Fever in travellers from India and South East Asia

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Plan

• General epidemiology
• Clinico-epidemiology of
  – Malaria
  – Enteric fever
  – Dengue
  – Chikungunya
• Conclusions
Incidence/month of health problems during a stay in developing countries – 2005

- Traveler’s diarrhea: 30 - 80%
- ETEC diarrhea: 10%
- Malaria (no chemoprophylaxis West Africa): 1%
- Influenza A or B: 1%
- PPD conversion: 0.1%
- Dengue infection (SE-Asia): 0.1%
- Animal bite with rabies risk: 0.01%
- Typhoid (South Asia, e.g. India): 0.01%
- Hepatitis B (expatriates): 0.01%
- Typhoid (other areas): 0.001%
- Legionella infection: 0.001%
- Cholera: 0.0001%
- Meningococcal disease: 0.0001%

Steffen R NECTM 2006
Incidence/month of health problems during a stay in developing countries – 2005

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- Hepatitis B (Africa, South America): 0.01%
- HIV-infection: 0.001%
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- Cholera: 0.0001%
- Meningococcal disease: 0.0001%
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- Legionella infection: 0.0001%
- Cholera: 0.0001%
- Meningococcal disease: 0.0001%

Steffen R
NECTM 2006
# Aetiology of travellers’ fever

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study 1 (n=587)</th>
<th>Study 2 (n=195)</th>
<th>Study 3 (n=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria %</td>
<td>32</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>25</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>11</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhoeal illness</td>
<td>5</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

3. O’Brien D *et al*, *Clin Inf Dis* 2001; 33: 603-609
English units 1998-9

4 centres 390/421 adult travel admissions infectious cause

93% UK domiciled
2918 bed days (21 ITU)

**Malaria** 20% bed days & 80% ITU stay (29% all cases)
Median length of stay 4 days

W Africa 39/65 (59%) malaria OR 5.22
E Africa 44/72 (61%) malaria OR 5.82
S Asia 8/82 (10%) malaria OR 0.21

Harling R et al. *J Infect* 2004; 48: 139-144
Factors in imported disease

- Changes in travel & immigration
- Changes in vectors
- Changes in behaviour
- Changes in host
- Eg immunosuppressed & leishmaniasis
- Risk avoidance
  - Bite avoidance
  - Vaccines
GeoSentinel fever (n=6957)

28% of 24,920 travellers 1997-2006

Wilson M et al. CID 2007;44:1560-8
GeoSentinel fever (n=6957)

South Central Asia 882

Wilson M et al. CID 2007;44:1560-8
GeoSentinel fever (n=6957)

Southeast Asia 1218

Wilson M et al. CID 2007;44:1560-8
GeoSentinel fever study \( n = 6957 \)

<table>
<thead>
<tr>
<th>Region</th>
<th>Fever</th>
<th>Mal</th>
<th>DEN</th>
<th>No diag</th>
<th>Resp</th>
<th>Diarrh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oceania</td>
<td>51</td>
<td>59</td>
<td>6</td>
<td>12</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>SS Africa</td>
<td>41</td>
<td>42</td>
<td>1</td>
<td>19</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>SE Asia</td>
<td>33</td>
<td>7</td>
<td>18</td>
<td>22</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>SC Asia</td>
<td>27</td>
<td>7</td>
<td>9</td>
<td>20</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>N Asia</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>26</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>N Africa</td>
<td>22</td>
<td>5</td>
<td>1</td>
<td>13</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>All</td>
<td>21</td>
<td>6</td>
<td></td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Figures are % of travellers returning from each region.

Wilson M et al. *CID* 2007;44:1560-8
Figure 1. Proportion (%) of different categories of returned patients among 17,228 patients seen in GeoSentinel sites in Europe,*

Travel behaviour
Eco-Challenge 2000
Multisport event

Sejvar J et al. EID
2003; 9: 702-7
Leptospirosis
reports from GeoSentinel & Idaho & LA Depts Health

*L. weilii*

189/304 (62%) athletes contacted

80/189 (42%) met case definition
Leptospirosis

White water rafting

Meningitis

Jaundice

Renal failure
Slide withheld at request of author
Thai imports - rash & fever
Thai imports - rash & fever

- HIV seroconversion
- Secondary syphilis
Slide withheld at request of author
Malaria is present in the countries listed. You can catch it on a short visit or on a stopover. Even if you used to live abroad you may have lost immunity.

