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Review

Imported malaria in children: a review of clinical studies

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Imported malaria is a preventable disease, yet it is responsible for several thousand cases and a substantial number of deaths every year. There has been a pronounced rise in the incidence of imported malaria in most developed countries over the past three decades and, more concerning, *Plasmodium falciparum*, which is responsible for almost all cases of severe malaria, is now the most prevalent species. Children account for around 15–20% of all imported malaria cases and must be considered separately from adults because they have different risk factors for developing malaria and a higher risk of developing severe disease since they are more likely to be non-immune to malaria. We did a thorough review of the literature since 1980 to identify and critically assess clinical case series on children with imported malaria with respect to travel destination, reason for travel, the use of antimalarial prophylaxis, clinical presentation, delay in diagnosis, laboratory features, complications, management, and outcome. Children living in non-endemic countries and travelling during school holidays to visit family and relatives in their parents' country of origin currently account for the largest proportion of cases in many European countries. This group of travellers deserves special attention because they often do not take antimalarial prophylaxis or other preventive measures. There is a need for standardised recommendations on management and prevention of imported malaria in children, which should be supported by large multicentre clinical trials. A prospective national surveillance study on imported malaria in children was launched in the UK and Ireland through the British Paediatric Surveillance Unit in 2006, which may provide answers to some of the questions raised in this Review.

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Introduction

An estimated 10% of the world's population will have a clinical attack of malaria.[1] More people are dying from malaria now than 30 years ago and malaria is returning to areas where it had previously been eradicated. It is estimated that there are between 300 million and 500 million cases of malaria every year and between 1 million and 3 million deaths attributable to malaria, mainly in young African children.[2] These deaths are almost all caused by infection with *Plasmodium falciparum*.

Imported malaria is defined as an infection acquired in a malaria-endemic area but diagnosed in a non-endemic country after development of clinical symptoms. In most developed countries where malaria is not endemic, there has been a pronounced rise in the incidence of imported malaria in the past three decades.[3,4] In particular, the proportion of imported malaria cases caused by *P falciparum* has increased substantially since the 1980s.[3,4] The Malaria Programme in the WHO European Region, which collects annual data on laboratory-confirmed malaria cases from 51 countries in the region, reported an eight-fold increase in the number of imported malaria cases between 1972 and 1988 (from 1500 to 12 000 cases), followed by a more gradual rise to 15 500 cases in 2000.[3] Most cases were imported into western Europe, with France, the UK, Germany, and Italy accounting for more than 70% of all cases in Europe in 1998. In 2002, the last year for which complete data is available, these four countries accounted for 78·5% of 13 227 cases. However, the true incidence of imported malaria is difficult to obtain because of substantial under-reporting—estimated at 20–60%—even in countries with enhanced surveillance.[4,5]

Children account for around 15–20% of all imported malaria cases (figure).[6] This group must be considered separately from adults because children have different risk factors for developing malaria and a higher risk of developing severe disease since they are more likely to be non-immune to malaria.[7] The aim of this paper is to identify and critically review clinical case series on children with imported malaria with respect to travel destination, reason for travel, the use of antimalarial prophylaxis, clinical presentation, delay in diagnosis, laboratory features, complications, management, and outcome.

Clinical studies identified

An extensive literature search identified seven European (table 1) and six North American (table 2) clinical studies on imported childhood malaria between 1980 and 2005 that fulfilled the search criteria. Individually, the clinical studies provided limited information because most

For more information on the **Malaria Programme in the WHO European Region** see http://www.euro.who.int/malaria

For more information on the **annual number of laboratory-confirmed cases of malaria** see http://data.euro.who.int/CISID

