CURRENT TOPIC

Imported malaria in children in the UK

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Children are particularly at risk from malaria since symptoms can be especially severe and can develop rapidly. Deterioration is related to rapid increases in parasite density, which probably relate to the lower red blood cell mass and immunological immaturity in children.[1] Symptoms may differ from those in adults and, as children often have febrile illnesses, malaria may not be suspected. Young children may be less likely to report specific symptoms and are more likely to have higher fevers and greater vomiting and hypoglycaemia than adults. The occurrence of side effects of antimalarial drugs is also different in children[2] and they can have greater difficulty in retaining drugs given by mouth, partly because of the bitter taste of some antimalarial drugs. Cases of imported malaria in children are increasing and it is timely to consider the background to this problem and to review approaches to prevention and management.

From 1 January to 31 December 1995 there were 2055 cases of imported malaria in the UK reported to the Malaria Reference Laboratory, of which 306 (14.9%) occurred in children less than 15 years of age (personal communication, 1996). For comparison, in the Netherlands a lower proportion of all cases of imported malaria between 1991 and 1994 occurred in children (26/280; 9.3%).[3] Figure 1 shows the number of children with malaria in the UK over the past five years grouped into three age categories. There is little difference in occurrence between these age groups, although there were fewer cases in younger children (1–5 years) for three of the five years shown. It is not known how many of the infants had congenital malaria. Most cases of malaria in children since 1991 have been due to *Plasmodium falciparum* (56.0%), with *P vivax* accounting for 35.7% (table 1). Overall the ratio of cases of *falciparum* to *vivax* has increased from about 37% in the mid-1980s to about 55% in the mid-1990s. The practical implications of an increasing proportion of cases of malaria due to *P falciparum* is the greater risk that these will be life threatening. The increased number of reported cases of malaria in children in 1995 may reflect the increasing incidence of chloroquine resistant *P falciparum* malaria in tropical countries.

Plasmodium vivax and *P ovale* can relapse from dormant liver stages (hypnozoites), whereas *P falciparum* only recrudesces after incomplete suppression of the asexual parasites in blood, as it has no dormant hepatic stages. RI drug resistance is defined as the clearance of parasitaemia for at least two days, followed by recrudescence. RII resistance occurs if there is a marked reduction of asexual parasitaemia to less than 25% of the pretreatment parasite density within 48 hours, but without the subsequent disappearance of asexual parasites. RIII resistance occurs if there is a modest change, no change, or an increase in asexual parasitaemia during the first 48 hours. The continued use of chloroquine in many parts of Africa and Papua New Guinea is possible because, despite the emergence of chloroquine resistant malaria, many strains maintain primarily RI resistance in semi-immune subjects. In non-immune subjects there is no possibility of acquired malaria immunity enhancing parasite suppression by chemotherapy and RI resistant strains will show a greater drug resistance in these subjects. For this reason chloroquine can no longer be used for the treatment of non-immune patients returning from most endemic regions.

Table 2 gives the geographical sources of malaria infection between 1991 and 1995. The highest proportion of infections was acquired in Nigeria, which reflects the large population of this country and the frequency of return travel of families of Nigerian descent. Ghanaian children were the second most frequently infected African group. Nearly all these West African infections were due to *P falciparum*. *P vivax* is not endemic in West African countries, which is attributed to protection from this infection due to the absence of the Duffy blood group in the indigenous people. Most of the *P*

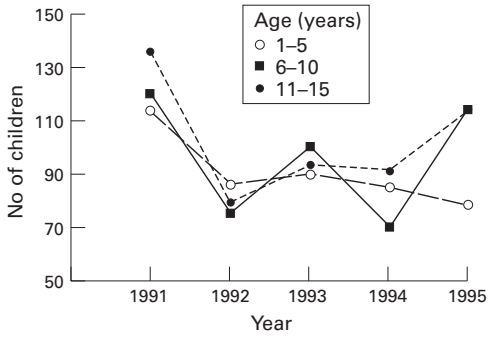

Figure 1 Cases of imported malaria in children in the UK notified to the Malaria Reference Laboratory between 1991 and 1995.

