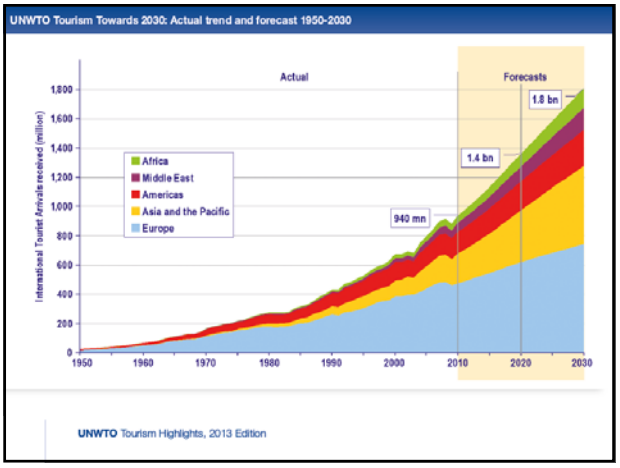
Fever after a stay in the Tropics

Bottieau Emmanuel, MD, PhD
Department of Clinical Sciences
Institute of Tropical Medicine
Antwerp, Belgium

Joint Symposium SBIMC/BVIKM – Scientific Study Group for Travel Medicine
Brussels, 24 October 2013

Outline

- Introduction
- Epidemiology of travel-related fever
- Update in the management of the main imported tropical conditions



Health problems in travelers “to the tropics”

- 15-65% experience some sickness
- 5-15% need to seek medical care
- 5-10% develop fever

Steffen et al. *J Infect Dis* 1987; **Hill.** *J Travel Med* 2000; **Cabada et al**. *Travel Med Infect Dis* 2009

Fever and travel: GeoSentinels studies

1996-2004
- 30 travel clinics
- 17,353 ill travelers

22.6% of consultations

Freedman et al. *N Engl J Med* 2006

2007-2011
- 53 travel clinics
- 42,173 ill travelers

23.3% of consultations

Leder K et al. *Ann Intern Med* 2013

5

Fever and travel

Differential diagnosis of imported fever

Keystone et al. Travel Medicine

Main causes of imported fever (%)

	ITMA, n=2071 Bottieau et al. *Medicine* 2007	GeoSentinel, n=6957 Wilson et al. *Clin Infect Dis* 2007
Malaria	27	21
Respiratory illness	10	14
Bacterial enteritis	6	8
Skin/soft tissue infection	4	4
Genito-urinary infection	3	4
Dengue	3	6
Enteric fever	1	2
Unknown etiology	23	22

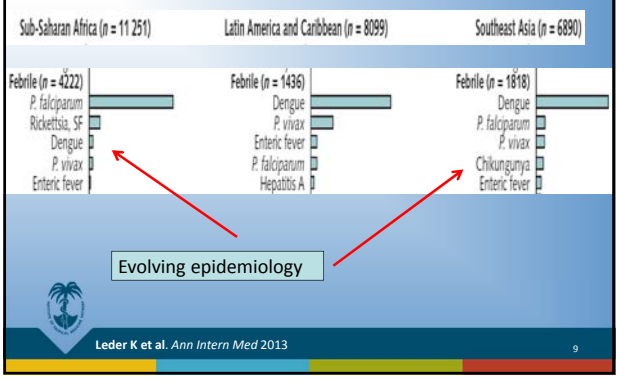
Top tropical conditions, ITMA 2000-2006

Africa (n=1401)	Asia (n=381)	America (n=146)
P.falciparum malaria (30%)	Dengue (13%)	
Non-falc. malaria (5%)	Non-falc. malaria (9%)	Dengue (9%)
Rickettsial infection (4%)	Enteric fever (3%)	Non-falc. malaria (4%)
Katayama (2%)	*P.falciparum* malaria (2%)	Protoz. enteritis (2%)

Bottieau et al. *Arch Intern Med* 2006; *Medicine* 2007

8

Top tropical conditions, GeoSentinel 2007-2011



Leder K et al. *Ann Intern Med* 2013

9

Tropical conditions (n,%) according to "latency"