Protect yourself by taking anti-malarial tablets before and during your stay abroad and for one month after your return home.

Tablets available from chemists and on some aircraft.
52 year old woman with fever, dyspnoea and headache after holiday in Goa in Oct 2006

Travelled with husband for 14 days
Air conditioned hotel in Candolim
last 2 weeks of October 2006
Used Mosiguard natural repellent
Took chloroquine/proguanil until 1 week after return (nausea)
Visited Dudhsagar falls on border with Karnataka State
Falciparum malaria

9 days after return became ill
Admitted to hospital 4 days later

Severe falciparum malaria
– Pneumonia
– DIC
– Moderate hepatitis

17 days in hospital with 9 days in intensive care

Full recovery
23 year old woman

Candolim & Dudhsagar falls with husband
4-18 Nov 2006
Bed & breakfast
Both:
  Used DEET
  Full CQ/P prophylaxis
She had few mosquito bites, he had many
Fever end of March 2006
Progress

Hospital after 4 days
Temp 39.5° C
Nil else

Hb 12.5 g/dL
WBC 4.5 x 10⁹/L
Platelets 105 x 10⁹/L
Bilirubin 25 mmol/L (<18)
AST 43 U/L (<40)

Blood film shows:
FIGURE 6: Cases of malaria in the UK by interval between arrival in the UK and diagnosis of malaria: 2003

- <1 month
- 1-5 months
- 6-12 months
- >1 year

% of cases

Malaria parasite species

P. falciparum
P. vivax
P. malariae
P. ovale

Health Protection Agency

NaTHNaC National Travel Health Network and Centre
Progress

Treated with chloroquine 1.5 g over 3 days

Rapidly improved

Glucose 6 phosphate dehydrogenase normal

Primaquine: 30mg per day for 2 weeks started at same time as chloroquine (0.5 mg/kg)

Lalloo DG et al. (UK guidelines) J Infect 2007; 54(2): 111-21
Figure: Life cycle of the human malaria parasite Plasmodium vivax

Case 3. 26 year old husband

Had been admitted to another hospital in late January (two weeks of symptoms) Quite ill with vivax malaria Treated with full dose chloroquine and primaquine 30mg/day for 14 days

Readmitted May 2006 with confirmed vivax malaria (1 day symptoms) Weight 92 kg Retreated with chloroquine 1.5 g and primaquine 45mg daily for 14 days
Malaria in Goa

Previously endemic
Risk assessment last 10 years – low risk for tourists so chemoprophylaxis not usually advised

Heavy rains Oct 2006
Falciparum cases in European travellers especially from Candolim area north of capital Panaji

Expect more cases of vivax
Chemoprophylaxis now advised
Rapid communications

CONTINUING IMPORTATION OF FALCIPARUM MALARIA FROM GOA INTO EUROPE

T Jelinek (jelinek@bctropen.de), on behalf of the European Network on Imported Infectious Disease Surveillance (TropNetEurop)
1. Berlin Center for Travel & Tropical Medicine, Berlin, Germany

A case of falciparum malaria acquired in Goa, India, has recently been reported to the European Network on Imported Infectious Disease Surveillance (TropNetEurop, http://www.tropnet.net). The report relates to a Swedish woman in her fifties who had spent two weeks in Goa (Candolim beach) and Kerala in India without taking malaria chemoprophylaxis. In mid-December 2007, approximately two weeks after returning to Sweden, she fell ill with fever and a mild cough. Ten days after the onset of symptoms, thick and thin films were done and an infection with Plasmodium falciparum with a parasitaemia of 1.8% was diagnosed. The patient was admitted to hospital, uneventfully treated with a standard dose of mefloquine and discharged four days later.

Life-threatening illness. The diagnosis can only be made if a careful travel history is taken, and testing done early, even for regions where malaria is not normally recognised.