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Table 1 Parasite species in childhood with imported malaria (1991-5)

Species	*No (%)*
P falciparum	809 (56.0)
P vivax	516 (35.7)
P ovale	59 (4.1)
P malariae	27 (1.9)
Mixed infections*	34 (2.3)

*P falciparum and *P vivax*.
Source: Malaria Reference Laboratory.

Table 2 Main countries of origin of infection with malaria (1991-5)

Country	*No (%)*
Nigeria	309 (21.4)
Pakistan	259 (17.9)
India	233 (16.1)
Ghana	172 (11.1)
Other countries	472 (32.7)

Source: Malaria Reference Laboratory.

ovale infections were from Nigeria and Kenya. Far fewer infections were reported from East Africa, where the risk was greatest for travellers from Uganda, Kenya, and Tanzania. The proportion of all cases of malaria in children from the Indian subcontinent was also high (34%), with most of these (>90%) due to *P vivax*.

Visits of long term immigrants and their children to their families in their country of origin were responsible for more imported cases of malaria in 1995 than any other single category of travel. In the same year children visiting parents living abroad accounted for only three cases. The large number of cases in immigrant travellers highlights the danger of assuming that African or Asian nationals are protected by a degree of immunity acquired earlier. Malaria immunity in children born in the UK to immigrant parents can be assumed to be effectively zero. In children born overseas, but brought up in the UK, naturally acquired malaria immunity will rapidly wane without repeated re-exposure to malaria infection.

Table 3 gives information on the date of arrival in the UK and the date on which malaria was diagnosed for all imported cases for which information was available in 1995 (adults and children). Eighty eight per cent of cases of *falciparum* malaria were apparent in the first month after return or arrival in the UK and 99% within six months. By contrast, only 30% of *vivax* cases were first diagnosed within a month of return or arrival. Untreated *vivax* or *ovale* malaria (if not fatal) is notoriously persistent, with relapsing fever over several years. This results from the reactivation of dormant hypnozoites which are present within the hepatocyte. In a subspecies the first clinical attack of malaria may not occur until several months after the initial infection because all the sporozoites infected by the mosquito are hypnozoites.[4] This subspecies appears to be restricted to the Mediterranean, parts of Russia, and the Indian subcontinent. Formerly, the malaria parasite which was undoubtedly transmitted in England was *P vivax*.

Diagnosis of malaria

Malaria can present in a variety of ways, which often leads to misdiagnosis or delayed treatment. A delay in diagnosis can lead to an increased risk of serious morbidity. The first essential step is to obtain a travel history in children with a history of fever. Any child with such a history who has travelled to a malarious area, particularly in the previous year, but even up to five years ago, must have a malaria blood slide taken. The pattern of fever the child experiences may not be typically periodic as it may be altered by previous malaria chemoprophylaxis and may anyway be irregular in early *falciparum* infection. Non-immune patients, receiving prophylaxis, and with drug resistant malaria often present with signs and symptoms that are different from the classical features of acute clinical malaria. The appearance of chloroquine resistance has important implications in relation not only to malaria diagnosis, but also for treatment and chemoprophylaxis.

A return of fever a number of months after the primary treatment of *falciparum* malaria may be due to a relapsing *vivax* or *ovale* infection if the child initially had a mixed infection. For this reason malaria must be excluded with recurrent fevers even after successful primary treatment of *falciparum* malaria which does not relapse, although it may recrudesce after inadequate treatment.

Not uncommonly, an initial diagnosis of 'flu' is made. The presenting disorders can mimic a wide range of infections and symptoms may include diarrhoea, vomiting, and a cough. Fever and headache are usually present.[5 6] In the younger child fever could precipitate a febrile convulsion. Symptoms may rapidly progress to coma. Congenital malaria may occur after previous infection in a semi-immune mother and these infants, who have a degree of passively acquired immunity, may not present until 3–6 weeks of age, when they become acutely ill with respiratory symptoms, anaemia, jaundice, and splenomegaly.[7 8] These infants are often initially misdiagnosed because their mothers have remained asymptomatic despite low grade parasitaemia and placental infection. Cases of congenital malaria have been described for all four human malaria species.

