Symposium: Fever in the returning Traveller

Fever in Travellers from Africa

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Ospedale S.Cuore - Negar

http://www.tropicalmed.eu/
Case

• Italian adult woman, one-month stay in Guinea Bissau

• Mid January: high fever and vomiting

• “Next time you will not miss flu vaccination!”, GP says

• After one week...
"Diagnostic delay due to family doctors first cause of fatal malaria in Europe"  (Jef Van den Ende dixit)
Today, there are 109 malarious countries in 4 regions

Source of all Malaria imported to the UK 1987-2006

- **Africa**: 98.0%
  - 67% P.f. West Africa
  - 54% from Nigeria and Ghana
- **Oceania**: 0.2%
- **South Asia**: 0.6%
  - C & S Asia: 0.4%
- **Middle East**: 0.2%
- **Far & SE Asia**: 0.6%
- **America**: 0.2%

*Smith et. Al. BMJ 2008*
(Source: R. Behrens, ECTMIH 2009)
Antwerp longitudinal fever database

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases (n)</th>
<th>Etiology</th>
<th>Infectious Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (n=1321)</td>
<td></td>
<td><em>Plasmodium falciparum</em> Malaria</td>
<td>395 (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown Etiology</td>
<td>324 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory Tract Infection</td>
<td>127 (10%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Nonfalciparum Malaria</strong></td>
<td>65 (5%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Bacterial Enteritis</strong></td>
<td>63 (5%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Rickettsial Infection</strong></td>
<td>53 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Skin/Soft Tissue Infection</strong></td>
<td>46 (3%)</td>
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<td></td>
<td></td>
<td><strong>Genitourinary Infection</strong></td>
<td>39 (3%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Mononucleosis-like Syndrome</strong></td>
<td>36 (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Acute Schistosomiasis</strong></td>
<td>33 (2%)</td>
</tr>
<tr>
<td>Asia (n=355)</td>
<td></td>
<td><em>Unknown Etiology</em></td>
<td>69 (19%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory Tract Infection</td>
<td>45 (13%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Dengue</strong></td>
<td>43 (12%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Nonfalciparum Malaria</strong></td>
<td>33 (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Bacterial Enteritis</strong></td>
<td>33 (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Mononucleosis-like Syndrome</strong></td>
<td>20 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Skin/Soft Tissue Infection</strong></td>
<td>14 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Enteric Fever</strong></td>
<td>12 (3%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Genitourinary Infection</strong></td>
<td>12 (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Plasmodium falciparum Malaria</em></td>
<td>8 (2%)</td>
</tr>
<tr>
<td>America (n=129)</td>
<td></td>
<td><em>Unknown Etiology</em></td>
<td>42 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory Tract Infection</td>
<td>20 (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Bacterial Enteritis</strong></td>
<td>12 (9%)</td>
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<td></td>
<td></td>
<td><strong>Dengue</strong></td>
<td>11 (9%)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Genitourinary Infection</strong></td>
<td>8 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Noninfectious Condition</strong></td>
<td>7 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Mononucleosis-like Syndrome</strong></td>
<td>6 (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Nonfalciparum Malaria</strong></td>
<td>5 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Skin/Soft Tissue Infection</strong></td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

Bottieau E et al. Etiology and outcome of fever after a stay in the tropics
Travel to Africa increases while imported malaria declines (UK data)

Annual increase in visits made by the three groups of travellers to and from West Africa between 1993 and 2006.

Change in annual incidence of malaria in the three groups of travellers

Behrens R et al. Malaria Journal 2008 7:235
African immigrants: “mild” malaria?

Severe malaria in VFRs, Verona 2000-2004

- 23 cases of severe malaria, no deaths
- 3 were VFR adult immigrants
- No severe malaria cases in immigrants in the previous 15 years
- Length of stay in Italy: patient 1: 13 y, patient 2: 13 y, patient 3: 19 y

Mascarello M et al. JTM 2009
Imported malaria in VFR immigrants

The observed differences only concerned the VFRs group

Mascarello M et al. JTM 2009
VFRs length of stay in non endemic area

- **1990-1994**
  - 1-3 years: 5.7
  - 4-6 years: 34%
  - 7-9 years: 18%
  - >10 years: 5%

- **2000-2004**
  - 1-3 years: 8.3
  - 4-6 years: 35%
  - 7-9 years: 24%
  - >10 years: 22%

Mascarello M et al. JTM 2009
Exchange transfusion in severe \textit{P. falciparum} malaria?

Riddle \textit{et al}. \textit{Clin Infect Dis} 2002; 34: 1192

1. Summary of studies showing ORs for survival after adjunct exchange transfusion (ET) compared with antimalarial chemotherapy alone.
E.v. artesunate drug of choice for severe falciparum malaria in adults since 2005: yet, unavailable in many hospitals because of GMP concern!! (NB included by EMEA among orphan drugs!!)

