Imported malaria in children: a national surveillance in the Netherlands and a review of European studies

Gertjan J. Driessen¹, Rob R. Pereira², Bernard J. Brabin⁴,⁵,⁶, Nico G. Hartwig¹

Background: Falciparum malaria or malaria tropica is one of the leading causes of childhood mortality worldwide. Malaria-related deaths occur mainly in sub-Saharan Africa, where an estimated 365 million clinical cases of Plasmodium falciparum malaria occur each year. In Europe, imported malaria cases occur due to returning travellers or immigration mostly from African countries. Children are more at risk than adults. The objective of this study was to identify high risk groups for imported childhood malaria in Europe in order to guide development of strategies for prevention, early recognition and management.

Methods: In the period May 2003–January 2005 we reviewed all cases of paediatric malaria in the Netherlands notified by the Dutch Paediatric Surveillance System (Nederland Signalerings Centrum Kindergeneeskunde, NSCK) and the literature on imported malaria in children in Europe published between 1996 and 2006. Results: Malaria occurred mainly in children of long-term (n = 15, 47%) and new (n = 8, 25%) immigrants and was mostly acquired in sub-Saharan Africa. The dominant species was P. falciparum. Only one quarter of children had used adequate malaria chemoprophylaxis. Complicated disease occurred in 10 (31%) of cases. We also reviewed the literature and found 6082 reported cases of imported malaria among children in Europe; among these, four died and only one was reported to develop neurological sequelae. Conclusion: Imported malaria in children remains an important problem and is unlikely to decrease unless the reasons for inadequate prophylaxis are addressed.

Keywords: chemoprophylaxis, child, fever, malaria, travel

Malaria-related deaths occur mainly in sub-Saharan Africa, where an estimated 365 million clinical cases of Plasmodium falciparum malaria occur each year.¹,² European countries are outside the endemic area, but malaria is imported through travel or immigration. There are an estimated 11 000 cases per year, of which 8000 cases are imported through travel or immigration. There are an estimated 11 000 cases per year, of which 8000 cases are caused by P. falciparum.³,⁴ The true number is probably higher. In the Netherlands the total number of cases (adults and children) has annually fluctuated between 569 in 2001 and 299 in 2005 (http://www.rivm.nl/isis/ggd/openbaar/index.html).

Malaria is the most prominent imported pathogen in children.⁵,⁶ Children below the age of 6 years are more at risk than adults.⁷ Information on imported malaria in children is relatively scarce and mostly only published in national medical journals.⁸–¹⁴ Furthermore, in several studies on imported malaria, a sub-group analysis for children is not included¹⁵–¹⁷ or very limited.¹⁸ The proportion of childhood cases varies nationally. In the period 2001–2006 the percentage of reported childhood malaria (0–19 years) in the Netherlands was 10.4% (http://www.rivm.nl/isis/ggd/openbaar/index.html).

Overall variation of childhood cases has been small in the period 1979–1988.¹⁹ The Netherlands has a lower proportion than other European countries. In the UK the proportion of paediatric cases was 14.9%,²⁰ in Spain, between 16 and 17%,²¹,²² and in France, 23%.²³ The objective of the present analysis was to identify high risk groups for imported childhood malaria in Europe, in order to guide the development of strategies for prevention, early recognition and management. We reviewed epidemiological and clinical data on imported malaria in children in Europe with an emphasis on recent prospective data from the Netherlands.

Methods

We searched PubMed for reports on imported childhood malaria for all European countries and published since 1996. Search terms included ‘malaria’, ‘imported’ and ‘travel’, without language restriction.

For the period May 2003 to January 2005 all cases of paediatric malaria (age 0–18 years) in the Netherlands were notified prospectively through the hospital-based Dutch Paediatric Surveillance System (Nederland Signalerings Centrum Kindergeneeskunde, NSCK), which covers all paediatric departments in the Netherlands.²⁴ Details of reported cases were obtained using an anonymous questionnaire, which was posted to paediatricians of all cases notified. Information was collected on sex, age, country of birth and residence of parents and children, malaria prophylaxis, malaria endemic area visited, clinical presentation, diagnosis, malaria species, treatment, complications and outcome. Data were entered in an Excel database.