Findings on physical examination may be non-specific. Fever is nearly always present, but anaemia, jaundice, and splenomegaly may be absent. Any child with *falciparum* malaria could deteriorate rapidly and if a diagnostic film is requested the result should be obtained immediately and always on the same day. Complications may occur within hours of the initial symptoms. Both a thick and a thin blood film should be made and the attending doctor should be familiar with these techniques. The film may be made directly from a finger prick sample or a venous sample collected into an EDTA tube. Ideally, 200 oil immersion fields of a thick blood film should be examined before a negative result is given. Two blood films should be prepared and examined separately for cross checking. If the laboratory is not familiar with

Table 3 Stated time interval between return to the UK and diagnosis of malaria (children and adults, 1995)

Interval	*P falciparum*	*P vivax*	*P malariae*	*P ovale*	*Mixed*
< 1 month	595	133	6	15	11
1-5 months	71	139	12	52	4
6-11 months	4	137	3	11	5
> 1 year	3	35	0	5	1

Source: Malaria Reference Laboratory.

examining thick films, then the whole of a thin film should be examined. The thin film is of most use for distinguishing parasite species. A negative film does not categorically rule out malaria and additional films must be made should symptoms persist.

New techniques for the rapid diagnosis of malaria are available. The quantitative buffy coat (QBC) tubes for detecting malaria parasites stained with acridine orange have good sensitivity and specificity in diagnosing malaria,[9] although it requires specialised equipment, does not distinguish between malaria species, and is an expensive technique. Thin blood films are required from a blood sample which is positive for malaria parasites by the QBC method to identify parasite species. The ParaSight-F test, for the detection of *P falciparum* antigen on a test strip, has been shown to have high sensitivity and specificity in patients with imported malaria, is performed quickly, and is easy to read visually. For cases of imported malaria the test's specificity and low threshold for detection could make it a valuable adjunct test, particularly in facilities where staff have little experience in malaria microscopy.[10] It is also a useful test when it is unclear whether a *P vivax* infection is mixed with a light *P falciparum* infection. It cannot replace microscopic techniques, however, which are species specific, quantitative, and show the parasite.

Treatment of malaria

COMPLICATED MALARIA

A practical approach to treatment has been summarised by Molyneux and Fox[6] and a detailed report on the features and management of complicated malaria has been published by the World Health Organisation (WHO) and the Royal Society of Tropical Medicine and Hygiene.[11] All patients with malaria should be admitted to hospital because of the possibility of rapid progression in severity. In the Dutch series of imported cases reported by Wetsteyn *et al*,[3] severe complicated *falciparum* malaria developed in 10% of 286 patients (children and adults), two of whom died.

In the UK complicated malaria would be considered in anyone with a parasitaemia of 2% or more, or vomiting, or who for any other reason is unable to take drugs by mouth. Children are especially likely to present with high fever, vomiting, and hypoglycaemia, and may have difficulty in retaining drugs given by mouth. The recognition of any of the severe clinical manifestations of malaria indicates a complicated course and any child with even a slight alteration of consciousness with peripheral parasitaemia should be considered to have cerebral malaria and should receive emergency treatment.

All patients with complicated malaria should be treated initially with quinine intravenously. In severe malaria an initial loading dose must be given by slow infusion. The dose is quinine dihydrochloride salt (20 mg/kg body weight) in 5% dextrose saline (5–10 ml/kg body weight depending on fluid balance) over four hours. Eight hours after starting the loading dose a maintenance dose is given (10 mg/kg), diluted as above, over four hours. The maintenance dose is repeated every eight hours until the child can take drugs by mouth. The total duration of treatment with quinine is seven days or longer until the blood smear is negative. If over 10% of red blood cells are parasitised in the presence of clinical complications, exchange transfusion should be considered.[12]