References

Figure 1. Trends of malaria incidence in India from 1960 to 2005. Nearing eradication in 1960s (< 100,000 cases) to resurgence in the mid-1970s (~6.4 million cases) and stabilizing trend to ~2 million cases.
### Malaria by continent, 1992-3

<table>
<thead>
<tr>
<th></th>
<th>Falciparum</th>
<th>Vivax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2216</td>
<td>5%</td>
</tr>
<tr>
<td>Asia</td>
<td>1065</td>
<td>89%</td>
</tr>
</tbody>
</table>

- **Falciparum**: 81% in Africa, 9% in Asia
- **Vivax**: 5% in Africa, 89% in Asia

*Malaria Reference Laboratory*
New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance

Ric N. Price\textsuperscript{a,b,c}, Nicholas M. Douglas\textsuperscript{a,c} and Nicholas M. Anstey\textsuperscript{a,b}

\textsuperscript{a}International Health Division, Menzies School of Health Research and Charles Darwin University, \textsuperscript{b}Division of Medicine, Royal Darwin Hospital, Darwin, Australia and \textsuperscript{c}Nuffield Department of Clinical Medicine, Centre for Clinical Vaccinology and Tropical Medicine, John Radcliffe Hospital, Oxford, UK

Correspondence to Dr Ric N. Price, Menzies School of Health Research, PO Box 41096, Casuarina, Darwin NT 0811, Australia
Tel: +61 8 8922 8197; fax: +61 8 8922 8429; e-mail: rnp@menzies.edu.au

Current Opinion in Infectious Diseases 2009, 22:430–435

\textbf{Purpose of review}

Unlike *Plasmodium falciparum*, *Plasmodium vivax* rarely causes severe disease in healthy travellers or in temperate endemic regions and has been regarded as readily treatable with chloroquine. However, in tropical areas, recent reports have highlighted severe and fatal disease associated with *P. vivax* infection. We review the evidence for severe disease and the spread of drug-resistant *P. vivax* and speculate how these may be related.

\textbf{Recent findings}

Studies from Indonesia, Papua New Guinea, Thailand and India have shown that 21–27\% of patients with severe malaria have *P. vivax* monoinfection. The clinical spectrum of these cases is broad with an overall mortality of 0.8–1.6\%. Major manifestations include severe anaemia and respiratory distress, with infants being particularly vulnerable. Most reports of severe and fatal vivax malaria come from endemic regions where populations have limited access to healthcare, a high prevalence of comorbidity and where drug-resistant *P. vivax* strains and partially effective primaquine regimens significantly undermine the radical cure and control of this relapsing infection. The mechanisms underlying severe disease in vivax malaria remain poorly defined.

\textbf{Summary}

Severe, fatal and multidrug-resistant vivax malaria challenge our perception of *P. vivax* as a benign disease. Strategies to understand and address these phenomena are needed urgently if the global elimination of malaria is to succeed.
Trends Parasitol 2008; 24: 406-10

Knowlesi malaria: newly emergent and of public health importance?

Janet Cox-Singh and Balbir Singh
Malaria Research Centre, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, 93150 Kuching, Sarawak, Malaysia

Macaque monkeys An. luecosphyrus
Malariotherapy for syphilis
1965 first natural human infection

Figure 5: Long tailed macaque (Macaca fascicularis)
Philippines
Simian Malaria in a U.S. Traveler --- New York, 2008

EID 2008;14(9):1434-6

ESCMID Online Lecture Library © by author

Monkey Malaria in a European Traveler Returning from Malaysia

Anu Kantele, Hanspeter Marti, Ingrid Felger, Dania Müller, and T. Sakari Jokiranta

In 2007, a Finnish traveler was infected in Peninsular Malaysia with Plasmodium knowlesi, a parasite that usually causes malaria in monkeys. *P. knowlesi* has established itself as the fifth *Plasmodium* species that can cause human malaria. The disease is potentially life-threatening in humans; clinicians and laboratory personnel should become more aware of this pathogen in travelers.

