severe
- Incubation 3 – 14 days
- Symptoms: fever, malaise, myalgia, severe headache, rash, nausea, vomiting
- Examination: lymphadenopathy, splenomegaly, **eschar**
- R/ Doxycycline



! ESCHAR (a necrotic skin lesion)

Eschars are an important and early clinical feature of some rickettsial diseases.



4. LEPTOSPIROSIS

- Rattenziekte, ziekte van Weill
- Spirochete bacteria genus *Leptospira*
 - Hosted in animal's kidneys for months/years
 - Survives weeks/months in urine-contaminated water and soil
- **Transmission:** contact with urine infected animals or contaminated water
- **Entry point:** skin abrasions, mucous membranes, inhalation of droplets of urine, drinking water
- Worldwide!
- **Incubation:** 2-30 days. Most illnesses: 5-14 days after exposure

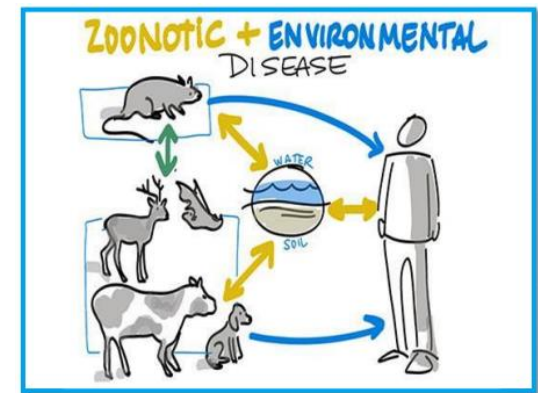
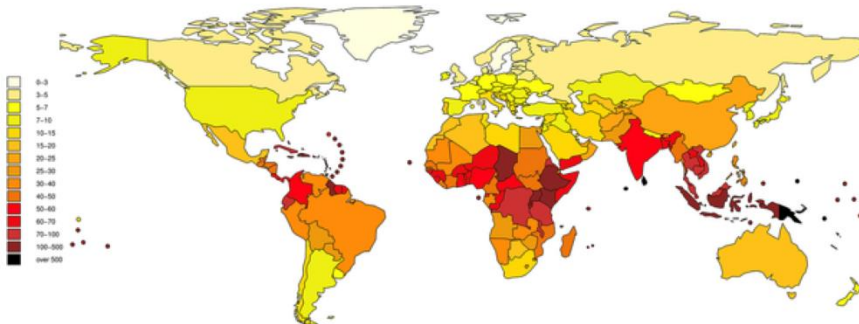


Fig 4. Burden of leptospirosis in terms of DALYs/100,000 per year.



Torgerson PR, Hagan JE, Costa F, Calcagno J, Kane M, et al. (2015) Global Burden of Leptospirosis: Estimated in Terms of Disability Adjusted Life Years. PLOS Neglected Tropical Diseases 9(10): e0004122. <https://doi.org/10.1371/journal.pntd.0004122>
<https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004122>

Lopers besmet met 'rattenziekte' na loopwedstrijd

03/10/2015 om 09:04 door (kld) | Bron: BELGA



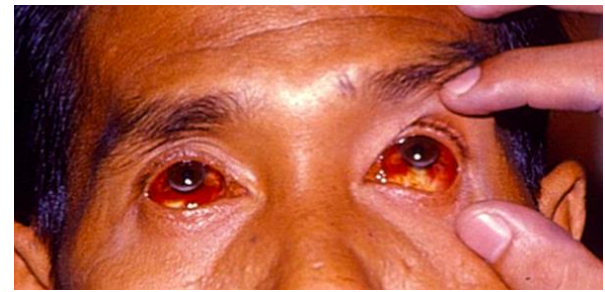
Foto: Joen De Weert

2.500 deelnemers aan de spectaculaire Titan Run in Nijlen, midden vorige maand, zijn tijdens deze obstakelloop mogelijk besmet geraakt met leptospirose, de zogenaamde rattenziekte of modderkoorts. Alvast drie deelnemers belandden erg ziek in het ziekenhuis.