	Within 1 month n=1619	During 2nd-3rd month n=228	From 4th to 12th month n=224
P. falciparum malaria	401 (25)	29 (13)	10 (4.5)
Non-falciparum malaria	34 (2)	41 (18)	38 (17)
Rickettsial infection	70 (4)	-	-
Dengue	64 (4)	-	-
Katayama	28 (2)	9 (4)	1 (0.5)
Enteric fever	15 (1)	1 (0.5)	-
Amebic liver abscess	8 (0.5)	1 (0.5)	1 (0.5)
Other tropical diseases	39 (3)	4 (2)	3 (1.5)

Bottieau et al. *Arch Intern Med* 2006; *Medicine* 2007

Main diagnoses (%) according to traveler demography

	Western travelers (n=1245)	Western Expatriates (n=300)	VFR travelers (n=286)	Foreign visitors/ migrants (n=240)
P.falciparum malaria	14	37	36	26
Non-falcip. malaria	6	7	3	8
Rickettsial infection	5	1	-	-
Dengue	4	2	1	-
Katayama	3	1	-	-
Bacterial enteritis	8	5	3	3
Tuberculosis	0.25	0	3	9
HIV infection, % tested	*6*	*6*	*14*	*40*

Less frequent febrile conditions, ITMA 2000-2006

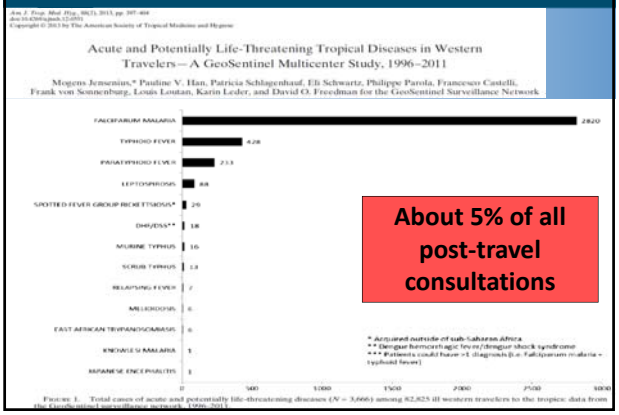
- Few cases
  - *Cyclospora* enteritis (7)
  - Histoplasmosis (6)
  - Leptospirosis (6)
  - Hepatitis E (4)
  - *Cryptosporidium* enteritis (4)
  - Loeffler syndrome (3)
  - Strongyloidiasis (3)
  - Human African trypanosomiasis (3)
  - Sarcocystosis (3)
- Single cases
  - Relapsing fever
  - *I. belli* enteritis
  - Angiostrongyloidiasis

12

Evolution and outcome, ITMA 2000-2006

- Hospitalization : 27% (n = 564)
- Intensive care : 2% (n = 43)
- Death : 0.5% (n = 9)
  - Tropical conditions = 5 (all *P. Falciparum* malaria)
  - Cosmopolitan infections = 2
  - Non-infectious diseases = 2
  - Fever of unknown etiology = 0

Severe tropical conditions: GeoSentinel


Acute and Potentially Life-Threatening Tropical Diseases in Western Travelers—A GeoSentinel Multicenter Study, 1996–2011

Mogens Jensenius,* Pauline V. Han, Patricia Schlagenhauf, Eli Schwartz, Philippe Parola, Francesco Castelli, Frank von Sonnenburg, Louis Loutan, Karin Leder, and David O. Freedman for the GeoSentinel Surveillance Network

FALCIPARUM MALARIA 2820
TYPHOID FEVER 428
PARATYPHOID FEVER 233
LEPTOSPIROSIS 88
SPOTTED FEVER GROUP RICKETTSIOSIS* 26
DHF/DSS** 18
MURINE TYPHUS 16
SCRUB TYPHUS 13
RELAPSING FEVER 7
MELIOIDOSIS 6
EAST AFRICAN TRYPANOSOMIASIS 6
KNOWLESI MALARIA 1
JAPANESE ENCEPHALITIS 1
0 500 1000 1500 2000 2500 3000