EID 2010;16(4):672-4

Plasmodium knowlesi in Human, Indonesian Borneo

Melanie Figtree, Rogan Lee, Lisa Bain, Tom Kennedy, Sonia Mackertich, Merrill Urban, Qin Cheng, and Bernard J. Hudson

*Plasmodium knowlesi* is now established as the fifth *Plasmodium* species to cause malaria in humans. We describe a case of *P. knowlesi* infection acquired in Indonesian Borneo that was imported into Australia. Clinicians need to consider this diagnosis in a patient who has acquired malaria in forest areas of Southeast Asia.
Cox-Singh J, Singh B. *Trends Parasitol* 2008; 24: 406-10
Clinical pointers

- Exposure to forest in Malaysia etc
- Daily fever (quotidien)
- Marked thrombocytopenia
- High parasitaemia
- Looks like *P. malariae* (need PCR)
- May be severe clinically
- Responds to chloroquine
- Primaquine not needed
Typhoid incidence

Most typhoid in USA is imported


*Figure 2*: Trends in incidence of typhoid fever in the USA and the proportion of cases of typhoid fever attributed to travel
Risk to travellers

Cases per million US travellers

**Americas**
- Mexico: 29-34
- Haiti: 29

**Asia**
- Pakistan: 481
- India: 318-415

**Africa**: 45-72

**Europe**: 1.5-2.5

Pilot of enhanced surveillance of enteric fever in England, Wales, and Northern Ireland

1 May 2006 – 30 April 2007
Summary data

- 406 cases
  - S typhi 203
  - S paratyphi A 198
  - S paratyphi B 5

- Travel related 94.2% (73% from UK)

- Risk per 100 000 visits overseas
  - ISC 17.32
  - Rest of world 0.05
Figure 5. Ethnicity for enteric fever cases (N=355)

- Indian: 43.7%
- Pakistani: 30.4%
- White: 11.3%
- Bangladesh: 5.9%
- Black African: 5.4%
- Other: 3.1%
## Risk by country & VFR

<table>
<thead>
<tr>
<th>Predominant</th>
<th>Bangladesh</th>
<th>India</th>
<th>Pakistan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhi</td>
<td>RR</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Paratyphi A</td>
<td>RR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VFR RR vs other</th>
<th>Bangladesh</th>
<th>India</th>
<th>Pakistan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.52</td>
<td>8.62</td>
<td>3.22</td>
</tr>
</tbody>
</table>
Chloramphenicol

Ampicillin/amoxicillin

Trimethoprim-sulfamethoxazole

Plasmid mediated multi-drug resistance to these = Multidrug Resistance (MDR)
Ciprofloxacin Treatment Failure in Typhoid Fever Case, Pakistan

Tariq Butt,* Rifat Nadeem Ahmad,* Abid Mahmood,* and Sabeen Zaidi*

We report a case of ciprofloxacin treatment failure in a typhoid fever patient at a tertiary care hospital in Rawalpindi, Pakistan. This case shows not only the emergence of fluoroquinolone resistance in typhoid salmonellae but also the inadequacy of the current laboratory guidelines for detection of this resistance.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 9, No. 12, December 2003
Dushanbe, Tadjikistan 1997

- January – June 1997
- 8901 cases of typhoid fever
- 95 deaths (1%)
- 93% MDR and Nalidixic R (NAR)
- Contaminated municipal water supply

Mermin et al. JID 1999;179:1416
Nalidixic acid resistant (NAR) S typhi

<table>
<thead>
<tr>
<th>Country</th>
<th>Proportion of NAR strains</th>
<th>% patients who failed on fluoroquinolone treatment</th>
<th>% cases with faecal carriage during early convalescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>23% (42/179)</td>
<td>24% (10/42)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Canada</td>
<td>33% (7/21)</td>
<td>80% (4/5)</td>
<td>Not reported</td>
</tr>
<tr>
<td>India</td>
<td>47% (82/174)</td>
<td>27% (22/82)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Vietnam</td>
<td>9% (46/504)</td>
<td>24%* (11/46)</td>
<td>21%† (8/39)</td>
</tr>
</tbody>
</table>

*By comparison, 5% (22/458) of nalidixic-acid-sensitive strains had clinical failure on ofloxacin. †By comparison, 2% (7/383) of nalidixic-acid-sensitive strains had faecal carriage during early convalescence.

Table 4: Key features of nalidixic-acid-resistant (NAR) strains of S typhi

NAR/FQ resistance correlates with clinical failure

Typhoid drug resistance

Figure: Global distribution of antimicrobial resistance in Typhi (1990–2004)
Adapted from Parry and colleagues and updated on basis of data from past 3 years.