4. LEPTOSPIROSIS

Symptoms:

- Asymptomatic forms
- Biphasic
 - Leptospiremic phase: influenza like illness (90%)
 - Immunologic phase: Weil's syndrome (febrile hepatorenal syndrome) (10%)



Mortality: overall 2-3%

DD: malaria, dengue, flu, yellow fever, VHF

Diagnosis: Serology + PCR (difficult!)

Treatment: AB

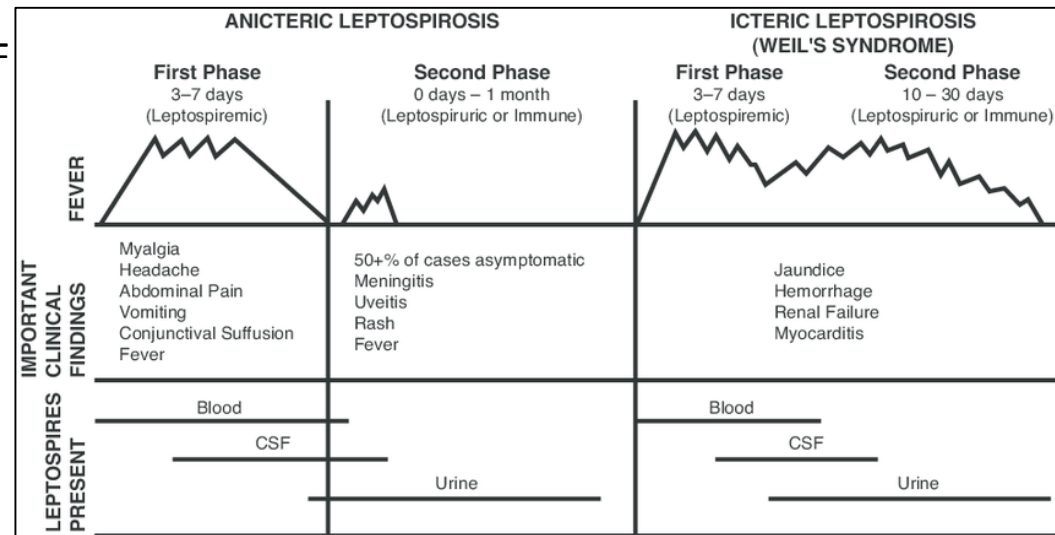


Table 1
Leptospirosis treatment: selection by disease indication.

Indication	Antibiotic	Dosage
Mild leptospirosis	Doxycycline	100 mg orally twice daily for 5-7 days, or 100 mg IV daily for 7 days
	Ampicillin	500-750 mg orally every 6 h, or 0.5-1 g IV every 6 h
	Amoxicillin	500 mg orally every 6 h
	Azithromycin	1 g orally, then 500 mg daily for 2 days
Moderate to severe leptospirosis	Penicillin G	1.5 million units IV every 6 h
	Ampicillin	500-750 mg orally every 6 h, or 0.5-1 g IV every 6 h
	Ceftriaxone	1-2 g IV daily for 7 days
	Doxycycline	100 mg orally, twice daily for 5-7 days or 100 mg IV daily for 7 days
Prophylaxis	Doxycycline	200 mg orally per week

Abbreviation: IV, intravenous.

Leptospirosis: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine.