Results

European review

A total of 6082 cases have been documented in reports since 1996. We identified eight single centre studies and seven national or multi-centre studies, solely investigating paediatric
in the reviewed studies, except for a highly selected intensive outcome was reported. Case fatality rate varied from 0 to 1.2% in sub-Saharan Africa. Most children were mildly anaemic and mean haemoglobin was 6.4 mmol/l. The majority of the patients were children of immigrants (64–100%) living in Europe, who were visiting friends or relatives abroad. The median age and age range of each study are presented in table 1. The use of antimalarial chemoprophylaxis was below 40% for all reports. Reasons for not taking prophylaxis were not reported. The dominant malaria species was *Plasmodium falciparum* (>75%), with the exception of one UK malaria reference laboratory survey published in 1997. More recent data, however, show that also in the UK more than three quarter of cases were falciparum malaria. The majority of the cases were acquired in sub-Saharan Africa (3463 of 4217 evaluable cases; 82%). Of 3043 children the outcome was reported. Case fatality rate varied from 0 to 1.2% in the reviewed studies, except for a highly selected intensive care population, where case fatality was 7%. One child was reported to develop severe sequelae.

**Dutch surveillance**

In the 20-month period, 32 malaria cases were reported in children. The response of paediatricians for questionnaire completion was 100%. Twenty-six cases (81%) were due to *P.falciparum*, acquired from sub-Saharan Africa. In addition there was one mixed infection (*F.vivax* and *P.falciparum*). The areas of acquisition and plasmodium species are summarized in table 2. The median age was 8 years (range 0.4–13), and 19 (59%) were girls. Fifteen patients (47%) were long-term immigrants living in the Netherlands with children or parents who were born in a malaria endemic area and who were revisiting their country of origin, and eight (25%) were new immigrants from malaria endemic areas. Of the nine (28%) indigenous Dutch children, two (6%) were resident abroad as expatriates, the others were travellers. Ten children (31%), including these expatriate children, had a previous history of a malaria. Only the new malaria episodes were included in this study.

**Malaria prophylaxis**

Only six (19%) cases had been counselled at a travel clinic and two children had used a bednet. Some form of chemoprophylaxis was taken by 13 (40%) children, but only 8 (25%) used chemoprophylaxis appropriately in terms of either compliance or appropriate choice of drug. More indigenous Dutch children used chemoprophylaxis than the long-term immigrants children (Fischer exact, *P* = 0.01).

**Clinical presentation and diagnosis**

Symptoms, signs and laboratory parameters at presentation are summarized in table 3. Nearly all presented with fever and in 22 cases (69%) followed referral to hospital by a primary care physician. For falciparum cases, complaints started a median of 12 days (1–34) after arrival from the malaria endemic area and 5 days (0–35) before consulting a physician. For vivax and ovale malaria cases these periods were longer, 180 days (18–210) and 6.5 days, respectively. On physical examination, half of the children were ill-looking, but only five children (16%) had splenomegaly. For eight cases the diagnosis of malaria had been made prior to hospital consultation. Half of the parents and 25 (78%) paediatricians were considered to have malaria in the differential diagnosis at first consultation. Thick blood smears were used for diagnosis and for three cases an additional antigen detection test (parasight®) also used. Most children were mildly anaemic and mean haemoglobin was 6.4 mmol/l.

**Treatment, complications and outcome**

Malaria was complicated by hyperparasitaemia (>5% infected red cells) in six (19%) children, convulsions in one (3%), anaemia (<5 mmol/l) in two (6%), and persistent high fever (>39.5°C) with prostration in one child. Following admission, mean fall in haemoglobin was 1.3 mmol/l, but only one child required blood transfusion. No child developed hypoglycaemia. Six (19%) had mildly elevated transaminases (data not shown). In the majority of cases (*N* = 29, 91%) a specialist in infectious disease or microbiology provided treatment advice. Most of the uncomplicated cases were treated with atovaquone-proguanil, and all complicated cases with intravenous quinine. Median admission time was 4 days (range 1–9) and four children required intensive care. All children recovered without sequelae, one required re-treatment after relapse.

**Discussion**

We report detailed prospective multi-centre data on imported malaria in children in the Netherlands, including clinical parameters. An assessment of European imported childhood malaria is summarized for studies published between 1996 and 2006. These data are important in terms of public health because they show that in order to prevent imported malaria in children, the problems must be addressed in the specific risk group of long-term immigrants.

Our surveillance data as well as the reviewed studies clearly demonstrate that children of immigrants need a targeted approach. In the Netherlands, 23 children (72%) were either long-term or newly arriving immigrants, which is consistent with the findings of other reports. Norwegian surveillance data have shown that malaria incidence in immigrants visiting friends or relatives (adults and children) was higher than in people of Norwegian origin. This was also the case for hepatitis A, shigellosis infection, typhoid and paratyphoid fever. Data in adults confirm that immigrants visiting friends or relatives disproportionately require treatment as inpatients and are less motivated to obtain pre-travel advice on use of chemoprophylaxis.

