Malaria imported to Belgium: new challenges

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Outline

- Epidemiology of malaria in Belgium
- New epidemiological challenges
- Management of malaria in Belgium
- Emerging challenges in management
Malaria case incidence rate (/1000 p.y), globally

- 18% decrease since 2010
- Stagnation since 3 years

WHO World Report 2018
Malaria trends in Europe

- **Top cause of travel-associated morbidity and mortality**
  - 10,000-30,000 cases globally in non-endemic areas; Tatem AJ *Lancet Infect Dis* 2017

- **Increasing** of reported cases in Europe
  - (5,897 in 2012 and 8,401 in 2017: 40% increase; *ECDC Malaria Report 2017*)

- **Underestimation**
  - reporting not compulsory in several countries (Belgium, France, UK)
Malaria trends in Belgium: Sciensano/ITM ref lab

Figure 1

Additional data sent directly to Sciensano
Data aggregated at Reference Lab ITM

> 2.5 infections/100,000 inhab.

INSTITUTE OF TROPICAL MEDICINE ANTWERP
Rovira-Vallbona E. *Trav Med Infect Dis* In press
Malaria trend in Belgium: Sciensano/ITM

- Surveillance based on a network of sentinel laboratories
  - Voluntary base
  - “Stable” contributors over the years
  - Very limited epidemiological metadata (age, sex, region of diagnosis)
  - No clinical data about presentation, drug exposure, outcome
- No mandatory notification, except for autochthonous malaria
Any sign of cerebral dysfunction
Severe anemia (hemoglobin < 7 g/dl)
Oligo-anuria < 400 ml/day
Jaundice

Shock
Bleeding/DIC

Table 1. Clinical and biological criteria for severe malaria according to the 2000 World Health Organization definition with modifications (see * and †).

<table>
<thead>
<tr>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired consciousness: Glasgow Coma Scale score &lt; 11*</td>
</tr>
<tr>
<td>Respiratory distress: requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with ( \text{PaO}_2 ) &lt; 60 mm Hg (if ( \text{FiO}_2 ) &lt; 0.21) †, and/or ( \text{PaCO}_2 ) &gt; 32 mmHg</td>
</tr>
<tr>
<td>Multiple convulsions</td>
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<td>Circulatory collapse: systolic blood pressure &lt; 80 mm Hg despite adequate volume repletion</td>
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<td>Abnormal bleeding</td>
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<tr>
<td>Jaundice: clinical jaundice or bilirubin &gt; 50 ( \mu )mol/L</td>
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<tr>
<td>Macroscopic hemoglobinuria: if unequivocally related to acute malaria (patients with blackwater fever were not included)</td>
</tr>
<tr>
<td>Laboratory criteria</td>
</tr>
<tr>
<td>Severe anemia: hemoglobin &lt; 5 g/dL</td>
</tr>
<tr>
<td>Hypoglycemia: blood glucose &lt; 2.2 mmol/L</td>
</tr>
<tr>
<td>Acidemia (pH &lt; 7.35) or acidosis (serum bicarbonate &lt; 15 mmol/L)</td>
</tr>
<tr>
<td>Hyperlactatemia: arterial lactate &gt; 5 mmol/L</td>
</tr>
<tr>
<td>Hyperparasitemia ≥ 4%</td>
</tr>
<tr>
<td>Renal impairment: serum creatinine &gt; 265 ( \mu )mol/L or blood urea nitrogen &gt; 17 mmol/L*</td>
</tr>
</tbody>
</table>

*Coma scale criteria of 11 instead of 6 respiratory rate > 32/minute and blood urea nitrogen > 17 mmol/L are modifications according to the SEAQUAMAT group [8].
†The requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with \( \text{PaO}_2 \) < 60 mm Hg (if \( \text{FiO}_2 \) < 0.21) was used specifically for this study.
DOI: 10.1371/journal.pone.0011235.t001
Risk factors for severe malaria

- Retrospective study
- 21,888 *P. falciparum* malaria, including 862 (4%) severe cases
- Independent risk factors for severity
  - Age (> 60 years)
  - European origin
  - Absence of chemoprophylaxis
  - Time to diagnosis (4 to 12 days)
  - First visit to GP