Journal of Critical Care. <https://doi.org/10.1016/j.jcrrc.2017.11.005>

5.DENGUE FEVER (= KNOKKELKOORTS)

- Arbovirus infection: Dengue Virus (Falviviridae)
 - 4 main serotypes (DEN1-4)
- Transmission: *Aedes aegypti* mosquitoes
- Incubation: 4 to 8 days (always < 2 weeks)
- South East Asia, Latin America
- **Spectrum of illness:** classic dengue fever (DF), hemorrhagic fever (DHF) and shock syndrome (DSS).
- **Classic dengue:** high fever, headache (retrobulbar), nausea and vomiting, myalgia, rash (late), abdominal pain (DHF, DSS)
- **R/** supportive



SEVERE DENGUE

DENGUE ± WARNING SIGNS



SEVERE DENGUE

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory; increase in HCT concurrent with rapid decrease in platelet count

*[requiring strict observation and medical intervention]

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT \geq 1000
- CNS: Impaired consciousness
- Heart and other organs



DENGUE, ZIKA, CHIKUNGUNYA?

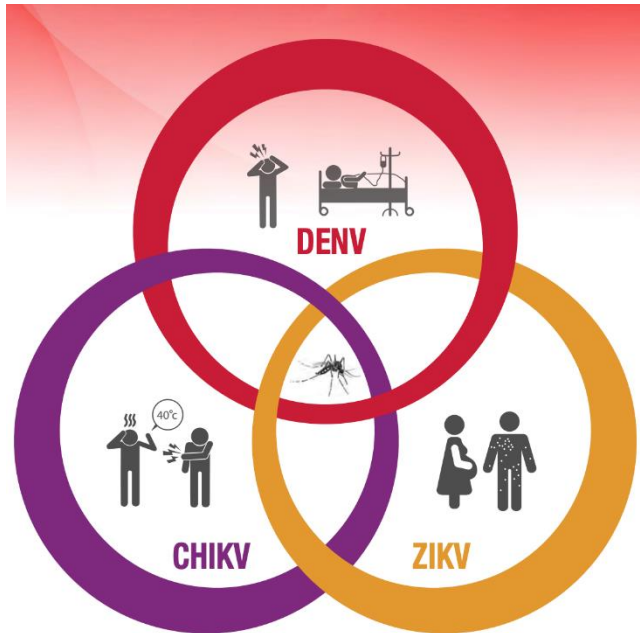


Table 4 Clinical comparison of dengue, chikungunya and Zika.

Disease	Dengue	CHIK	Zika
Fever	++++	+++	+++
Myalgia/Arthralgia	+++	++++	++
Oedema in limbs	—	—	++
Maculopapular exanthema	++	++	+++
Retro-orbital pain	++	+	++
Conjunctivitis	—	+	+++
Lymphadenopathy	++	++	+
Hepatomegaly	—	+++	—
Bleeding	+	—	—

Pan American Health Organization/WHO. **Tool for the diagnosis and care of patients with suspected arboviral diseases.**
http://iris.paho.org/xmlui/bitstream/handle/123456789/33895/9789275119365_eng.pdf?sequence=1&isAllowed=y ; 2017.

WEST NILE VIRUS

1 489 cases

reported in 10 EU countries

171 deaths

in EU countries, up to 9 November

- Flaviviridae
- Incubation 2-17 days
- Symptoms:
 - 80% asymptomatic
 - 20% WNF
 - 1/150 severe (meningitis, encephalitis)
- Mortality: meningitis 2%, encephalitis 10%