Most cases of imported malaria are preventable, since adequate malaria chemoprophylaxis is highly effective in non-immune travellers, including children. We report that 24 children (75%) acquiring malaria did not use adequate chemoprophylaxis, a finding that is consistent across the reviewed studies (table 1). Our data illustrate for the first time that children of immigrants were less likely to use malaria chemoprophylaxis than indigenous Dutch children. Our study did not investigate why some children got malaria despite adequate chemoprophylaxis. We hypothesize that adherence to prophylaxis was not as good as reported by parents, or that their exposure to malaria might have been high due to lack of use of protective measures such as bed-nets, which were hardly used.

Early diagnosis and treatment are critical in order to avoid severe disease. In our study the median diagnostic delay was 5 days (range 0–35, table 1). Although we could not calculate the period of delay due to the doctor’s referral time, it has been reported that this accounts for one-third of the total diagnostic delay. For non-falciparum malaria, longer delays in presentation may reduce the suspicion of a malaria diagnosis by the paediatrician, but these infections are less common and the clinical course is usually milder.

The early diagnosis of malaria needs a careful travel history and a high level of clinical suspicion. As indicated in table 3 symptoms are non-specific, but fever was almost always present. In our study half of the parents had already suspected malaria and in 25 (78%) of the cases, malaria was considered in the differential diagnosis at the first paediatric
<table>
<thead>
<tr>
<th>Author, year country (ref)</th>
<th>n</th>
<th>Study characteristic Age in years*</th>
<th>Chemo prophylaxis (%)</th>
<th>Delay diagnosis (days*)</th>
<th>Complicated malaria (%)</th>
<th>Admission rate and duration in days Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brabin, 1997 U.K. (20)</td>
<td>1442</td>
<td>Malaria reference laboratory data</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Minodier, 1999 France (12)</td>
<td>315</td>
<td>single centre 4(1–16)</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hay, 2000 France (27)</td>
<td>15</td>
<td>PICU cases multi-centre 7(0,7–16)</td>
<td>40</td>
<td>2(1–25)</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Huerga, 2001 Spain (22)</td>
<td>49</td>
<td>single centre [6,4]</td>
<td>0b</td>
<td>–</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Williams, 2002 U.K. (28)</td>
<td>249</td>
<td>single centre</td>
<td>41</td>
<td>4(0–32)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Parez, 2002 France (29)</td>
<td>80</td>
<td>children single centre 8(0,2–15)</td>
<td>38</td>
<td>–</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Huerga, 2002 Spain (6)</td>
<td>56</td>
<td>children single centre</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eloy, 2003 France (11)</td>
<td>60</td>
<td>children single centre</td>
<td>8b</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ladhani 2003 U.K. (26)</td>
<td>211</td>
<td>children 2 centres 9(0,8–14,9)</td>
<td>15b</td>
<td>(1–14)</td>
<td>7,1</td>
<td>2(0–20)</td>
</tr>
<tr>
<td>Hau, 2004 France (30)</td>
<td>52</td>
<td>children halofantrin study 7,2(0–16)</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Ladhani, 2006 U.K. (32)</td>
<td>1456</td>
<td>children Malaria reference laboratory data</td>
<td>39</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chalumeau, 2006 France (25)</td>
<td>29</td>
<td>children multi-centre 10(1–17)</td>
<td>34b</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Driessen, Netherlands</td>
<td>32</td>
<td>children national survey 8 (0,4–13)</td>
<td>25b</td>
<td>5(0–35)</td>
<td>31</td>
<td>4 (1–9)</td>
</tr>
</tbody>
</table>

a: [mean, median(range)]
b: reported to be ‘adequate’
#: no data available

15 relapses (5%) 1 death (7%) 1 sequela
no deaths
no deaths 1 exchange transfusion
no deaths ‘few’ relapses
1 death (1,2%) 5 relapses(6,2%)
no deaths
2 deaths (0,16%)
no deaths
no deaths
no deaths
no deaths
14 relapses (27%)
2 deaths (0,14%)
no deaths 1 relapse (3%)
van Hest et al. reported cases in our study is in line with estimates of laboratories over the same study period (malaria cases (adults and children) reported by Dutch were fewer than expected, compared to the total number of cated cases. The number of cases reported by paediatricians might contribute to the relatively high proportion of compli-
study is hospital based, it is subject to selection bias, which in the Dutch study, since the proportion of complicated children who have visited a malaria endemic area.