Molecular characterization of ciprofloxacin-resistant *Salmonella enterica* serovar Typhi and Paratyphi A causing enteric fever in India

R. Gaind¹, B. Paglietti², M. Murgia², R. Dawar¹, S. Uzzau², P. Cappuccinelli³, M. Deb¹, P. Aggarwal¹ and S. Rubino²*

¹Department of Microbiology, Safdarjung Hospital and Assoc VMMC, New Delhi, India;
²Department of Biomedical Sciences, Division of Experimental and Clinical Microbiology, University of Sassari, Sassari, Italy

Received 7 April 2006; returned 26 July 2006; revised 20 August 2006; accepted 6 September 2006
Treatment options MDR strains

- Fluoroquinolones - rapid response, resistance
  - new eg gatifloxacin?
- Cephalosporins - slow response
- Azithromycin - effective, less carriage
- Imipenem
- Aztreonam
- Combinations - more to protect new agents
- Tigecycline? - Pongratz P Abstract 1230
Vectors

Figure 1: Mosquito vectors of chikungunya virus
(A) Blood-gorged *A. albopictus* female feeding on a human host. *A. albopictus* is the primary chikungunya virus vector in the current Indian Ocean outbreak. (B) *A. aegypti* mosquito. *A. aegypti* is the primary chikungunya virus vector in Asian chikungunya outbreaks. Images from United States Department of Agriculture.

Dengue

- Most important and commonest ARBOvirus (RNA flavivirus)
- No significant animal reservoir
- Found mainly in Asia, also in South/Central America and Africa
- 4 antigenic varieties of virus
- Carried by Aedes mosquitoes
- Female day biter
- Breeding in stagnant water
• Dengue from Vietnam
• Jan 2008
• Convulsion in plane home
• Fever & rash
Presence of dengue worldwide and areas infested by the main vector, *Aedes aegypti*
Dengue source in 282 Europe domiciled travellers (%)

Jelinek T et al. CID 2002; 35:1047–52

Figure 1. Geographical regions where dengue fever was acquired by 282 travelers living in Europe. Data are percentages.
Dengue incidence in travellers

• Israeli travellers 6.7% seroconvert after 3/12 in tropics
  
  Potasman *EID* 1999; 5: 824-71

• Dutch travellers to Asia 1 month 2.9%
  
  Cobelens FG. *TMIH* 2002; 7: 331-8

• Australian 4/324 (1.2%) = 4.17 (CI 1.7-10.7) per 10,000 travel days
  
  Ratnam I et al Oral O46 ECCMID 2010

• 4% had prior exposure
Figure 3. Seasonality of dengue in returned travelers by region. Dengue in returned travelers is shown as a proportion of monthly morbidity in all ill returned travelers to each region. Horizontal
Dengue models - Singapore

Figure 1  Force of infection from 2002 to 2005.

# Dengue models - Singapore

## Table 1  Risk in percentages (per 100,000) of dengue acquisition for low and high season*

<table>
<thead>
<tr>
<th>Time</th>
<th>Low 2002</th>
<th>High 2002</th>
<th>Low 2003</th>
<th>High 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wk</td>
<td>0.0043 (4.23)</td>
<td>0.0124 (12.4)</td>
<td>0.00735 (7.35)</td>
<td>0.0305 (30.5)</td>
</tr>
<tr>
<td>1 mo</td>
<td>0.0144 (14.4)</td>
<td>0.049 (49)</td>
<td>0.0373 (37.3)</td>
<td>0.151 (151)</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.0858 (85.8)</td>
<td>0.235 (23.5)</td>
<td>0.328 (32.8)</td>
<td>0.584 (584)</td>
</tr>
<tr>
<td>1 y</td>
<td>6.569 (656.9)</td>
<td>6.794 (679.4)</td>
<td>4.93 (493)</td>
<td>1.83 (183)</td>
</tr>
<tr>
<td>2 y</td>
<td>1.28 (1,280)</td>
<td>2.6 (2,600)</td>
<td>3.51 (3,510)</td>
<td>6.09 (6,090)</td>
</tr>
<tr>
<td>3 y</td>
<td>3.53 (3,530)</td>
<td>6.84 (6,840)</td>
<td>8.0 (8,000)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Low 2005</th>
<th>High 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wk</td>
<td>0.0429 (42.9)</td>
<td>0.17 (170)</td>
</tr>
<tr>
<td>1 mo</td>
<td>0.218 (218)</td>
<td>0.413 (413)</td>
</tr>
<tr>
<td>6 mo</td>
<td>1.89 (1,890)</td>
<td>4.57 (4,570)</td>
</tr>
</tbody>
</table>

*Assuming a ratio of 10:1 for asymptomatic to symptomatic cases.