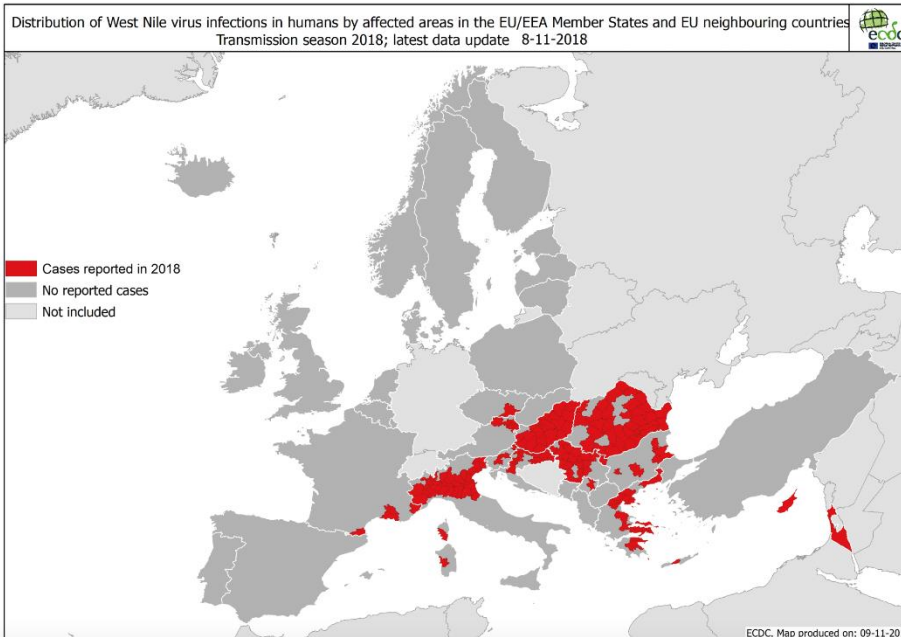
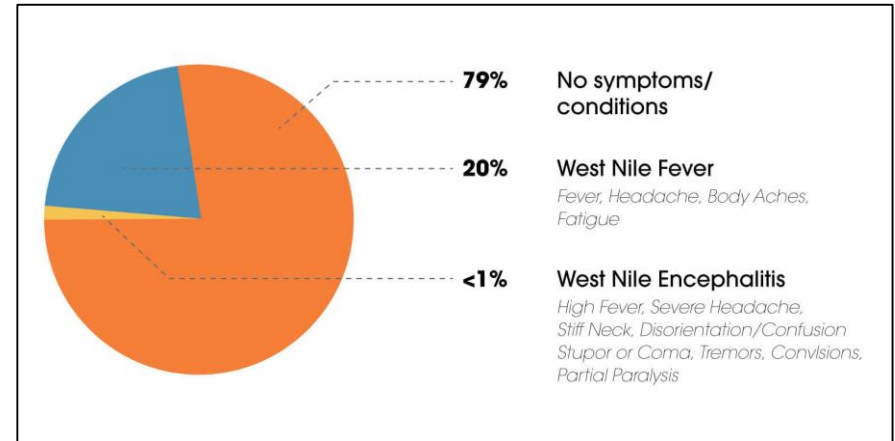
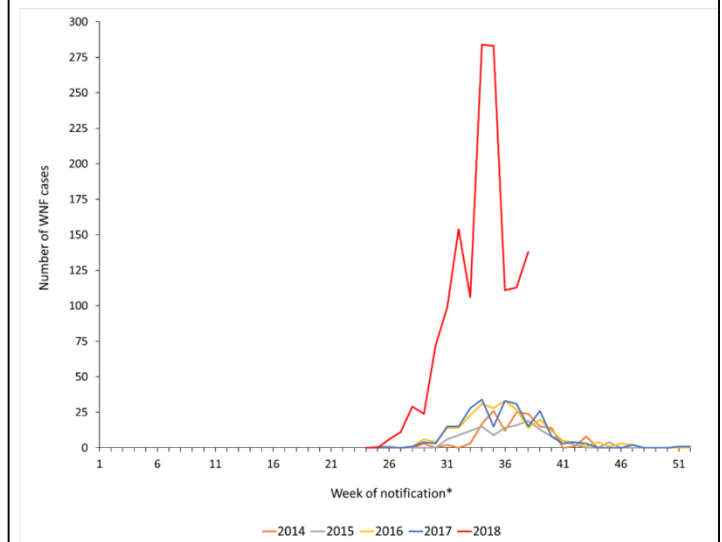


Figure 1. Number of West Nile fever cases in EU/EEA and EU enlargement countries by epidemiological week of notification, 2014 to 2018, as of 20 September 2018





European Centre for Disease Prevention and Control

An agency of the European Union

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Dengue cases in Spain and France

In early October, 9 autochthonous cases of dengue were reported in the EU: 3 in Spain and 6 in France. The likelihood of onward local transmission into other areas in the EU/EEA with sustained local transmission is very low.