We expect that less severe malaria cases were under-reported in the Dutch study, since the proportion of complicated malaria cases was relatively high (n = 10, 31%). Because the study is hospital based, it is subject to selection bias, which might contribute to the relatively high proportion of compli-
cases. The number of cases reported by paediatricians were fewer than expected, compared to the total number of malaria cases (adults and children) reported by Dutch laboratories over the same study period (n = 533, of which ~10% were paediatric malaria). The number of under-
reported cases in our study is in line with estimates of van Hest et al., who calculated for Dutch cases 60% under-reporting by physicians and 30% by laboratories using a capture-recapture method.

Young children are at a high risk of acquiring malaria abroad and the reported morbidity in terms of complica-
tions and hospital admissions is considerable. Furthermore, children show different clinical presentation to adults and are completely dependent on their parents in terms of use of chemoprophylaxis or for obtaining medical attention. As a consequence children should be considered as a distinct group. The currently existing surveillance systems on imported diseases, such as the GeoSentinel Surveillance Network, the European network on surveillance of imported infectious diseases and TropNetEurop, do not separately report relevant paediatric data. If these data would be available it would be easier for public health professionals to monitor this high risk group.

Prioritising the prevention of imported malaria is essential to reduce disease burden. In a prospective survey of children presenting with malaria in the emergency department of a French hospital, only 23% had used insecticide-impregnated bednets and 22% correct chemoprophylaxis. In children there was no improvement in the percentage taking adequate prophylaxis over a 25-year period. In another study there was even a decrease in compliance over time. There is little information on why immigrant families with children do not protect themselves. There is probably a lack of awareness of the potential risks in non-immune children. Parents may consider their children immune from malaria, during visits to their ‘home’ country. Furthermore the taste and side effects of paediatric antimalarial agents may influence a child’s com-
pliance. Dosage errors may occur due to uncertainty of the child’s weight. Costs, accessibility of pre-travel services and cultural barriers may all play a role.

Further efforts to improve prevention, including educating groups at risk and health care professionals, travel agents and airline personnel will be important initiatives. Increased awareness will help to decrease delays in patient and doctors diagnosis, reducing the risk of complications. In the Netherlands initiatives have been taken to contact and educate groups at risk in schools and even in churches. In this way public health organizations, most often at regional level, can try in creative ways to develop effective strategies to reduce this morbidity. Further studies on the preventive and cultural aspects of travel-related health in children are needed to determine which interventions are most effective. Concerted initiatives of public health professionals will be required to effectively address this problem.

Acknowledgements

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Conflicts of interest: None declared.

Key points

- Imported malaria in children throughout Europe is mainly caused by Plasmodium falciparum and acquired in sub-Saharan Africa.
- Imported malaria occurs predominantly in children of immigrants.
- The use of chemoprophylaxis in this group is exceptional.
- The reasons for inadequate chemoprophylaxis are unknown and require further study.
- To decrease disease burden in children, greater priority with preventive measures must be achieved.

References


Table 2 Area of acquisition of malaria and plasmodium species

<table>
<thead>
<tr>
<th>Area</th>
<th>West Africa n (%)</th>
<th>Africa, S5* n (%)</th>
<th>Asia n (%)</th>
<th>Surinam n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>19 (59)</td>
<td>7 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. ovale</td>
<td>1 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. vivax</td>
<td>3 (10)</td>
<td></td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>P. vivax + P. falciparum</td>
<td>1 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: S5; South of the Sahara, other than West Africa

Table 3 Symptoms, signs and laboratory parameters at initial presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>Cyclic fever</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>General malaise</td>
<td>27</td>
<td>84</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>53</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Convulsions</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ill looking</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>Pale</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>CRP &gt;100mg/l</td>
<td>13</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocyten &lt; 150 × 10⁹/L</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Parasitaemia &gt; 5%</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

Note: CRP: C-reactive protein

a: % of red cells infected

consultation. The presence of thrombocytopenia in combina-
tion with mild anaemia and an elevated C-reactive protein was often, but not always, present. In a population with a high proportion of ethnic groups travelling to endemic areas, the presence of thrombocytopenia alone can be an indicator of the presence of malaria. However, laboratory parameters are non-specific and a thick film is mandatory in all febrile children who have visited a malaria endemic area.

Young children are at a high risk of acquiring malaria abroad and the reported morbidity in terms of complica-
tions and hospital admissions is considerable. Furthermore, children show different clinical presentation to adults and are completely dependent on their parents in terms of use of chemoprophylaxis or for obtaining medical attention. As a consequence children should be considered as a distinct group. The currently existing surveillance systems on imported diseases, such as the GeoSentinel Surveillance Network, the European network on surveillance of imported infectious diseases and TropNetEurop, do not separately report relevant paediatric data. If these data would be available it would be easier for public health professionals to monitor this high risk group.