If the child contracted malaria in a country with suspected quinine resistance (for example, South America and Asia), the addition of a second antimalarial drug is indicated. Quinine treatment should then be combined with seven days of daily doxycycline (children >12 years) or a treatment dose of sulfadoxine pyrimethamine. These drugs should be added two to three days after the start of quinine treatment to avoid the confusion of the adverse effects of quinine with the second drug. In children less than 12 years of age clindamycin (8–16 mg/kg daily in four divided doses) is a treatment option in combination with quinine, although it is a more toxic drug and experience with its use in children is limited.[13]

Artemisinin[14] and derivatives should primarily be restricted to the management of severe malaria in cases acquired in areas with multidrug resistant *P falciparum* infection where quinine may not be effective (for example, Southeast Asia). Artemisinin compounds clear malaria parasites more rapidly than all other antimalarial drugs without apparent toxicity. Children tolerate the drugs well and show as good a therapeutic response as adults. If used alone a seven day course is necessary in a non-immune child. In semi-immune patients in endemic areas shorter courses can be combined with a longer acting antimalarial drug such as mefloquine. This combination gives a rapid initial therapeutic response and protects artemisinin compounds from developing resistance as the longer acting antimalarial drug eliminates residual parasites. There are several chemotherapy strategies under development which combine artemether type compounds with more traditional quinoline type drugs. One example currently in phase III clinical trials is co-artemether (CGP.56697), which is a combination of artemether and benflumetol.

UNCOMPLICATED MALARIA

Chloroquine was the drug of choice for the treatment of acute uncomplicated *P falciparum* malaria for many years, but it is no longer recommended in view of the widespread resistance which has developed progressively since the first reported resistant cases in 1960 in Colombia. The first chloroquine resistant case of *falciparum* malaria from East Africa was

Table 4 Malaria prophylaxis reported in children with imported malaria (1991-5)

Antimalarial prophylaxis	*No (%)*
Unknown	538 (37.3)
None	712 (49.4)
Chloroquine weekly	77 (5.3)
Chloroquine weekly and proguanil daily	73 (5.1)
Proguanil daily	12 (0.8)
Mefloquine weekly	4 (0.3)
Pyrimethamine/dapsone	7 (0.5)
Amodiaquine	1 (0.1)
Drug(s) taken but not specified	18 (1.2)

Source: Malaria Reference Laboratory.

reported in 1979, but now almost all countries of sub-Saharan Africa have chloroquine resistant malaria and it is an increasing problem in West Africa. Chloroquine remains effective against malaria acquired in the Middle East, the Caribbean, and Central America. Children with uncomplicated *falciparum* malaria could be treated with either quinine by mouth for at least seven days or until the blood smear is negative, or sulfadoxine pyrimethamine, or mefloquine. The decision rests on the area of origin of the infection and the clinical state of the child.

Monotherapy with quinine by mouth in children may become complicated because the seven day regimen causes compliance problems due to the drug's side effects (cinchonism), which occur in up to 70% of patients. Hypoglycaemia is the most serious common side effect. Quinine toxicity (hypotension, central nervous system disturbances, visual and auditory side effects) may be confused with the development of severe malaria, which should be differentiated by determining blood levels of quinine. A shorter three day course by mouth can be combined with a treatment dose (on day 3) of sulfadoxine pyrimethamine, which has a longer duration of action and should clear residual parasites. Shortened courses of quinine (three days) with antibiotic combinations are most appropriate in semi-immune children, however, and cannot be recommended for UK residents. Resistance to sulfadoxine pyrimethamine is now emerging in Africa and is widespread in Southeast Asia. Sulfadoxine is contraindicated in children with sulphonamide hypersensitivity.

Mefloquine is not recommended for children weighing less than 15 kg or less than 2 years of age, or in those with epilepsy or pre-existing neurological or psychiatric disease. Significant neuropsychiatric adverse effects have been reported after mefloquine treatment in between one in 200 in one in 1200 adults. Encouraging data from a clinical trial in Gabon has shown that the drug combination atovaquone plus proguanil is a highly effective and safe drug combination in patients with acute uncomplicated *P falciparum* malaria.[15] The combination acts synergistically and therefore may overcome the problem of resistance with individual drugs.