About 5% of all post-travel consultations

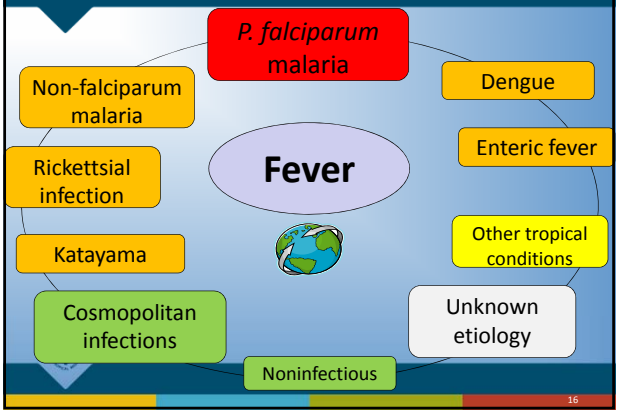
* Acquired outside of sub-Saharan Africa
** Dengue hemorrhagic fever/dengue shock syndrome
*** Patients could have >1 diagnosis [i.e. Falciparum malaria + typhoid fever]

FIGURE 1. Total cases of acute and potentially life-threatening diseases (*N* = 3,666) among 82,825 ill western travelers to the tropics; data from the GeoSentinel surveillance network, 1996–2011.

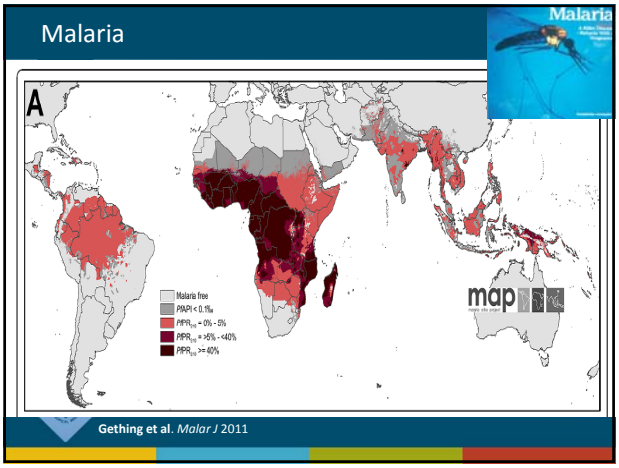
Epidemiology of imported fever: conclusions

- Both tropical and cosmopolitan infections
- Etiological spectrum depending on
  - Travel destination
  - Latency period
  - Traveler demography
- Considerable morbidity
- *P. falciparum* malaria is the leading life-threatening condition

Fever and travel: diagnostic panorama

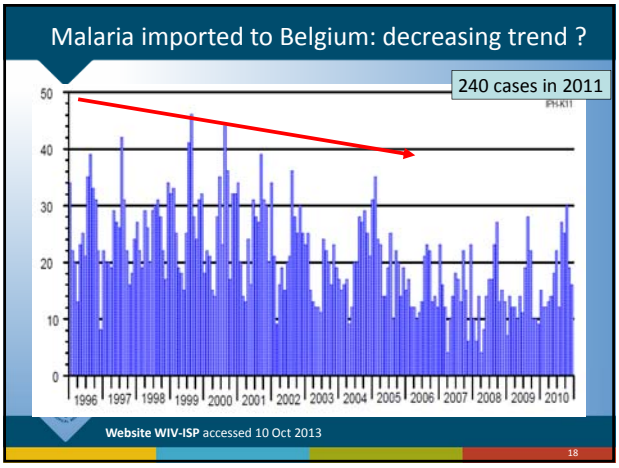


Malaria



Gething et al. *Malar J* 2011

Malaria imported to Belgium: decreasing trend ?



Website WIV-ISP accessed 10 Oct 2013

Malaria: clinical and laboratory predictors

Does This Patient Have Malaria?

Steve M. Taylor, MD, MPH
Malcolm E. Molyneux, MD, FRCP
David L. Simel, MD, MHS
Steven R. Meshnick, MD, PhD
Jonathan J. Juliano, MD, MSPH

Context Malaria commonly infects residents of and travelers to tropical regions. The clinical features of infection are notoriously nonspecific but have not been comprehensively evaluated.