[Read the risk assessment](#) ▶

[Countdown to the European Antibiotic Awareness Day](#)

[Ebola outbreak in the DRC](#)

[Listeriosis outbreak linked to salmon](#)

[Dengue cases in Spain and France](#)

KEY POINTS

- Ask about travel in **every** patient who presents with fever
- **Travel history:** where, when, what?
- Patients with fever after tropical travel have **malaria** until proven otherwise
- Fever in returned travelers is often caused by common, cosmopolitan infections which should not be overlooked in the search for exotic diagnoses (zebras)



Extremely useful:

Online clinical decision-making tools:

- <http://www.fevertravel.ch/> (free)
- <https://www.gideononline.com/> (commercial)

Disease Outbreak News (DONs):

<http://www.who.int/csr/don/en/>

Others:

CDC: - <https://wwwnc.cdc.gov/travel/destinations/list/>

ITG: - <http://reisgeneeskunde.be>

Practice Guidelines for Evaluation of Fever in returning Travelers or Migrants

Version 2012

This website is targeted to health professionals only

In just a few clicks:

Get your own **differential diagnosis**
based on **your patient's destination and time of travel**
with a suggestion of investigations and attitudes!



CEPIC

Start



The screenshot shows the Gideon website interface for clinical decision-making. The top navigation bar includes 'gideon', a search box, and links for 'Ebooks', 'Updates', 'Content', and 'Help'. Below the navigation bar, there are tabs for 'Infectious Diseases', 'Microbiology', 'Travel', 'Drugs', and 'Vaccines'. The main content area is divided into several sections:

- Suggestions:** A list of checkboxes for clinical features such as 'Cultures positive', 'Severe (hospitalized, hemorrhagic fever, fatal, etc)', 'GI and intrabdominal - disease or dysfunction', and 'Icterion'.
- Clinical Presentation:** A section for entering patient details, including 'Country' (set to Central African Republic), 'Incubation Period (week)', 'Disease onset', 'Exposure began', 'Exposure ended', and 'Outbreak or case cluster'.
- Clinical Summary:** A summary of the entered data, including 'Country: Central African Republic', 'Fever', and 'The patient is an adult'.
- Diagnosis results:** A table listing various diseases with their associated probabilities and a 'Probability' column with a color-coded indicator (blue for high, green for medium, red for low).

Disease	Probability
Influenza	25%
Malaria	18%
Amebiasis	12%
Shigellosis	7%
Urinary tract infection	3%
Infectious mononucleosis or EBV infection	3%
Variola	2%
Amoebic abscess	2%
Babesiosis	2%
Erysipelas or cellulitis	2%
Enterovirus infection	1%
Gastroenteritis - viral	1%
Herpes simplex infection	1%
Mycoplasma pneumoniae infection	1%
Pharyngitis - bacterial	1%
Escherichia coli diarrhea	1%
Plasmodium - Sarcophila	1%
Herpes zoster	1%
Infection of wound, puncture, IV line, etc	1%
Campylobacteriosis	1%
Common cold	1%
Hepatitis A	1%
Pneumonia - bacterial	1%
Sinusitis	1%
Laryngotracheobronchitis	<1%
Leish	<1%
Septicemia - bacterial	<1%
HSV infection - initial illness	<1%
Tuberculosis	<1%
Rotavirus infection	<1%
Schistosomiasis - mansoni	<1%
Schistosomiasis - haematobium	<1%
Adenovirus infection	<1%

At the bottom, there are buttons for 'Compare', 'Why Not', and 'Diagnosis limitations'. The footer indicates 'Central African Republic note' and 'Bubonic note'.

Questions?



Thanks for your attention