Malaria trend in Belgium: National Institute Health & Disability Insurance (RIZIV/INAMI)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Hospital stays with a diagnostic: malaria ICD9 084 until 2014 From 2016 ICD10: B50 to B54</td>
<td>340</td>
<td>366</td>
<td>320</td>
<td>390</td>
<td>400</td>
<td>Poor quality data: will not be available for analysis</td>
<td>396</td>
<td>421</td>
<td>Data available in May 2020</td>
</tr>
<tr>
<td>Total cost hospital stays INAMI/RIZIV (€)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,483,236</td>
</tr>
<tr>
<td>Hospital stays with artesunate reimbursed(CNK 7706336)</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>21</td>
<td>39</td>
<td></td>
<td>35</td>
<td>Data available in May 2020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data source: SHA</th>
<th>Artesunate delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>8</td>
</tr>
<tr>
<td>Cost for INAMI/RIZIV (€)</td>
<td>3,965</td>
</tr>
</tbody>
</table>

Source: courtesy NIHDI
Malaria trend in Belgium: severe cases

- IV artesunate indications well respected by Belgian physicians
- Good surrogate for severe cases

Source: courtesy Dr Clerinx J. & NIHDI
Malaria trend in Belgium: hospital/severe cases (NIDHI)

- 421 admissions in 2017 (ICD9-ICD10)
- Increasing trend since 2010
- 40 IV artesunate treatments administered in 2017 (10% of admitted cases)
- Annual hospital costs related to malaria: 1,500,000 euros
- Data limited to hospital care
Severe malaria in Belgium: historical series

- Prospective study (2000-2005)
- 387 *P. falciparum* cases
- 25% of VFR travelers
- 33% seen first by GP
- 60% of diagnostic delay (> 3 days)
- 15% of severe cases
Severe malaria in GeoSentinel travel clinics

- Retrospective analysis of surveillance data
- 5,689 malaria, including 4,011 *P. falciparum* cases
  - 62% admissions
  - 441 severe cases (11% of *Pf*)

Angelo K. et al. *Malaria J* 2017
Malaria trend in Belgium: causes of increase?

- Clinical experience
  - “Most cases of malaria occur in travellers visiting friends and relatives (VFR)”

- High proportion of VRFs in all recent surveys
  - “Assessing the burden of key infectious disease affecting migrants in the EU”; ECDC 2014
  - Angelo KM et al. Malaria in international travelers: a GeoSentinel analysis
    - 53% of 5689 malaria cases (2003-2016) were VFR travelers

- VFRs as contributors of the increase
  - De Gier B et al. Increase in imported malaria in the Netherlands in asylum seekers and VFR travellers. Malaria J 2017
Malaria trend in Belgium: causes of increase?
Malaria prevention in Belgium: A-B-C-D

Awareness

Bite prevention

Chemoprophylaxis

- Atovaquone/proguanil
- Doxycycline
- (Mefloquine)

Diagnosis
Malaria diagnosis in Belgium

- Good quality of microscopy in Belgium for diagnosis of *P. falciparum*

- Use of LAMP assay as very sensitive screening tool?
Treatment severe malaria (2019)

- Artesunate (AS) IV, followed by artemisinin-based combination therapy (ACT)
  - Clinically superior to quinine (improved survival) in endemic settings
    - SEAQUAMAT; *Lancet* 2005
    - AQUAMAT *Lancet* 2010
  - Clinical benefit also in Europe

- Intravenous Artesunate Reduces Parasite Clearance Time, Duration of Intensive Care, and Hospital Treatment in Patients With Severe Malaria in Europe: The TropNet Severe Malaria Study
  - Florian Kurth, Michel Develoux, Matthieu Mechain, Jan Clerinx
  - *Clinical Infectious Diseases* 2015; 61(9): 1441–4

- Reduction by at least 1 day of fever, ICU and hospital duration

70 AS vs 115 Q
Treatment uncomplicated malaria (2019)

First-line

- 3 or 4 tab OD fasting

Second-line

- 4 tab BID with food

Third-line

- 4 tab OD with food

First-line medications:
- Dihydroartemisinin/piperaquine
- Artemether/lumefantrine

Second-line medications:
- Atovaquone/proguanil

Third-line medications:
- Quinine + doxycycline
- OR clindamycine
Treatment uncomplicated malaria (2019)

ACTs
n=59

Shortest parasite and fever clearance time

Retrospective
AL (n=25) vs AP (n=44)
New challenges: artemisinin-related toxicity