Objective To systematically review and synthesize data related to the predictive value of clinical findings for the diagnosis of malaria in endemic areas and in travelers returning from endemic areas.

	LR+	95% CI
• Splenomegaly	6.5	(3.9-11.0)
• *No localizing symptoms*	*4.5*	-
• Hyperbilirubinemia	7.3	(5.5-9.6)
• Thrombocytopenia	5.6	(4.1-7.5)

Bottieau et al. *Medicine* 2007; Taylor SM et al. *JAMA* 2010

Malaria: progress in diagnosis

Microscopy

card

dipstick

hybrid

Rapid diagnostic test (RDT)

cassette

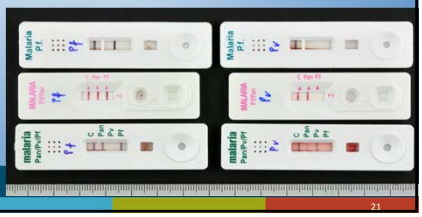
Malaria RDTs: multiple combinations

	HRP-2	pLDH	Aldolase
***P.falciparum*- specific**	+	+	
Pan-specific		+	+
***P.vivax*-specific**		+	

Two-band tests

Three-band tests

Four-band tests



Malaria RDTs in 2013: which one to choose?

Malaria RDTs: performance in 2013

- Accurate for diagnosis of (uncomplicated) *P. falciparum* malaria
  - Sensitivity > 95% at parasitemia > 100/µL; specificity > 95%
  - May replace microscopy in **ENDEMIC SETTINGS**
    - Abba K et al. *Cochrane Database Syst Rev* 2012
- Less accurate than EXPERT microscopy
- Equivalent to/better than ROUTINE microscopy
  - In endemic settings (Batwala *Malar J* 2010; Hendriksen *Clin Infect Dis* 2011)
  - In US hospitals (Palmer *J Clin Microbiol* 2003; Stauffer *Clin Infect Dis* 2009)

Malaria RDTs: limitations in accuracy

False negative

- Low *P. falciparum* parasitemia
- Plasmodium other than *P. falciparum*
- High *P. falciparum* parasitemia (prozone); only HRP-2
- *P. falciparum* with *pfhrp2 or 3* gene deletions; only HRP-2
- Faint test line…

False positive

- Persistence HRP-2
- Delayed reading
- Buffer substitution
- Cross reactions between species
- Concomittant conditions

Maltha J et al. *Clin Microbiol Infect* 2013

Malaria RDTs in travel medicine

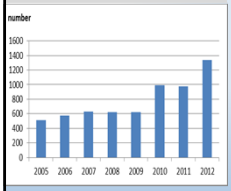
- ALWAYS perform both RDT AND microscopy
  - If RDT negative and no malaria predictor, microscopy may be delayed
    - Rossi et al. *Malar J* 2012
  - If RDT positive, microscopy immediately
    - Parasite load; species differentiation
  - If both tests negative
    - Repeat RDT/microscopy within 12-24h especially if presence of malaria predictors (Bottieau. *Eur J Clin Microbiol Infect Dis* 2006)
- Self/peer testing during travel ?
  - Need of safety studies

Dengue

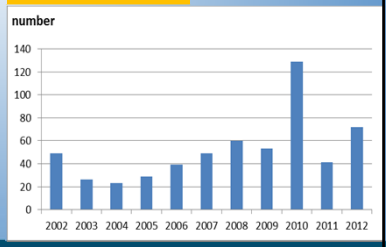
Dengue, countries or areas at risk, 2010

Dengue in Belgium (2005-2012)

Performed tests



Positive results



Courtesy Dr Van Esbroeck M. CLKB, ITM Antwerp 2013

Dengue (n=64): clinical and laboratory predictors

	Adjusted LR+
• Leucopenia (< 4000/µL)	3.3
• Skin rash	2.8
• Thrombocytopenia (150,000/µL)	2.0