![Graph showing survival curve of in-hospital mortality]

- artesunate: 107 deaths out of 730 (15%)
- quinine: 164 deaths out of 731 (22%)

Reduction of 34.7% (18.5 – 46.6) p=0.002

*Figure 2: Survival curve of in-hospital mortality*

Patients either died in hospital or were discharged well, so all deaths included. To construct plot survival time of all discharged patients was set to 35 days.
Not only malaria… 1. Fever with rash

Chikungunya 2007

“… the possibility of introducing CHIKV into Italy cannot be ruled out on the basis of current evidence”

Chikungunya outbreak in Northern Italy identified end of August, 2007

Index case? (23th June!!!*)

Lab Confirmation

Not only malaria… 1. Fever with rash
Chik clinically similar to other arboviral diseases with suitable vectors in Europe… (dengue, WNV…)
West Nile meningoencephalitis in three Italian regions in two consecutive years, but no “simple” WN fever: shouldn’t we enhance surveillance?? One finds what one looks for...
Not only malaria… 1. Fever with rash

Not only viruses… African tick–borne Rickettsial fever (R. africae), clinically similar to the Mediterranean R. fever
An African child with fever and generalized rash.

Courtesy Prof. Manuel Corachan - C.S.I. Hospital Clinic. Universidad de Barcelona
Not only malaria... 2. Haemorrhagic Fevers

- In October 2009, an immigrant traveller returning from Senegal to Italy was hospitalised with symptoms suggestive of a haemorrhagic fever of unknown origin
- Immediately transported by specially equipped military aircraft to bio containment unit in Rome

**A case of dengue type 3 virus infection imported from Africa to Italy, October 2009**


Euro Surveill. 2010;15(7)

- dengue occurs in Africa, too!
Not only malaria... 2. Haemorragic Fevers

- Exceedingly rare, but the most serious threat
- Difficult surveillance!!

<table>
<thead>
<tr>
<th>VHF virus</th>
<th>Geographic Distribution</th>
<th>Annual Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>Africa</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Marburg</td>
<td>Africa</td>
<td>&lt;300</td>
</tr>
<tr>
<td>Lassa</td>
<td>Africa</td>
<td>100,000-300,000</td>
</tr>
<tr>
<td>S.America</td>
<td>Argentine pampas</td>
<td>~300</td>
</tr>
<tr>
<td>Hantaan</td>
<td>Asia, Europe</td>
<td>50,000-150,000</td>
</tr>
<tr>
<td>Rift Valley</td>
<td>Africa</td>
<td>100-100,000</td>
</tr>
<tr>
<td>(CCHF)</td>
<td>Euroasia, (Africa)</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Yellow F</td>
<td>Africa, South America</td>
<td>5,000-200,000</td>
</tr>
<tr>
<td>Dengue</td>
<td>Tropics, worldwide</td>
<td>DF: 100 million, DHF: 100,000-200,000</td>
</tr>
<tr>
<td>Omsk</td>
<td>Siberia</td>
<td>100-200</td>
</tr>
<tr>
<td>Kyasanur</td>
<td>Karnataka state, India</td>
<td>400-500</td>
</tr>
<tr>
<td>Alkhumra</td>
<td>Saudi Arabia</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
Not only malaria… 2. Haemorragic Fevers

Marburg epidemic, Uige, Angola, 2005

E De Vivo, ECTMIH 2009
On Thu 10 Jul 2008, … one confirmed case of Marburg fever diagnosed in the Leiden University Medical Centre.

- 40-year-old woman returned from Uganda
- 2 caves in the Maramagambo forest
- exposed to fruit bats
MARBURG
Maramagambo forest
On July 5, 2008, a 41-year-old woman was referred by her general practitioner to the Elkerliek Hospital because of fever (39°C) and chills of 3 days' duration after returning from a June 5–28 holiday in Uganda. She was placed in a hospital room with 3 other patients. Malaria was ruled out by 3 negative blood films. …….

On July 7, hemorrhagic fever was included ….. in the differential diagnosis because of rapid clinical deterioration and impending liver failure.


- 9 Jan 2008... unexplained febrile illness
- woman who had returned from travel in Uganda
- no evidence of ... tropical febrile illnesses, including VHF.

Six months later, in July 2008, the patient requested repeat testing after she learned of the death from MHF of a Dutch tourist ......

Convalescent serologic testing revealed evidence of prior infection with MARV, and MARV RNA was detected in the archived early convalescent serum.
Online Lecture Library

Slide withheld at request of author
The Plague Doctor
(Venice, 16th Century)
Conclusions

• Fever in returning travelers: a challenge
• Should be managed in specialized centres
• Diagnostic – decision tools would help...