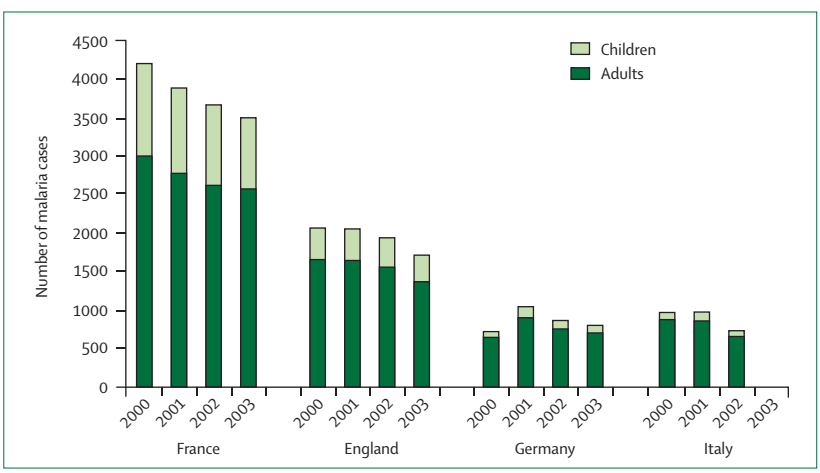

***Figure*: Number of malaria cases in adults and children (under 20 years of age) in the four countries with the highest prevalence of imported malaria**
Data from Karen Taksøe-Vester, Roll Back Malaria, WHO. Data for Italy for 2003 was not available.

Reference	Year, location, number of cases (proportion male; proportion immigrants)	Median age (range)	Malaria acquired in				White	Reason for travel*	Recent malaria in family or sibling	Prophylaxis†	Misdiagnosis‡	Delay in diagnosis
			Africa (West Africa)	Asia	Central/ South America	Other						
Minodier et al[8]	1987–1997, Marseilles, France 315 (50%; 15%)	5 years (0 –16 years)	97% (6%)	0%	1%	2%	0%	Visiting family	NR	208/259 (48/259)	NR	NR
Ladhani et al[9]	1996–2001, London, UK 211 (53%; 18%)	9 years (11 months to 15 years)	94% (77%)	6%	0%	0%	0%	Visiting family	23%	72/173 (26/173)	53%	1–14 days
Parez et al[10]	1999–2000, Paris, France 80 (NR; 0%)	8 years (3 months to 15 years)	100% (75%)	0%	0%	0%	NR	NR	NR	30/85 (4/85)	NR	NR
Begue et al[11]	1987–1988, Paris, France 70 (NR; 44%)	6·5 years (7 months to 15 years)	97% (41%)	0%	3%	0%	1%	NR	NR	30/38 (NR)	17%	Mean 3·3 days
Eloy et al[6]	1997–2001, Versailles, France 60 (53%; 0%)	9 years (3 months to 15 years)	100% (82%)	0%	0%	0%	10%	Visiting family	NR	42/60 (5/60)	NR	NR
Huerga and Lopez-Velez[12]	1990–1999, Madrid, Spain 49 (55%; 90%)	Mean 6·4 years (0 to 14 yrs)	98% (NR)	0%	2%	0%	2%	Visiting family	NR	3/5 (0/5)	2%	12 days
Cilleruelo Ortega et al[13]	1978–1988 Madrid, Spain 26 (69%; 0%)	5·8 years (10 months to 14 years)	100% (96%)	0%	0%	0%	8%	NR	54%	0/26 (0/0)	NR	NR

NR=not reported. *Most common reason for travel among non-immigrants. †Data are any/total (completed/total). ‡Initial proportion of cases misdiagnosed.

Table 1: **Cases of imported malaria in children in Europe**

Reference	Year, location, number of cases (proportion male; proportion immigrants)	Median age (range)	Malaria acquired in				White	Reason for travel*	Recent malaria in family or sibling	Prophylaxis†	Misdiagnosis‡	Delay in diagnosis
			Africa (West Africa)	Asia	Central/ South America	Other						
McCaslin et al[14]	1983–1992, Washington, USA 52 (NR; 33%)	6·2 years (5 months to 18 years)	98% (90%)	0%	2%	0%	4%	Visiting family	NR	19/35 (NR)	38%	NR
Miller and Banerji[15]	1984–2001, Vancouver, Canada 42 (67%/29%)	6·7 years (1 month to 14·8 years)	7% (NR)	91%	2%	0%	0%	Visiting family	5%	10/30 (0/30)	48%	1–7 days
Lynk and Gold[16]	1978–1988, Toronto, Canada 40 (NR; 60%)	5 years (1 month to 15 years)	40% (NR)	50%	10%	0%	10%	NR	25%	6/24 (NR)	44%	NR
Rivera-Matos et al[17]	1988–1993, Houston, USA 34 (56%; 26%)	NR (19 days to 18 years)	65% (44%)	15%	20%	0%	0%	Visiting family	10%	12/22 (3/22)	NR	NR
Viani and Bromberg[18]	1987–1995, New York, USA 20 (NR; 50%)	Mean 7·3 years (2 years to 16 years)	80% (80%)	0%	20%	0%	0%	Visiting family	NR	1/10 (0/10)	35%	3–6 days
Emanuel et al[19]	1985–1990, Chicago, USA 20 (75%; 85%)	NR (8 months to 18 years)	50% (NR)	50%	0%	0%	0%	NR	10%	0/3 (0/3)	90%	4–8 days

NR=not reported. *Most common reason for travel among non-immigrants. †Data are any/total (completed/total). ‡Initial proportion of cases misdiagnosed.