Bottieau et al. *Medicine* 2007

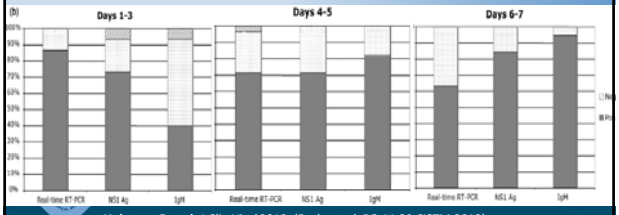
Dengue: RDTs for diagnosis

		Sensitivity
RDT IgM/IgG		70-80%
RDT NS1 Ag		50-75%
Dengue Duo Rapid Test Dengue Ag NS1 Dengue IgG/IgM		> 90%

Blacksell SD et al. *Clin Vaccin Immunol* 2011; **Chappuis et al.** *Clin Microbiol Infect.* 2013

Dengue: early diagnosis with NS1 Ag in travelers

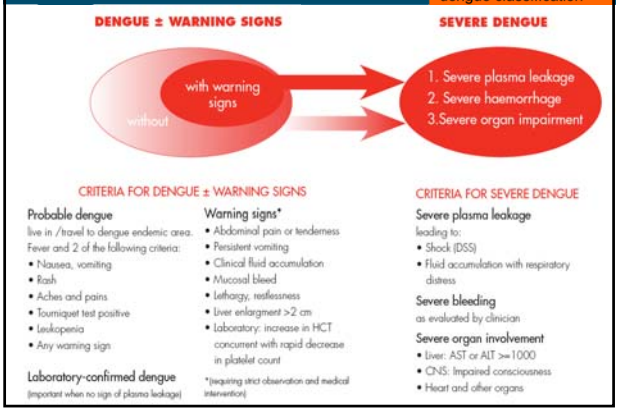
- Study on 99 early phase serum samples of dengue patients seen at Helsinki
- Evaluated against conventional RT-PCR and virus isolation



Huhtamo E et al. *J Clin Virol* 2010; (Fuchs et al. PO 11.20 CISTM 2013)

Dengue: management

The 2009 revised WHO dengue classification



Rickettsial infection in travelers

	ITMA, n=70 2000-2006 Bottieau *Medicine* 2007	GeoSentinel, n=261 1996-2008 Jensenius *Emerg Infect Dis* 2009
Spotted fever group *(R. africae, R. conorii,…)* **Tick-borne** 	63 (90%)	231 (88%)
Typhus group *(R. typhi)* **Flea-borne** 	4	10
Orientia tsutsugamushi **Mite-borne** 	3	16
Others/indeterminate	-	4

Rickettsial infection: predictors

	Adjusted LR+
• Skin ulcers	11.1
• Skin rash	3.8

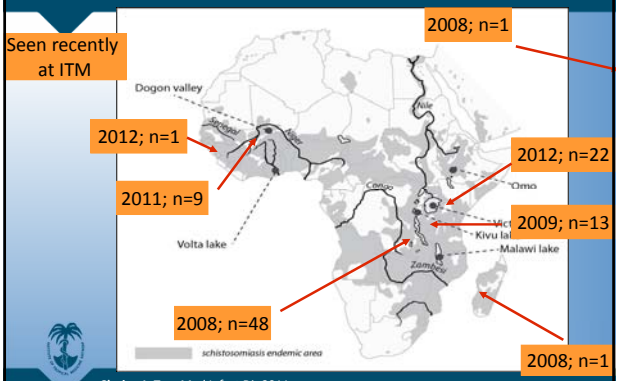
Bottieau et al. *Medicine* 2007

Rickettsial infection (n=70): diagnosis

- Most of the time clinical
- (Paired serology)
- PCR on eschar, (blood)

34

Acute schistosomiasis (Katayama) and travel



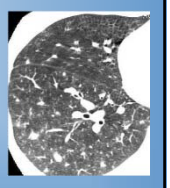
Clerinx J. *Trav Med Infect Dis* 2011

35

Katayama (n=38): predictor

	Adjusted LR+	Adjusted LR-
• Eosinophil count > 500/µL)	32	0.06





Bottieau et al. *Medicine* 2007

Katayama: diagnosis


Journal of TRAVEL MEDICINE

ORIGINAL ARTICLES

Acute Schistosomiasis in a Cluster of Travelers From Rwanda: Diagnostic Contribution of Schistosome DNA Detection in Serum Compared to Parasitology and Serology

