The rising incidence of imported malaria in developed countries reflects increasing travel in tropical areas, where malaria is endemic and is a major cause of morbidity and mortality. Each year more than 1.45 million people arrive in Australia from malarious areas and, although Australia was declared free of endemic (indigenous) malaria in 1981, there have been 7,381 cases reported in the last decade (Fig.), with 7 deaths. During the same period in the United States, there were 12,386 cases of malaria with 63 deaths.

Returned travelers, migrants, and overseas visitors with malaria, usually present within days or weeks of arriving in a nonendemic country with the classic features of fever and headache. Atypical clinical features or delayed presentation may make diagnosis difficult and every effort must be made to examine multiple blood smears to exclude the infection. Inadequate or no chemoprophylaxis, as well as delayed diagnosis, may increase

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Figure Total number of malaria cases in Australia by year.
the risk of severe *Plasmodium falciparum* infection and result in life-threatening cerebral malaria, renal failure, coagulopathy or prolonged hypoglycemia.

This study was undertaken to document the epidemiological and clinical features of patients with imported malaria in Melbourne, Victoria. Approximately 60% of the 460 malaria cases reported in the state of Victoria during the study period were admitted to Fairfield Infectious Diseases Hospital, a specialist infectious diseases teaching hospital, providing a unique opportunity for clinical data collection.

**Methods**

**Study Design**

This study was designed as a retrospective case series.

**Patient Selection**

The medical records of all patients admitted to Fairfield Hospital with a clinical diagnosis of malaria (International Statistical Classification of Diseases 9 code of 084.0–084.6) between January 1, 1990 and June 30, 1994 were retrospectively examined by one of two authors (PR or MT). A pro forma was used to record abstracted data relating to demographic details, travel history, chemoprophylaxis, clinical features, laboratory tests and management. All patients for whom there was microscopic confirmation of malaria were included in the study. Staff in the malaria reference laboratory at the Victorian Infectious Diseases Reference Laboratory examined all thick and thin blood films. All identified records were crosschecked with laboratory logbooks to ensure that no cases were missed. Severe falciparum malaria was defined according to WHO criteria (i.e., parasitemia and one or more of the following: unrousable coma, repeated generalized convulsions, pulmonary edema or acute respiratory distress syndrome, glucose $\leq 2.2$ mmol/L, systolic blood pressure $< 70$ mm Hg, creatinine $> 0.265$ $\mu$mol/L, arterial pH $< 7.25$, hemoglobin $< 5$ g/dL, hemoglobinuria, or spontaneous bleeding. A parasitemia $> 5\%$ was also included as a defining criteria as nonimmune patients predominated in the study group). The adequacy of antimalarial chemoprophylaxis was assessed by the authors using guidelines that were current during the study period.

**Data Handling and Analysis**

Data relating to social background, travel history, clinical history, diagnostic procedures, treatment and outcome details, were abstracted and entered into Microsoft Excel. Data were subsequently exported to Epi-Info 6.04 for descriptive analysis and hypothesis testing. The chi-squared statistic with Yates’ correction for continuity, relative risks (with 95% confidence limits), or Fisher exact statistic, were used for categorical data. A 2-sample *t*-test, or analysis of variance were used to compare the means of two or more groups for normally distributed data, and the Kruskal–Wallis *H* test was applied when the data had a nonnormal distribution.

**Results**

Two hundred and forty-six people were admitted to Fairfield Hospital with confirmed malaria on 264 occasions. There were 158 (64.2%) males and 88 (35.8%) females. The median age was 29 years. Ninety (36.6%) were born in a country with endemic malaria and 54% of these acquired malaria in India, Sri Lanka, Pakistan, or Southeast Asia. One hundred and thirty-three were Australian-born, of whom 51% acquired malaria in Papua New Guinea (PNG), Bougainville, or the Pacific Islands (Table 1).

**Chemoprophylaxis**

One hundred and thirty-nine people (56%) took malaria prophylaxis. Of these, only 29% were assessed by the authors (AJ, BB) to have taken the drugs according to manufacturers’ recommendations (i.e., took medications regularly during, and for 4 weeks after, travel at the recommended dose). Even if taken as recommended, the antimalarial prophylaxis was assessed by the authors as inadequate protection against *P. falciparum* in 76% of cases because of likely drug resistance in the area visited. Prophylaxis regimens included chloroquine alone (n = 37), chloroquine and Maloprim (pyrimethamine/dapsone, n = 57), Maloprim alone (n = 4), mefloquine (n = 26), and doxycycline (n = 5). People born in malaria-endemic countries were less likely to have used chemoprophylaxis (15/84) compared with those from nonendemic countries (124/147, Relative Risk [RR] 5.25, 95% confidence intervals [CI] 3.56–7.74, p < .001).