Post-arteresunate delayed hemolysis (PADH) after severe malaria in travelers
- Zoller T. et al. Emerg Infect Dis 2011; retrospective; 6/25 (24%)
- Kreeftmeijer-Vegter AR et al. Malaria J 2012; retrospective; 7/55 (13%)
- Kurth F et al. Malaria J 2017; retrospective 19/70 (27%)
- Jaureguiberry S et al. Emerg Infect Dis 2015; prospective; 21/78 (27%)

- 15% had a hemoglobin level drop below 7 g/dl
- Other persistent hemolysis than PADH
New challenges: artemisinin-related toxicity

- **PADH after severe malaria in endemic countries**
  - Rolling T et al. *J Infect Dis* 2014; prospective; 5/72 (7%)
  - Burri C et al. *Am J Trop Med Hyg* 2014; prospective; 22/201 (11%)

- **PADH after ACT for uncomplicated malaria**
  - Kurth F et al. *Emerg Infect Dis* 2016; prospective; 8/20 (40%)

Mean Hb drop: 1.3 g/dl
New challenge: late ACT failure

N=5 late failures, in Sweden (2012-2015)  
No resistance found

N=4 late failures, in UK (2015-16)  
No resistance found

N=4 late failures, in Japan  
(2005-2016)  
Resistance not tested

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>male</td>
<td>male</td>
<td>female</td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>40</td>
<td>50</td>
<td>56</td>
<td>33</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>86</td>
<td>86</td>
<td>62</td>
<td>95</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td>Belgium</td>
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<td>Belgium</td>
<td>Belgium</td>
<td>Belgium</td>
<td>Belgium</td>
</tr>
<tr>
<td><strong>Chemoprophylaxis</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>First episode (day 0)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days with fever before diagnosis</strong></td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Parasitaemia at diagnosis</strong></td>
<td>300,138</td>
<td>152,601</td>
<td>1,242,537</td>
<td>98,714</td>
<td>842,771</td>
<td>1521a</td>
</tr>
<tr>
<td><strong>Criteria of severe malaria</strong></td>
<td>disorientation; hyperparasitaemia</td>
<td>disorientation; kidney failure</td>
<td>hyperparasitaemia</td>
<td>disorientation; kidney failure</td>
<td>shock; kidney failure; hyperparasitaemia</td>
<td>none</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>AS (2 days) + DP</td>
<td>AS (3 days) + AL</td>
<td>AS (1 day) + AL</td>
<td>AS (1 day) + AL</td>
<td>AS (1 day) + AL</td>
<td>AL</td>
</tr>
<tr>
<td><strong>Recurrent episode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days after first diagnosis</strong></td>
<td>37</td>
<td>35</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td><strong>Days with fever before diagnosis</strong></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Parasitaemia at diagnosis</strong></td>
<td>34,474</td>
<td>35,454</td>
<td>14,737</td>
<td>19</td>
<td>1951</td>
<td>(0.5%)b</td>
</tr>
<tr>
<td><strong>Criteria of severe malaria</strong></td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>QN-doxy</td>
<td>AP</td>
<td>AP</td>
<td>AP</td>
<td>AP</td>
<td>QN-doxy</td>
</tr>
</tbody>
</table>
New challenge: artemisinin resistant malaria in SE Asia


Threat of artesunate resistance: new ACTs?

- **Artesunate-pyronaridine** 3-day
- **Arterolane-piperaquine** 3-day
- **Artemisinin-naphthoquine** 3-day; SD?
- **Artefenomel (OZ439)** SD?
Threat of artesunate resistance: new class of drugs?

- **Spiroindolone KAE609**
  
  Phase 2 (n=21 cases): “safe and effective”

- **Imidazolopiperazine KAF156**
  
  Phase 2 (n=43 cases): “safe and effective”
Conclusions (1): emerging epidemiological challenges

- Increasing burden of malaria in Belgium
  - Unclear reasons due to limited surveillance data
  - VFR contribution?

- Stable proportion of severe cases
  - Good quality of diagnosis
  - Diagnostic delays ? (patient ? doctor?)
Conclusions (2): emerging clinical challenges

- Artemisinin-related toxicity
  - Delayed/persisting hemolysis
  - Risk factors? Management?

- Treatment failures
  - No early treatment failure reported in Europe so far
  - Late treatment failure due to non-adherence? subtherapeutic partner drug concentration? resistance?

- Spread of resistance to artemisinin
  - Need for molecular surveillance?