Table 2: **Cases of imported malaria in children in North America**

reported a small number (fewer than 100) of cases diagnosed over many years and involved children who developed malaria in different parts of the world and through different *Plasmodium* species. Only two studies, one from France and the other from the UK, reported more than 200 cases.[8,9] Furthermore, it was difficult to make comparisons between studies because they spanned over 25 years and involved many countries spread over two continents, each with their own treatment policies. The studies also included a heterogeneous paediatric population travelling to and from different destinations with varying risks of acquiring malaria.

However, summarising these studies into a single Review has provided a useful insight into many clinically important aspects of imported malaria in children.

Travel destinations and *Plasmosium* species

The *Plasmodium* species responsible for malaria varies considerably with the destination chosen by the traveller and the area the immigrant comes from (table 1 and table 2). The vast majority of *P falciparum* infections are acquired in sub-Saharan Africa, mainly west Africa.[20] In the UK between 1999 and 2003, for example, 99% (946 out of 954 cases) of *P falciparum* infections in children were acquired in Africa, whereas 88% (123 of 140 cases) of *Plasmodium vivax* infections were acquired in Asia.[21] The species responsible for malaria may also change over time as immigration and travel patterns change. Until the 1980s, *P falciparum* accounted for less than 30% of all cases in Europe but now accounts for more than 70% of all cases in most European countries.[3] Similarly, in the USA, the proportion of *P falciparum* infections increased from around 40% in the early 1990s[4] to more than 50% in 2001–2002.[22,23] This increase is considered to be a result of increasing numbers of visitors and immigrants from Africa, increasing popularity of holiday travel destinations to tropical countries, a reduction in the number of visitors and immigrants from the Indian subcontinent, and increasing *P falciparum* transmission in Asia. Even within a country, the species responsible for malaria in any particular region is related to the local population. In the UK, 80–90% of paediatric malaria in London is caused by *P falciparum*,[9,24] whereas in Birmingham over 80% of cases are caused by *P vivax*,[25] reflecting differences in ethnicity between these two cities.

Reason for travel

The past few decades have seen a pronounced shift in the reason for travel among patients with malaria. In the 1970s and 1980s, malaria was mainly diagnosed among immigrants travelling from malaria-endemic areas to non-endemic countries, particularly western Europe. Over the past decade, the majority of malaria cases in Europe have occurred in adults and children who are settled in non-endemic countries, but have travelled to their home country on holiday to visit friends and relatives (table 1 and table 2).[20] It has been suggested that the visiting friends and relatives group deserves separate consideration because they are less likely to seek pre-travel advice, or take antimalarial prophylaxis or bite prevention measures, and are more likely to travel to rural malaria-endemic areas for longer periods.[4,9,20,26] This group is also more likely to delay seeking medical help when returning to their country of residence, often because of cultural and language barriers.[7] In addition to the visiting friends and relatives group, there have been shifts in immigration patterns in recent years, particularly with many countries accepting large refugee populations from malaria-endemic areas. Immigrants and refugees, who account for up to 90% of imported malaria cases in some of the reported paediatric series (table 1 and table 2), usually have partial immunity to malaria and are, therefore, likely to present with more subtle, atypical, or no symptoms. Malaria diagnosis in this group is often made through routine screening.[27–30]

Seasonal association and age at infection

The seasonal incidence of imported malaria in children shows a distinct peak in the summer months and a smaller peak between December and January.[9,13,17,24,31] These peaks coincide with children travelling during school holidays. Imported malaria is seen in children of all ages, with similar numbers of infected children in the 1–5, 6–10, and 11–15-year age-groups.[7] Imported malaria in children under 1 year is uncommon.[9] A number of imported cases of congenital malaria (ie, the baby acquired the malaria infection from the mother during the latter stages of pregnancy and became symptomatic soon after birth in a non-endemic country) have been reported, but these, too, are rare.[22,32–36] One study reviewed the published literature between 1950 and 1992 and identified only 49 cases of congenital malaria in the USA, with *P vivax* accounting for 40 (82%) of the cases, most likely reflecting the epidemiology of endemic malaria in the country where the mothers acquired the infection (mainly southeast Asia, and South and Central America).[32]