Five of the 26 people who took mefloquine prophylaxis had *P. falciparum* infection. None of these took prophylaxis for the recommended 4 weeks after leaving the malarious area. (One person who had traveled for a month in Ghana developed infection while still taking mefloquine, and 3 others 11, 14, and 21 days respectively after its cessation). Twenty of the mefloquine users had *Plasmodium vivax* and one had *Plasmodium ovale* infection. Six of these developed symptoms within 4 weeks of returning to Australia, but only one was a true mefloquine failure. This case, a 16-year-old male student who had camped in northwest PNG for 1 month, developed
P. vivax infection 2 weeks after leaving PNG, while still taking mefloquine. Five people taking doxycycline developed malaria after ceasing the drug: 3 had P. vivax, 1 P. falciparum, and 1 P. ovale infection. None took doxycycline for 4 weeks after leaving the risk area, as recommended by the manufacturer.

Parasite Species and Country of Acquisition

P. vivax was the causative organism in 182 (68.9%) episodes, P. falciparum in 71 (26.9%), P. ovale in 5 (1.9%), and there was 1 (0.4%) case of Plasmodium malariae. Five people had mixed infections: P. vivax/P. falciparum in 4 (1.5%) and P. falciparum/P. ovale in 1 (0.4%). All 264 episodes of malaria were microscopically confirmed on admission. In 10 episodes, a different species of Plasmodium was identified to that diagnosed elsewhere.

The likely countries or regions where malaria was acquired are shown in Table 1. Twenty-seven (25%) of 107 people who traveled in PNG, the Solomon Islands or Vanuatu, and 22 (69%) of 32 who traveled in Africa were diagnosed as having P. falciparum malaria. Travel in Africa was the only significant association between geographic area and species (p < .0001).

Duration of Illness before Diagnosis

The median times to diagnosis after the most recent return to Australia for P. falciparum and P. vivax infections were 1 and 9 weeks respectively. P. falciparum was more likely to be the diagnosis if the patient had returned to Australia in the last 3 weeks (RR 5.95, 95% CI 3.63–9.75, p < .0001). However, 10 (14%) people with P. falciparum infection had arrived in Australia more than 4 weeks previously, and 8 (11%) of these had arrived more than 8 weeks before presentation. The longest interval between last arrival in Australia and presentation with malaria for P. falciparum was 32 weeks, and for P. vivax was more than 2 years. P. vivax was significantly more likely if presentation was more than 3 weeks after return (RR 2.31, 95% CI 1.75–3.04, p < .001).

The median duration of symptoms prior to the patient presenting for diagnosis was 4 days for P. falciparum (range 1–42 days) and 6 days for P. vivax (range 1–42 days). If the patient presented for initial consultation (not necessarily at Fairfield Hospital) within 4 days of the start of symptoms, P. falciparum infection was significantly more likely to be the diagnosis than P. vivax, (RR 1.9, 95% CI 1.26–2.86, p = .003).

Treatment before Admission to Fairfield Hospital

Some form of treatment was commenced in 174 episodes prior to admission to Fairfield Hospital. In 42 episodes the diagnosis of a bacterial or viral illness had resulted in treatment with antibiotics (24) or panadol (18), and in 70 episodes antimalarial chemotherapy was commenced. In 62 patients the type of treatment was unknown. The duration of this prior treatment was recorded in 160, of whom 120 (69%) had been treated for 2 days or less. In 15 (9%) episodes, treatment had continued for 7 days or more, prior to presentation at Fairfield Hospital. Only 3 of these 15 had received antimalarial therapy (all had P. vivax). Three of the 15 had P. falciparum infection and none of these had received antimalarial therapy. They presented with parasitemias of 0.6, 1.8, and 47% respectively.

Clinical Features and Treatment at Fairfield Hospital

The main clinical features of the 264 episodes are shown in Table 2. Overall, fever (temperature ≥ 37.5°C) was documented in 187 (70.8%) cases, and in 76 cases where fever was not recorded 75 individuals reported

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Table 1 Region or Country of Likely Acquisition of Malaria in 246 Patients Admitted to Fairfield Hospital