RESEARCH ARTICLE Open Access

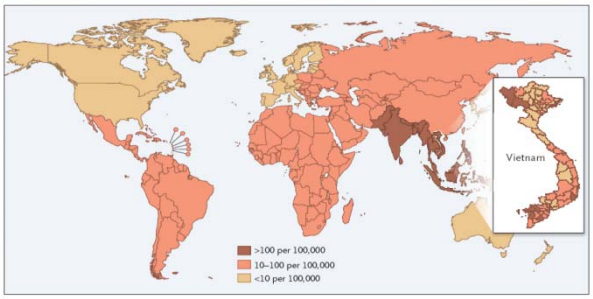
Prospective European-wide multicentre study on a blood based real-time PCR for the diagnosis of acute schistosomiasis

	n=13	n=37
•Egg detection:	69%	25%
•Serology:	77%	72%
•Serology AND egg detection:	85%	
•**Serum *Schistosoma* DNA (PCR):**	**100%**	**95%**

Clerinx J et al. *J Trav Med* 2011; **Wichmann D et al.** *BMC Infect Dis* 2013

37

Enteric fever (*Salmonella* Typhi and Paratyphi A).



Mean Annual Incidence of Typhoid Fever per 100,000 Persons.

Country-specific incidence rates, some of which are estimates, are for 2000. Province-specific incidence rates for Vietnam are for children 5 to 14 years of age, between 1999 and 2003 (inset). Country data are from Crump et al.[2] Provincial data for Vietnam are from a meta-analysis conducted by the DOMI Program.

DeRoeck D et al. *N Engl J Med* 2007; **Crump JA et al.** *Bull World Health Organ* 2004

38

Enteric fever (n=16): predictors

	Adjusted LR+
• Splenomegaly	10.0
• Elevated transaminases (ALT > 70 IU/L)	2.5

Bottieau et al. *Medicine* 2007

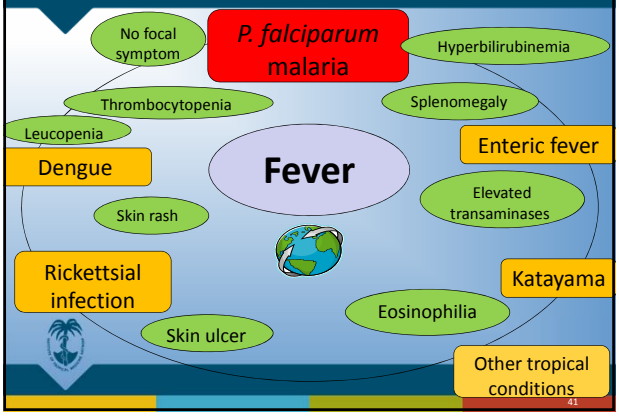
Enteric fever in Belgium (2011)

- *S.* Typhi (n=25) and *S.* Paratyphi A (n=6)
- Resistance to nalidixic acid ("decreased cipro susceptibility": MIC>0.064 mg/ml)
  - *S.* Typhi: 33%
  - *S.* Paratyphi A: 50%
- Resistance to ciprofloxacine (MIC>1 mg/ml): 3%

WIV/ISP National Reference Centre. Annual Report 2011

40

Fever and travel: diagnostic panorama



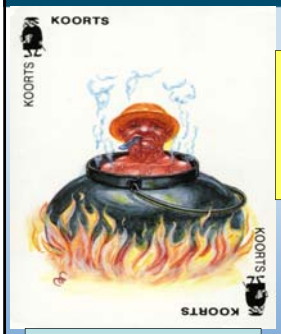
41

Website ITG/IMT - NRC/CNR

http://www.itg.be

https://nrchm.wiv-isp.be/default.aspx

Thank you for your attention



Interesting websites/diagnostic aids

- GIDEON at www.gideononline.com
- FEVERTRAVEL at www.fevertravel.ch
- KABISA TRAVEL at www.kabisa.be

Van Den Ende J. KABISA