Antimalarial prophylaxis

Uptake of antimalarial chemoprophylaxis has consistently been shown to be poor. Around 60% of travellers to malaria endemic countries take no prophylaxis, a further 15–20% do not take antimalarial drugs according to national recommendations and, of the remainder, over half do not complete prophylaxis.[20,22] Non-compliance varies with ethnicity,[37,38] with one study reporting that 78% of white British travellers took antimalarial prophylaxis compared with only 13·5% of travellers from

	Plasmodium species					
Reference	*P falciparum*	*P vivax*	*P ovale*	*P malariae*	Mixed	Unknown
Minodier et al[8]	72%	9%	3%	2%	9%	5%
Ladhani et al[9]	91%	6%	2%	0%	1%	0%
Parez et al[10]	73%	2%	5%	4%	16%	0%
Begue et al[11]	77%	13%	0%	1%	1%	8%
Eloy et al[6]	84%	5%	7%	0%	2%	2%
McCaslin et al[14]	100%	0%	0%	0%	0%	0%
Huerga and Lopez-Velez[12]	71%	2%	4%	4%	10%	9%
Miller and Banerji[15]	7%	88%	0%	0%	0%	5%
Lynk and Gold[16]	38%	60%	2%	0%	0%	0%
Rivera-Matos et al[17]	56%	23%	0%	3%	0%	18%

Case series with fewer than 30 children were excluded. For year of study, location, and number of cases see tables 1 and 2.

***Table 3: Plasmodium* species in children with imported malaria**

ethnic minorities.[39] Patients who take some form of prophylaxis are more likely to have a milder course of malaria, with fewer complications and lower parasitaemia even if the species is resistant to the antimalarial drug taken.[16,18]

In children, chemoprophylaxis uptake is particularly poor. The retrospective clinical series identified in table 1 and table 2 reported failure to take appropriate antimalarial prophylaxis in 20–100% of the children, with only 3–15% completing prophylaxis appropriately.[7,9,24] It remains unclear why prophylaxis uptake is so poor in children, but there is some suggestion that parents (particularly those born in a malaria-endemic country who subsequently emigrate to a non-endemic country) falsely assume that they and their children are protected from malaria because of their ethnic origin.[40]

Clinical features

Most individuals who develop symptoms of malaria do not become ill until after they return to their country of residence.[41] The duration between infection and development of symptoms varies considerably with the species responsible. *P falciparum* malaria mostly presents within a month, whereas *Plasmodium ovale* and *P vivax* infections can present up to a year (and sometimes longer) after travel.[7,9] In the published case series, presenting symptoms varied considerably, mainly reflecting the heterogeneity of the population studied and the infecting *Plasmodium* species (table 3 and table 4). Studies that included a substantial proportion of refugees, for example, reported that many children were asymptomatic, probably because they were partly immune to malaria.[12,15]

When compared with adults, children are less likely to complain of chills, arthralgia/myalgia, or headaches.[42] Instead, they are more likely to present with non-specific symptoms (fever, lethargy, malaise), with gastrointestinal symptoms (nausea, abdominal pain, vomiting, diarrhoea) being particularly common. Children also have hepatomegaly (56% of children *vs* 25% of adults), splenomegaly (48% *vs* 25%), and jaundice (48% *vs* 34%) more often than adults.[42] The characteristic regular tertian and quartan patterns of fever associated with malaria are seen in less than a quarter of paediatric cases. However, children are more likely to have high fever greater than 40°C (56% of children *vs* 25% of adults) and may present with febrile convulsions. Symptoms and signs can be masked in those who have received prophylaxis or partial treatment for malaria.[43]

It is interesting to note the number of studies (six of 13) reporting other travelling family members (mainly siblings) who also developed symptomatic malaria at around the same time as the index case (table 1 and table 2). In the largest of these studies, 49 of 211 (23%) children with malaria had at least one family member diagnosed with malaria (68 in total); 58 were siblings of the index case (30 boys, 28 girls), eight were parents (six mother, two father), and two were cousins.[9] Although these studies were all retrospective, a small prospective study offered screening to asymptomatic family members of 16 children diagnosed with malaria in one east London hospital and found that 15% were positive for *P falciparum*.[44] However, further larger studies are required before routine screening of travelling family members can be recommended.