<table>
<thead>
<tr>
<th>Place of Birth</th>
<th>Australia (%)</th>
<th>NZ, Europe (%)</th>
<th>Endemic Malaria (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of People with Malaria</td>
<td>133 (54)</td>
<td>23 (9)</td>
<td>90 (37)</td>
<td>246</td>
</tr>
<tr>
<td>Area of Travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia*</td>
<td>32 (24)</td>
<td>9 (39)</td>
<td>20 (22)</td>
<td>61 (25)</td>
</tr>
<tr>
<td>Asia†</td>
<td>5 (4)</td>
<td>2 (9)</td>
<td>29 (32)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Africa‡</td>
<td>20 (15)</td>
<td>3 (13)</td>
<td>9 (10)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>PNG, Bougainville</td>
<td>55 (41)</td>
<td>7 (30)</td>
<td>24 (27)</td>
<td>86 (35)</td>
</tr>
<tr>
<td>Solomon Islands and Vanuatu</td>
<td>13 (10)</td>
<td>8 (9)</td>
<td>21 (9)</td>
<td></td>
</tr>
<tr>
<td>Central, South and North Americas</td>
<td>4 (3)</td>
<td>2 (9)</td>
<td>4 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Multiple countries§</td>
<td>4 (3)</td>
<td>2 (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Southeast Asia: Indonesia, Myanmar, Thailand, Malaysia, Indochina, or not otherwise specified.
†Asia: refers to travel in India, Sri Lanka, or Pakistan.
‡Includes 5 who had traveled in both southeast Asia and Asia.
¶Multiple countries refers to travel in at least 3 of the other areas in the Table.
Rigors and/or sweats before admission. One PNG-born schoolgirl had no fever or history suggestive of fever, but had malaria previously and was likely to have been semi-immune. Rigors were reported in 154 (58.3%) cases and were less common in P. falciparum infections compared with P. vivax (RR 0.70, 95% CI 0.53–0.93, p = .008). Gastrointestinal symptoms were reported in 137 (52%) cases. Although diarrhea was reported in only 47 (18%) cases it was more common with P. falciparum (21/71) than P. vivax (25/177) infections (RR 1.90, 95% CI 1.27–2.84, p = .006). This association was still significant after exclusion of 13 patients with coincidental fecal pathogens. There were 6 patients with severe falciparum malaria (8.4% of P. falciparum episodes) according to WHO criteria. Several patients had more than one criterion; these included severe anemia (1), pulmonary edema (1), renal failure (2), and hyperparasitemia (4). There were no deaths.

A variety of standard treatment regimens including quinine and Fansidar or doxycycline, chloroquine, and chloroquine and primaquine, were used for these patients, depending on the species of Plasmodium and the initial response to therapy.

Laboratory Results

The median parasitemia for P. falciparum was 0.33% (range 0.0001–47%), for P. vivax was 0.20% (range 0.0001–1.78%), and for P. ovale was 0.01% (range 0.01–0.02). The first thick and thin smear at Fairfield Hospital was negative in 5 patients. All had self-medicated or received antimalarial therapy from an outside source. Seven patients with P. falciparum had a parasitemia of ≥5%. One hundred and fifty-eight patients had an abnormal C-reactive protein (CRP) (≥10 mg/L) and in 64 it was ≥100 (mean 87.2, range 7–309). One hundred and sixty-nine patients had thrombocytopenia, and severe thrombocytopenia (platelets ≤50 × 10^9/L) was more common in P. falciparum infections (RR 2.35, 95% CI 1.09–5.08, p < .05). Two patients had Glucose-6-diphosphate (glucose-6-phosphate dehydrogenase) deficiency. Other hematological and biochemical investigations are shown in Table 3.

Duration of Hospitalization and Readmissions

There were 48 admissions where inpatient management was required for 5 days or longer. Fifteen had P. vivax and 33 had P. falciparum infection. P. falciparum was significantly more likely to cause a hospital stay of more than 4 days when compared with P. vivax infection (RR 5.64, 95% CI 3.27–9.73, p < .0001). The gender of the patient, the country of birth (malarious or nonmalarious), the use of prophylaxis, and the duration of symptoms before treatment were not associated with a hospital stay of more than 4 days. Fever persisted for 5 days or more after commencement of antimalarial chemotherapy in 8 patients (range 0–13 days, median 1 day). All but one of...
these patients had *P. falciparum* infection. Blood cultures were taken for 7 of these patients and were negative.

Fifteen people were readmitted to Fairfield Hospital with recurrent malaria during the study period. Twelve were admitted twice, and 3 were admitted three times. Three of the 15 became reinfected when they returned to a malaria country. One patient with *P. vivax* infection who did not receive primaquine therapy was readmitted after 4 weeks with recurrent *P. vivax*. Six patients (4%) with *P. vivax* infection (from Southeast Asia [3], PNG [2], and the Solomon Islands [1]) who had received chloroquine and primaquine therapy were readmitted with recurrent *P. vivax*. Four patients with *P. falciparum* represented between 7 and 36 weeks after treatment with *P. vivax* infection. Three of these had received primaquine therapy. One patient had quinine-resistant *P. falciparum* malaria acquired in Thailand. He was admitted three times with recurrent parasitemia. On the first two occasions he was treated with quinine and doxycycline and on the third occasion was treated successfully with halofantrine and doxycycline.