---

WHO dengue classification

Figure 1. World Health Organization classification of dengue virus infections
## Predictors for severe dengue

**Table 5.** Laboratory values and other factors associated with spontaneous bleeding and other severe clinical manifestations in 176 travelers with dengue virus infections.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Spontaneous bleeding&lt;sup&gt;a&lt;/sup&gt; (n = 17)</th>
<th>Severe clinical manifestations&lt;sup&gt;b&lt;/sup&gt; (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis, OR (95% CI)</td>
<td>Multivariate analysis, OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low platelet count (&lt;100,000 cells/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>3.1 (0.95–10.7)</td>
<td>NS</td>
</tr>
<tr>
<td>AST increase (~3-fold)</td>
<td>3.5 (1.1–11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>ALT increase (~3-fold)</td>
<td>3.3 (1.1–10.4)</td>
<td>5.4 (1.3–21.3)</td>
</tr>
<tr>
<td>Non-European origin</td>
<td>3.7 (0.9–15.2)</td>
<td>6.4 (1.3–32.3)</td>
</tr>
<tr>
<td>Secondary immune response</td>
<td>5.3 (1.4–20.8)</td>
<td>3.9 (1.04–14.5)</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>4.9 (0.6–107.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** In multivariate analysis, odds ratios (ORs) are adjusted for age and sex. Bold type indicates significant results. ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; CI, confidence interval; LDH, lactate dehydrogenase; NS, not significant.

<sup>a</sup> Defined as bleeding from nose/gums, ecchymosis, or internal hemorrhage (bleeding from the gastrointestinal tract or hypermenorrhea).

<sup>b</sup> Defined as the presence of internal hemorrhage, signs of plasma leakage, shock, and/or platelet count ≤50,000 cells/mm<sup>3</sup>. Because a very low platelet count was used in the definition, the variable was not included in the logistic regression model.
50 year old woman with fever, rash and chest pain from Mauritius in March 2006

2 week holiday in Mauritius returned 4 days ago
Injured leg and admitted to hospital on day 9 for antibiotics
Many patients on ward with fever
No mosquito bites remembered
4 days later fever and headache for 3 days
Improved as flew back to UK
Full immunisations, no malaria chemoprophylaxis
Now has 2 days of

Fever to 39°C
Migratory joint pains
Headache
Photophobia
Rash
Pleuritic chest pain

Temp 38.9°C  P100
BP 120/85  RR 12
Discrete rash on legs
Chest clear
No neck stiffness
Joints normal
Investigations

Hb 11.0 g/dL (>11.5)
WBC 6.1 x 10⁹/L
  Lymph 0.6 (1.5-4)
  Mono 0.2 (0.2-0.8)
  Neut 5.2 (2-7.5)
Plt 270 x 10⁹/L (>150)
ESR 12 mm/hr

Malaria smears neg
Liver function normal
CXR normal
Initial diagnosis & progress

• **Concern about meningococcal disease**
  - CT of head normal
  - Given ceftriaxone
  - No lumbar puncture
  - Transferred to Liverpool

• **Diagnosis presumed chikungunya**
  - Pulmonary embolus excluded by VQ scan

# Clinical features - CHIK

<table>
<thead>
<tr>
<th></th>
<th>Malaysia 1998 (%)</th>
<th>Réunion 2005-Feb 2006 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Myalgia</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Headache, spinal pain</td>
<td>50, 50</td>
<td>70, NR</td>
</tr>
<tr>
<td>Arthralgia (all types)</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Large joints</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Fever</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Number of reported cases</td>
<td>51</td>
<td>504</td>
</tr>
</tbody>
</table>

NR = not reported. Data for Malaysia from Lam and colleagues (2001) and data for Réunion from http://www.invs.sante.fr.