Severe malaria

P falciparum is almost entirely responsible for severe disease in imported as well as endemic malaria worldwide.[45] The WHO definition of severe malaria aims to identify individuals most at risk of dying from malaria (panel).[45] For imported cases, the risk of developing

Reference	Symptoms									Signs			
	Fever	Chills/ rigors	Gastro-intestinal symptoms*	Upper respiratory tract symptoms†	Rheumatological symptoms‡	Drowsiness or irritability	Headache	Lethargy	Convulsions	Pallor	Hepatomegaly	Splenomegaly	Jaundice
Minodier et al[8]	92%	NR	50%	14%	NR	3%	15%	0%	1%	NR	28%	61%	NR
Ladhani et al[9]	98%	27%	68%	7%	2%	16%	40%	0%	14%	NR	32%	28%	NR
Parez et al[10]	98%	NR	44%	NR	NR	0%	40%	0%	3%	NR	NR	NR	NR
Begue et al[11]	96%	20%	30%	6%	NR	0%	27%	9%	1%	10%	44%	57%	NR
Eloy et al[6]	100%	15%	43%	22%	NR	7%	34%	24%	22%	NR	11%	13%	NR
McCaslin et al[14]	96%	56%	69%	21%	12%	0%	62%	0%	12%	27%	46%	40%	17%
Huerga and Lopez-Velez[12]	57%	NR	4%	18%	NR	0%	8%	0%	10%	NR	49%	39%	NR
Miller and Banerji[15]	100%	52%	62%	17%	NR	48%	52%	12%	10%	NR	14%	38%	NR
Lynk and Gold[16]	100%	50%	54%	5%	NR	0%	18%	44%	5%	NR	23%	64%	NR
Rivera-Matos et al[17]	97%	44%	44%	NR	NR	0%	35%	9%	0%	32%	24%	68%	12%

NR=not reported. *Abdominal pain, anorexia, vomiting, diarrhoea. †Mainly cough. ‡Arthralgia/myalgia. Case series with fewer than 30 children were excluded. For year of study, location, and number of cases see tables 1 and 2.

Table 4: **Clinical symptoms in children with imported malaria**

***Panel:* WHO criteria for severe malaria[45]**

Criteria for severe malaria (any one of the following)

- Impaired consciousness or coma
- Severe normocytic anaemia (haemoglobin less than 50 g/L)
- Renal failure
- Pulmonary oedema/acute respiratory distress syndrome
- Hypoglycaemia
- Circulatory collapse/shock
- Spontaneous bleeding/disseminated intravascular coagulation
- Repeated generalised convulsions
- Metabolic acidosis
- Haemoglobinuria
- Parasitaemia more than 5% in non-immune individuals
- Jaundice
- Fever more than 40°C

severe malaria includes young age (less than 5 years), delayed diagnosis, and non-immunity to malaria.[46] It is difficult to reliably estimate the incidence of severe malaria among imported cases. The WHO definitions were developed for use in malaria-endemic countries and may not necessarily be appropriate for imported malaria. The large number of criteria also makes it difficult to collect reliable data through notification systems. However, around 5–10% of children with imported malaria in reported clinical studies had features of severe malaria consistent with the WHO definition (table 1 and table 2).[10]

Diagnosis and investigations

Malaria remains a rare cause of fever in non-endemic areas and requires a high index of suspicion.[9,15] Frequently, not enough attention is given to obtaining a history of foreign travel or of immigration from a malaria endemic area.[9] This problem is exacerbated by families who delay seeking medical advice because of unfamiliarity with health-care systems.[7,47,48] In children, delays in diagnosis occur in 2–90% of cases in the reported series (table 1 and table 2), resulting in treatment delays of up to 2 weeks in some cases. Delays in diagnosis are associated with an increased risk of developing severe malaria, requirement for intensive care,[9,14] and death.[40,43,49,50]

The diagnosis of malaria is usually made by microscopic examination of thick and thin blood films, which should be requested in any unwell child who has travelled to a malaria-endemic area in the preceding 12 months, irrespective of chemoprophylaxis taken. Thick blood smears are more sensitive in detecting malaria parasites because the blood is more concentrated allowing for a greater volume of blood to be examined. However, even when malaria is suspected, a diagnosis may be missed because of a lack of experienced laboratory support.[18,51] Additionally, the initial blood film may be negative in up to 7% of cases, because the degree of parasitaemia varies considerably with time in any one patient.[52] Thus, patients suspected with malaria who have a negative blood film at presentation should have at least two repeat blood films before the diagnosis of malaria can be safely excluded.