Experience with halofantrine, previously recommended as a standby drug, has shown adverse effects on the heart.[16] Consequently, the Malaria Reference Laboratory Committee no longer recommends its use for the traveller as standby treatment.[17] The committee states 'use should be restricted to the treatment of acute multi-drug resistant falciparum infections in hospital or clinical settings following parasitological and careful clinical diagnosis'. It has been shown to prolong the QTc interval, which occurs particularly with the recent or concomitant use of mefloquine. Because of its variable bioavailability and toxicity it should only be used as an emergency treatment in patients known to have normal QT intervals.

Plasmodium vivax and *P ovale* malaria should be treated with chloroquine over three days, followed by primaquine daily for 14–21 days for antirelapse treatment. The duration of primaquine treatment depends on the area of origin of *vivax* malaria. In most instances it should only be used for 14 days, but for Southeast Asia and Western Pacific *vivax* strains it should be used for 21 days.[18] Glucose-6-phosphate dehydrogenase deficiency should be excluded before treatment is given. Primaquine resistance does exist and in resistant cases the dose can be increased or used for 21 days. With a suspected deficiency an intermittent treatment regimen (0.75 mg base kg) weekly for eight weeks may be used under medical supervision. Primaquine is contraindicated in children less than 1 year of age. Potentially chloroquine resistant *vivax* malaria (that is, those from Papua New Guinea, Irian Jaya, the West Pacific, and Cambodia) should be followed up with weekly blood smears for at least four weeks. *P malariae* infections should be treated with chloroquine only. Unclassifiable infections should be managed as *falciparum* malaria.

Malaria prophylaxis

That prophylactic antimalarial drugs reduce the incidence of malaria is illustrated by the fact that 49.4% of children with imported malaria in 1995 had not received any malaria chemoprophylaxis (table 4). This arises partly because many people from overseas living in this country do not feel they need prophylaxis when returning home. This table also shows that, of those who took drugs, imported malaria was most common with chloroquine use, although it is not possible from the statistics available to say anything about compliance in these children. The principles of prevention have been summarised by Bradley and Warhurst[17] and Bradley.[19]

(1) Be aware of the risk.

(2) Avoid being bitten by mosquitoes. This can be achieved with the use of insect repellents, impregnated bed nets, and appropriate clothing. Preparations containing diethyltoluamide may be applied to the exposed skin as repellents. The manufacturer's recommendations should be carefully followed, especially with young children. Bedrooms should be properly screened and the room should be sprayed with a knockdown insecticide in the evening. Mosquito coils may be burned.

(3) Take appropriate chemoprophylaxis. This should be started one week before leaving for and for four weeks after return from infected areas. It should be taken even for the briefest exposure if visiting a malarious area.

Table 5 Prophylactic antimalarial drugs for children

Age	*Weight (kg)*	*Weekly chloroquine* (Nivaquine)*	*Daily proguanil† (Paludrin)*	*Weekly mefloquine‡ (Lariam)*	*Weekly dapsone-pyrimethamine§ (Maloprim)*
0-5 weeks	< 4	5 mg base/kg	0.25 tablet	NR	NR
6-52 weeks	4-10	5 mg base/kg	0.25 tablet	NR	1/8 tablet or syrup
1-5 years	10-19	0.5-0.75 tablet	0.50-0.75 tablet	0.25-0.5 tablet‡	0.25 tablet
6-11 years	20-35	0.75-1.25 tablet	1.0 tablet	0.50-0.75 tablet	0.5 tablet
⩾ 12 years	>36	1.25-2 tablet	1.0-2.0 tablet	0.75-1.0 tablet	1.0 tablet

* 150 mg base chloroquine tablet. Prophylactic dose 5 mg base/kg body weight weekly. Paediatric syrup available.
† 100 mg proguanil hydrochloride tablet. Prophylactic dose 3 mg/kg body weight daily, for younger children powdered on to food.
‡ 250 mg base tablet. Prophylactic dose 5 mg base/kg body weight weekly. Only if over 2 years or >15 kg.
§ Pyrimethamine 12.5 mg, dapsone 100 mg tablet. Paediatric syrup for infants, only available in Zimbabwe.
NR = not recommended.