*Table: Frequency of clinical manifestations during the 1998 Malaysian epidemic and the 2005 Réunion epidemic*
Fever & exanthems: differences

Clinical manifestations of chikungunya and dengue infections in returned travelers

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Chikungunya (22 cases)</th>
<th>Dengue (16 cases)</th>
<th>Significance (P)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Cephalalgia</td>
<td>9 (41)</td>
<td>11 (69)</td>
<td>0.087</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15 (68)</td>
<td>13 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (32)</td>
<td>8 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22 (100)</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (48)</td>
<td>5 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>14 (64)</td>
<td>7 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>Macular exanthema</td>
<td>16 (73)</td>
<td>13 (81)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* NS, nonsignificant.

### Fever & exanthems: differences

<table>
<thead>
<tr>
<th>Biological finding</th>
<th>Chikungunya (22 cases) N (%)</th>
<th>Dengue (16 cases) N (%)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>8 (40)</td>
<td>12 (75)</td>
<td>0.033</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (10)</td>
<td>13 (81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18 (90)</td>
<td>9 (56)</td>
<td>0.049</td>
</tr>
<tr>
<td>Circulating lymphocytosis</td>
<td>6 (30)</td>
<td>5 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (15)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Thrombopenia</strong></td>
<td>7 (35)</td>
<td>14 (88)</td>
<td>0.002</td>
</tr>
<tr>
<td>Increased ALAT*</td>
<td>13 (65)</td>
<td>14 (88)</td>
<td>NS</td>
</tr>
<tr>
<td>Increased CRP†</td>
<td>9 (64)</td>
<td>10 (77)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* ALAT, alanine aminotransferase.
† CRP, C-reactive protein.

Progress

6 weeks later
Severe fatigue
Mild joint pain
Sore leg wound – osteomyelitis excluded

3 months later
Improving
Compensated by travel health insurance

Serology
Positive IgM & IgG for chikungunya
Epidemiology

- Tanzania 1953
- Asia
- West Africa

- Réunion, Mauritius etc from 2000
- 1.5M visitors in 2004
- UK importations >130 in 2006

Figure 2: Chikungunya and dengue incidence in India and Indian Ocean Status as of March 17, 2006. Data from WHO, http://www.who.int.

Figure 3: Chikungunya cases in Réunion and imported cases into metropolitan France, April 2005–December 2006
Weekly notifications based on an estimated mathematical extrapolation (http://www.invs.sante.fr and reference 52) and imported cases in France.
India—Nasik district/Malegaon town
>2000 suspected chikungunya cases

India—Orissa state
4904 suspected cases

India—Andhra Pradesh state
5761 suspected chikungunya cases

Maldives
602 suspected dengue cases

Seychelles
6099 suspected chikungunya cases

Mayotte

Legend:
- Pink: Country with occurrence of dengue and/or chikungunya
- Red: Affected areas
- Green: Country
Reemergence of Dengue in Mauritius

Mohammad I. Issack, Vidula N. Pursem, Timothy M. S. Barkham, Lee-Ching Ng, Masafumi Inoue, and Shyam S. Manraj

Dengue reemerged in Mauritius in 2009 after an absence of >30 years, and >200 cases were confirmed serologically. Molecular studies showed that the outbreak was caused by dengue virus type 2. Phylogenetic analysis of the envelope gene identified 2 clades of the virus. No case of hemorrhagic fever was recorded.

EID April 2010; 16(4): 716-8
The arrival, establishment and spread of exotic diseases: patterns and predictions