The use of antigen detection tests by means of a dipstick format has increased recently. These tests, which can detect *P falciparum* alone or all four *Plasmodium* species,[6,53] are both sensitive and specific for malaria and have the potential of improving the speed and accuracy of diagnosis.[6,54] It is therefore likely that future studies on imported malaria will include cases that are diagnosed by antigen detection tests. In some countries, serological

Reference	Peripheral parasitaemia levels (%) in proportion of cases (%)	Haemoglobin levels (g/L) in proportion of cases (%)	Platelet levels ($x10^9$ per L) in proportion of cases (%)	White blood cell count ($x10^9$ per L) in proportion of cases (%)	White blood cell count less than $5x10^9$ per L	Jaundice	Alanine transaminase more than 40 IU/L	Hypoglycaemia
Minodier et al[8]	NR	<90 in 50%	<157 in 50% <50 in 3%	NR	NR	NR	NR	0·30%
Ladhani et al[9]	<2% in 91% >10% in 2%	<100 in 32% <50 in 1%	<150 in 65% <20 in 2%	>15 in 3%	24%	18% (>25 mmol/L)	36%	0%
Parez et al[10]	>5% in 14%	<100 in 50% <50 in 0%	<171 in 50%	NR	NR	NR	NR	1%
Eloy et al[6]	>5% in 8%	<110 in 60%	<150 in 50%	NR	NR	NR	NR	NR
McCaslin et al[14]	<2% in 73%	<100 in 50% <50 in 0%	<150 in 48	NR	NR	17% (clinical jaundice)	NR	NR
Miller and Banerji[15]	NR	NR	<130 in 66%	NR	NR	NR	NR	NR
Lynk and Gold[16]	>5% in 0%	<110 in 72% <60 in 10%	<150 in 54% <100 in 14%	>10 in 54%	20%	0%	NR	NR
Rivera-Matos et al[17]	>2% in 26%	<100 in 64% <50 in 0%	<150 in 65% < 100 in 44%	NR	NR	50% (>10 mg/L)	50%	NR

NR=not reported. Case series with fewer than 30 children were excluded.

Table 5: **Laboratory parameters in children with imported malaria**

tests are sometimes used to confirm the diagnosis.[8] Parasite nucleic acid detection by PCR is more sensitive and specific than microscopic examination for diagnosis,[27,53,55] and can rapidly identify antimalarial resistance,[56,57] but is usually done in reference laboratories and reserved for retrospective diagnosis and epidemiological research.

Haematological and biochemical parameters are often abnormal in children with imported malaria (table 5). Anaemia occurs in 31–100% of cases and is more common in children than in adults (78% occurrence in children *vs* 29% in adults).[42] However, severe anaemia (haemoglobin levels less than 50 g/L) requiring transfusion is uncommon, occurring in 3 of 211 (1·4%) children in one study.[9] This is by contrast with paediatric *P falciparum* malaria in endemic countries, where severe anaemia occurs in 5–15% of those requiring hospital admission.[58–62]

Thrombocytopaenia (platelet levels less than 150x10⁹ per L) is a characteristic feature of malaria. It is present in around 45–71% of imported malaria in both adults and children but, unlike adults, thrombocytopaenia is not associated with bleeding, even at very low platelet counts.[8,9,63] This incidence is similar to paediatric malaria in endemic countries (50–65%), where it is also not associated with bleeding problems.[64,65] Thrombocytopaenia in children with fever is highly predictive of malaria following travel to a malaria-endemic area.[25,66]

Leucocytosis has been reported in 19–30% of children with imported malaria but is usually not associated with severity of malaria or concurrent bacterial infection,[9] by contrast with malaria in endemic countries.[64,67–71] Leucopenia can occur in up to a quarter of children with imported malaria but is also not clinically significant.[9,16] Similarly, in children with imported malaria, jaundice is relatively common (30–50% of cases) together with raised liver enzymes (25–40% of cases), but is not associated with an adverse outcome,[63] by contrast with children with malaria in endemic areas.[61]

Only one study has reported the course of the laboratory parameters in children with malaria.[59] In children with imported *P falciparum* malaria treated with quinine, the parasite count rose within 12–24 h by a median of 1% (range 0·3–20·4%) in 28 (20%) of 139 children before falling, but none of the children required an exchange transfusion. Haemoglobin levels had dropped by a median of 9 g/L (range 1–41 g/L) at 5–21 days after initiating treatment, but remained above 68 g/L in all cases. Finally, in 45% (63 of 139 children), the platelet count dropped by a median of 17x10⁹ per L (range 1–148x10⁹ per L) within 12–24 h of starting treatment before rising but the count never fell below 50x10⁹ per L and all platelet counts returned to normal within 5 days.