### Discussion

We describe here the epidemiological and clinical features of 264 consecutive patient admissions with imported malaria, representing the largest Australian case series reported, and over half of the cases of malaria notified in the state of Victoria during the study period.

Papua New Guinea, the Solomon Islands and Vanuatu, were most frequently recorded as the presumed areas in which malaria was acquired in this series (44%). This is likely to be a significant association as the total number of travelers arriving in Australia directly from these countries in 1994/1995 constituted only 11% of travelers returning from malaria-endemic areas during that 12 month period. The high incidence of malaria in Australian residents returning from these countries has been recorded in previous reports. In one of these the risk of malaria in those returning from PNG and the Solomon Islands was estimated as 5–6 times that of residents returning from Africa. Anantimalarial chemoprophylaxis prevents and reduces the severity of malaria if appropriate medications are taken for the areas visited, and if the drug(s) are taken regularly during travel and for 4 weeks after leaving the malaria endemic area. Several factors resulted in 139 people in this study acquiring malaria despite having used chemoprophylaxis. Chemical prophylaxis does not prevent recurrences of or late-onset *P. vivax* malaria, and 113 people (46%) developed *P. vivax* at least 4 weeks after return to Australia. Importantly, less than one-third who took prophylaxis, and for whom information was available, took the medications regularly during, and for the required period after, travel. Even though more than half of the 139 cases were prescribed the correct drug(s) according to guidelines that were current during the study period (1990–1995), it is now evident that the use of chloroquine and/or Maloprim was insufficient protection against *P. falciparum* malaria in many areas during this period because of rapidly developing parasite resistance to these drugs. As the study was conducted in the first half of the 1990s, information collected about the types of drugs used for chemoprophylaxis is now less relevant. The current CDC and WHO guidelines have been simplified, as Fansidar and Maloprim are no longer routinely used. Mefloquine or doxycycline is now the usual agent of choice if chemoprophylaxis is required.

Settlers and visitors from malaria-endemic areas (37% of our series) were identified as a group significantly less likely to take chemoprophylaxis. Antimalarial prophylaxis would not have been prescribed as a routine in their home country, and so those who had recently arrived would have been susceptible to acute malaria acquired before departure, or to relapses of *P. vivax* and *P. ovale*. In addition, settlers who have had previous exposure to malaria may not perceive the need for chemoprophylaxis for home visits. However, immunity to clinical malaria is short-lived (months rather than years), and malaria in those living abroad and returning home for short visits is well documented.

*P. vivax* and *P. falciparum* infection are clinically indistinguishable, although the finding that diarrhea occurred more frequently in *P. falciparum* is of interest and has been reported elsewhere. Rigors were more common in *P. vivax* infections, which is in keeping with the known rapid synchronization of *P. vivax* asexual stage parasites. *P. vivax* infection is also more likely to present with classical paroxysmal fever (cold, hot, sweaty stages) than *P. falciparum*, which often presents in a more atypical fashion. We found no association between *P. vivax* infections and high temperature on admission (≥39.5°C), although others have reported this finding.
P. falciparum did cause significant morbidity with 46% of patients requiring a hospital stay of 5 days or longer. Six patients met WHO criteria for severe falciparum malaria, which is similar to other reports, and required exchange transfusion for hyperparasitemia. The selection of patients admitted to an infectious diseases hospital may have led to an identification bias as these cases may have been sicker than those admitted elsewhere. However, the proportion of P. falciparum patients in this series was similar to that reported in two series from Queensland and New South Wales.

There were no deaths in this study but there were 3 deaths elsewhere in Victoria between 1990 and 1996 due to P. falciparum, emphasizing the need for early detection and prompt treatment of imported malaria infections. The finding of thrombocytopenia (71% of episodes in this series) should alert medical practitioners to the possibility of malaria even if the initial thick and thin blood smears are negative.

The number of malaria cases imported into developed countries is likely to continue to increase due to increasing numbers of travelers to malaria-endemic areas each year, and the growing problem of parasite resistance to antimalarial drugs. Accurate surveillance of both the epidemiological and clinical features of imported malaria infections must therefore remain a public health priority. Medical practitioners need to be vigilant in excluding the diagnosis of malaria in patients presenting with fever, or a history of chills, sweats or rigors, and who have traveled in a malaria endemic area in recent weeks or months.

Acknowledgments

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References