Sarah E. Randolph and David J. Rogers

Abstract | The impact of human activities on the principles and processes governing the arrival, establishment and spread of exotic pathogens is illustrated by vector-borne diseases such as malaria, dengue, chikungunya, West Nile, bluetongue and Crimean–Congo haemorrhagic fevers. Competent vectors, which are commonly already present in the areas, provide opportunities for infection by exotic pathogens that are introduced by travel and trade. At the same time, the correct combination of environmental conditions (both abiotic and biotic) makes many far-flung parts of the world latently and predictably, but differentially, permissive to persistent transmission cycles. Socioeconomic factors and nutritional status determine human exposure to disease and resistance to infection, respectively, so that disease incidence can vary independently of biological cycles.
Slide withheld at request of author
Cos'è la chikungunya?
La febbre Chikungunya è una malattia nota per eventi epidemici, il primo dei quali è stato registrato in Tanzania nel 1952. Da allora, sono stati descritti focolai epidemici in Asia ed Africa.
La Chikungunya è una malattia virale acuta, caratterizzata da sintomi simili influenzali quali: febbre elevata, cefalea, debolezza, dolori articolari diffusi, che talora costituiscono il paziente ad assumere una posizione piegata nel tentativo di alleviare il dolore causato dall'inflamazione delle articolazioni,(in swahili, “Chikungunya” significa “che contorce”), tale quadro è accompagnato, in un’elevata percentuale di casi, da manifestazioni cutanee maculopapulari pruriginose, che talora possono assumere caratteristiche di tipo emorragico benigno (petecchie, ecchimosi, epistassi, gonfioraglie).
I sintomi durano tre-cinquem giorni e si risolvono spontaneamente, ma i dolori articolari, accompagnati da astenia, possono persistere anche per mesi. Le complicanze più gravi sono rappresentate dalla meningoencefalite e dallo shock settico da coagulazione vasale disseminata.
La Chikungunya è generalmente a decorso benigno, ma può essere fatale, particolarmente in soggetti anziani con sottostanti patologie di base (pazienti oncologici, trapiantati, pazienti affetti da malattie croniche quali broncopneumopatia cronica ostruttiva, cardiopatie, diabete).

Come si trasmette?
Il virus responsabile della Chikungunya è un togavirus (arborvirus) che viene trasmesso dalle zanzare del genere Aedes, come Aedes aegypti e Aedes albopictus, comunemente chiamata zanzara tigre. Queste zanzare possono trasmettere l'infezione punendo una persona malata, nella fase acuta. La zanzara si infetta e successivamente punge un’altra persona può trasmettere il virus. Il virus non si trasmette invece da persona a persona con i normali contatti di vita quotidiana.

Dopo quanto compaiono i sintomi?

Chikungunya - Italy
September 2007

- 197 cases reported (Ravenna Province)
- 1-95 yr old; 52% female;
- 36 laboratory confirmed
- 31 being investigated
- 11 cases required hospital admission (incl. 83yr old man - multiple morbid chronic disease who died)

Index case
- Foreigner arrived Italy June 21 2007
- Travel history - Indian sub Continent
- Developed symptoms 2-3 days later
- Castiglione di Cervia, Ravenna Province

C/o Graham Lloyd
HPA Porton
Vector involvement

- Isolate made from *Aedes albopictus*
- *Aedes albopictus* introduced & well-established in several parts of Europe
- First occasion been associated with human illness in Europe
- First event resulting in indigenous transmission of Chikungunya in Europe
- Vigilance required in Albania, Italy, France, Belgium, Montenegro, Switzerland, Greece, Spain, Croatia, Netherlands, Slovenia, & Bosnia-Herzegovina
Points

• Differential diagnosis of fever and rash from tropics is wide
• Case of probable nosocomial chikungunya infection
• As part of large epidemic
• More severe and prolonged joint sequelae than dengue
• Aedes vectors spreading and climate change may exacerbate this

Summary 1

- Less malaria than from SS Africa/Oceania
- BUT patterns changing in India, with more *P. falciparum*
- Chloroquine resistant vivax rarely a clinical problem (except Oceania)
- Use higher dose primaquine, with CQ
- Vivax may be severe
- Think *P. knowlesi* forest exposure: SE Asia
Summary 2

• The history usually provides the clue
• Remember leptospirosis, rickettsiae etc
• Enteric fever: increasing MDR and NaR resistant S paratyphi A? treatment?
• Dengue and chikungunya major problems
• Potential for autochtonous spread in Europe (Aedes albopictus)
• WHO severity scoring for dengue doesn’t always work in adult travellers
Summary 3

- Surveillance is passive, patchy and subject to many biases
- Reporting standards vary
- Failure to engage VFR
- Failure to use current prevention
- Awaiting new vaccines
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