For more information on **malaria treatment guidelines for clinicians** see http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf

Management

The management of malaria varies according to the plasmodium species responsible, national guidelines, antimalarial availability, and individual patient factors.[20] Therapy usually does not differ between non-immune travellers and immigrants. There are no randomised controlled clinical trials on the optimum treatment of children with imported malaria and most of the recommendations are extrapolated from studies and experience with paediatric malaria in endemic countries.

Falciparum malaria

Many current guidelines advocate that children with falciparum malaria should be admitted to the hospital for at least 24 h because of the possibility of rapid progression in severity of malaria.[7,16,72] In general, children with uncomplicated malaria, low parasitaemia, and no vomiting are treated with oral antimalarial drugs. The choice of antimalarial drug will depend on a range of different factors. The country travelled to is particularly important because it will provide information on the risk of the different infecting *Plasmodium* species and the antimalarial resistance pattern of endemic malaria in that country. To avoid re-treating with potentially ineffective antimalarial drugs, it is also important to consider any antimalarial prophylaxis taken by the patient (and whether the patient completed the prophylaxis) or any antimalarial treatment received during travel. In general, chloroquine (which was the treatment of choice in many of the older reported case series) has now been replaced by other therapies because of high levels of resistance in most parts of the world.[8]

In France, halofantrine remains the treatment of choice for acute uncomplicated malaria.[72,73] Treatment failure is uncommon with halofantrine, but relapses appear to be more frequent, usually because the recommended second course of halofantrine 7 days after the first dose is not given, mostly because of concerns about cardiac toxicity.[73] One French retrospective study reported that 48 of 93 children were treated with one dose of halofantrine and nine relapsed (19%).[74] By contrast, none of the 21 children treated with mefloquine relapsed but gastrointestinal side-effects were common.[74] In the UK and the USA, quinine for 7 days in combination with one dose of pyrimethamine-sulfadoxine is generally recommended because it is highly effective,[9,14,16,63] with a very low (less than 1%) relapse rate.[63] Clindamycin, doxycycline, and tetracycline can also be used with quinine, although tetracyclines should not be given to children under 8 years of age because it can cause dental hypoplasia and permanent discolouration of teeth.[8] Some experts recently recommended that oral quinine should never be given to children because it is unpalatable, which could lead to poor adherence and clinical relapse.[75] Instead they recommend oral proguanil-atovaquone, mefloquine, or arthemeter-lumefantrine, which are all substantially more expensive than the quinine combinations.[76] The atovaquone-proguanil combination, although expensive,

is increasingly gaining popularity in adults and children for both the prophylaxis and treatment of malaria but has not been properly evaluated in children under the age of 12 years.[74] Further studies are required before recommending newer antimalarial drugs that would serve a more useful role as second or third-line therapy in an era of rapidly emerging resistance.

Non-falciparum malaria

Uncomplicated *P vivax* and *P ovale* infections do not usually require hospital admission and are usually treated with chloroquine followed by primaquine to eradicate hepatic hypnozoites.[9,15,16,19]

Severe malaria

There are few studies on the optimum management of severe imported malaria because the number of cases in individual studies is often small. Recently proposed guidelines for the management of severe imported childhood malaria in the UK suggest aggressive management for those with depressed conscious level, active seizure activity, irregular breathing, hypoxia, shock, dehydration, hypoglycaemia, metabolic acidosis, and hyperkalaemia.[73] Children presenting to the emergency department with severe malaria should initially be managed in accordance with the current Advance Paediatric Life Support guidelines.[77] In patients with malaria, tachypnoea and increased work of breathing (respiratory distress) usually indicate underlying hypovolaemia, which should be treated with volume resuscitation.[78] Electrolyte imbalances such as hyponatraemia and hyperkalaemia as well as hypoglycaemia should be corrected at the earliest opportunity. Children with anaemia associated with severe malaria may require blood transfusion, although the haemoglobin level at which transfusion should be given remains uncertain.[79] A recent Cochrane Review found no difference in mortality between initial and expectant blood transfusion among children with malarial anaemia (without respiratory distress/cardiac failure), but found that adverse events were more common with initial transfusion.[80] Exchange transfusion for hyperparasitaemia more than 10% has been used in adults with severe malaria requiring intensive care, but there is little evidence that it improves overall outcome.[81]