(4) Seek early diagnosis and treatment. Do not assume that compliance with a recommended prophylactic schedule will guarantee protection. No chemoprophylaxis will ensure this.

There are three alternative drug regimens to be taken by mouth for prophylaxis of malaria in children (table 5).[17 20]

CHLOROQUINE AND PROGUANIL

Weekly chloroquine is effective only in areas without chloroquine resistant *falciparum* malaria, which are very few, mainly Central America and parts of the Middle East. In areas with a low prevalence of chloroquine resistant *falciparum* malaria, such as the Indian subcontinent, proguanil is also given daily with weekly chloroquine. Serious side effects from chloroquine are rare, but pruritus is common among dark skinned people and may be reduced by calamine lotion. Transient headaches and gastrointestinal symptoms may occur and rarely blood or neurological disorders. It is contraindicated in children with epilepsy. Irreversible visual impairment due to retinopathy is a recognised rare side effect with long term use (cumulative total dose 1 g base/kg body weight within 3–5 years). Intermittent eye checks are recommended with long term use.

MEFLOQUINE

Weekly prophylaxis with this drug is recommended by the WHO for travellers to areas with a significant risk of chloroquine resistant *falciparum* malaria. Information on its use in children is scanty and because of a lack of experience it is usually recommended that mefloquine should not be given to children weighing less than 15 kg. Studies in Africa and Thailand have shown it to be safe in treatment doses in young children,[21] although fatal toxic epidermal necrolysis associated with mefloquine prophylaxis has been reported in a child.[22] Neuropsychiatric side effects are the main cause for concern (dizziness, nightmares, anxiety, fits). In a British survey adverse events with mefloquine which were more than trivial occurred in 17.3% of users.[23] Overall side effects with mefloquine occur in about 20% of users. Most events with prophylaxis occurred within one to three weeks of starting prophylaxis. Serious adverse events may be as infrequent as 1/10 000, which is not high enough to interfere with the recommendation to use mefloquine in highly chloroquine resistant areas. Mefloquine is contraindicated in children with a history of convulsions, epilepsy in first degree relatives, or pre-existing psychiatric disorders.

DAPSONE PYRIMETHAMINE

This weekly prophylactic has been used in white adults in Papua New Guinea and the Western Pacific, sometimes in combination with chloroquine. It is only currently available as a liquid preparation in Zimbabwe. Experience with its use in young children (<5 years) is limited, but it has been recommended as a prophylactic by the Malaria Reference Laboratory when other drugs cannot be used. Side effects, which primarily relate to the sulphone component, include methaemoglobinaemia and haematological changes; fatalities have occurred. These are most likely to have their onset shortly after starting prophylaxis. The manufacturers recommend monitoring for bone marrow depression if the drug is taken for a prolonged period. If the child reports a sore throat, a blood film to check for leucopenia must be taken. The drug should not be given to children with a known history of hypersensitivity to sulphonamides, sulphones, or pyrimethamine.

Maintenance of compliance with prophylaxis is a particular problem as this decreases with the length of stay abroad, although reliable figures for this in children are not available.

Conclusions

Cases of imported malaria in children are likely to increase in Britain in the next few years with the emergence of increasing resistance of parasites to several antimalarial drugs. No prophylactic drug(s) can guarantee protection. It is essential that any child with fever who has travelled to a malarious area in the last year should be screened with a blood smear for malaria as soon as possible. Early diagnosis and treatment of such children will prevent serious sequelae or death.

The authors are grateful to staff at the Public Health Laboratory Service, Malaria Reference Laboratory, and to Dr G Wyatt and Dr J W Bailey for their advice on this paper.

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