Concurrent bacterial infections are rare, even in children with severe imported malaria. However, most clinicians would advocate empiric broad-spectrum antibiotics such as a third-generation cephalosporin until bacterial co-infection (meningitis or septicaemia) can be safely excluded through appropriate blood and cerebrospinal fluid cultures.[79] Platelet transfusions for thrombocytopaenia, even at platelet levels less than $20x10^9$ per L, are generally not recommended because thrombocytopaenia is not associated with bleeding problems in children.[9,63] The presence of serious complications such as renal or liver impairment or raised intracranial pressure may warrant early transfer to an intensive care unit for careful assessment, close monitoring, and specialist management. Patients with severe falciparum malaria or those with non-severe malaria who are unable to tolerate oral medication should be treated with parenteral quinine therapy.[7,75,82] A loading dose of quinine at the start of therapy is usually recommended[75] but remains controversial.[16] Intravenous treatment should be changed to oral medication once the patient's condition improves and parasite levels fall.[75]

Outcome

Data on outcome currently relies on national notification systems, which may grossly underestimate case fatality rates. Notifications to WHO have reported case fatality rates of around 1% in most European countries, which have remained constant since the 1970s. However, the number of malaria-related deaths has increased from fewer than ten in 1971 to more than 60 in 1999.[3] A Review of deaths attributed to malaria in the USA identified specific risk factors for fatal malaria, including failure to take recommended antimalarial chemoprophylaxis, refusal to seek or delay in seeking medical care, and misdiagnosis.[83] Non-immune patients are more likely to have serious complications (55 out of 869 [6·3%] non-immune cases compared with 29 out of 790 [3·7%] immune cases) and are subsequently more likely to die—five out of the 55 (9·1%) non-immune patients who developed serious complications died compared with none of the immune cases.[20] In children, mortality rates because of malaria remain low (less than 1%). In France, only two of 1256 children diagnosed with malaria (0·16%) between 1995 and 1997 died,[82] whereas in the UK there were only two deaths among 1456 children diagnosed with malaria (0·14%) between 1999 and 2003.[21] The two largest retrospective studies on paediatric imported malaria reported no deaths among 526 cases.[8,9] However, medical centres that publish large series on imported malaria are in areas more familiar with malaria and are, therefore, likely to diagnose and manage children with malaria more effectively.

Conclusions

Imported malaria is a preventable disease, yet it is responsible for several thousand cases and many deaths every year. The past three decades have seen a pronounced shift in the epidemiology of imported malaria as a result of increasing speed and ease of travel. The incidence of imported malaria in children has increased substantially and, more concerning, *P falciparum*, which is responsible for almost all severe malaria, is now the most prevalent species. Poor control of malaria in many endemic countries is likely to increase the risk of malaria among travellers, and increasing resistance to antimalarial drugs will complicate future management.

Children living in non-endemic countries and travelling to visit friends and relatives in their parents' country of

Search strategy and selection criteria

Information was obtained from Medline and PubMed searches for years between 1980 and 2005. Using the search term "imported malaria", original articles in any European language relating to clinical case series on children with imported malaria were retrieved and their references searched for relevant clinical studies. Articles that focused only on epidemiology or those that combined children with adults were excluded. Online public-health sites for different countries were also scanned for information on imported malaria in children.

origin account for the largest proportion of cases in many European countries. This group of travellers deserve special attention because they often do not take antimalarial prophylaxis. The increasing number of refugees from malaria-endemic areas also merits further attention.

Complications of imported malaria in children are uncommon. However, when they do occur, they can be associated with long-term morbidity and death. This Review indicates a clear need for standardised recommendations on management and prevention of imported malaria in children, which should be supported by large multicentre clinical trials. In particular, we know little about imported severe malaria, especially in relation to risk factors, clinical presentation, management, and outcome.

For more information on the **British Paediatric Surveillance Unit** see http://bpsu.inopsu.com

A 12-month surveillance study of imported malaria in the UK and Ireland through the British Paediatric Surveillance Unit began in January, 2006, and finished in February, 2007. This study aimed to collect comprehensive epidemiological, clinical, and laboratory information about children with imported malaria. We hope that this study and similar studies will provide objective data to support future recommendations for the prevention and management of uncomplicated and severe imported malaria.

Conflicts of interest

We declare that we have no conflicts of interest.

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