Malaria in adolescence: burden of disease, consequences, and opportunities for intervention

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The problem of malaria in adolescence has largely been overshadowed by the huge burden of disease in young children. A substantial number of adolescents are at risk from malaria infection, but the burden of disease and consequences of infection in this age-group have rarely been studied. Our understanding of specific risk factors and beneficial interventions for adolescents is also limited. Data show that, from an adolescent viewpoint, malaria is a common cause of clinical illness and a preventable cause of death, even in areas of stable malaria transmission. Younger adolescents might be at a higher risk than older adolescents, because of immunological and hormonal factors. There are limited data about the adverse consequences of malaria in non-pregnant adolescents. However, in pregnant adolescents, the consequences of malaria are of great concern and simple interventions might lead to a substantial benefit. Malaria infection in adolescents is an under-recognised problem, and the prevention, diagnosis, and treatment of malaria should have a high priority within adolescent health programmes.

Introduction

Malaria is one of the most important infections in the tropics with an estimated 1 to 2·7 million deaths annually.[1] The age-groups at highest risk are primarily determined by the intensity of malarial transmission. Where transmission is intense, clinical disease is most common in young children: immunity develops with increasing age and adults are far less affected. In areas of lower transmission, clinical disease occurs throughout life.[2] Although much has been learnt about the epidemiology and clinical effects of malaria in children, malaria in adolescence has been relatively neglected. Approximately 914 million adolescents (aged 10–19 years) live in low-income countries, and many of them will be exposed to malaria, but this group has rarely been targeted for malaria control.[3] This review was undertaken to collate evidence and observations from different sources to better understand the burden and consequences of malaria in adolescents, and to identify relevant interventions or opportunities for improved control.

Methods

To obtain data for this review, we searched the 26 Cochrane systematic reviews on malaria for data relevant to adolescents (up to December, 2005). The Cochrane clinical trial register was searched for trials by use of the keywords “malaria” and “adolescence” in any field. Abstracts of these trials were examined to identify interventions relevant to adolescents. We also searched the English and French literature by use of PubMed (1966 to December, 2005) for articles containing the words “malaria”, “adolescence or adolescents” (including MeSH age-group subheadings) and the following MeSH headings in any field: “epidemiology”, “clinical pattern”, “signs and symptoms”, “severe malaria”, “drug therapy”, “pregnancy”, “prophylaxis”, “knowledge”, “health care seeking behaviour”, “health promotion”, and “delivery of health care”. Searches were also done using “malaria and practice guidelines”, “malaria and schoolchildren”, and “severe malaria and pathogenesis”. Abstracts of papers from the search were read to identify those likely to contain information relevant to the aims of the review, and all identified papers were examined for data that should be included in the review. Publications were also identified as a result of citation in papers unearthed by the search. In addition to these searches, we estimated malarial mortality and morbidity in adolescents based on country reporting from the WHO Global Programme on Evidence database.[4]

Burden of disease in adolescents

Stable transmission areas

Clinical illness

Few studies have examined directly rates of clinical illness in adolescents. Observations in younger children indicate that, even within stable transmission areas, the intensity of transmission has a strong influence on the peak age of clinical illness (panel 1).[5] This is shown by a comparison of two villages in Senegal with different transmission rates (200 *vs* 20 infective bites per year): clinical disease was rare in adolescence in the high-transmission area, but did occur in the area of stable but lower transmission intensity (figure 1).[6] Published estimates of the incidence of clinical disease in adolescents in stable areas of transmission vary from 0·13 to 1·18 attacks per year (table 1). Other studies show a wide variation in the

***Panel 1:* Malaria epidemiology**

- Malaria can affect people at all ages.
- Malaria can be epidemic (unstable transmission) or endemic (stable transmission).
- Susceptibility to, severity of, and age distribution of malarial disease depend on acquisition of immunity and are strongly related to the intensity of transmission.
- As the intensity of transmission increases, people are exposed earlier in life and more frequently, partial immunity develops earlier, and risk of severe malaria declines.

proportion of fevers attributable to malaria, from none in an intense transmission area of Tanzania, to 43·6% in the Republic of the Congo.[8,14–16]

Despite limited direct data, age-specific burdens of disease in Africa have been estimated. Brooker and colleagues[17] calculated the clinical malaria rate in African schoolchildren to be 0·252 attacks per year in 10–20-year-olds compared with 0·692 attacks per year in 5–9-year-olds. Another study used long-term rainfall and temperature data and a geographic information system population database to define the risk by age-group across areas of stable endemicity. The number of malaria attacks (estimated using these data and all available studies for adults and children) were 81·3 million in 0–4-year-olds, 16·0 million in 5–9-year-olds, 13·4 million in 10–14-year-olds, and 96·8 million in those older than 15 years.[18]

Severe disease

Incidence of severe disease declines at an earlier age than clinical illness.[5] Three studies estimate incidence rates for severe malaria, albeit with very wide confidence intervals (table 2).[19–21] Severe malaria is much less of a problem in adolescents than in younger children. In Nigeria, only 2·8% of cases of severe malaria in 501 paediatric admissions occurred in 11–14-year-olds and there were no deaths in those aged over 5 years;[22] in Tanzania, only two of 72 deaths occurred over the age of 5 years.[23]

However, unpublished hospital admission data from Malawi and The Gambia show that malaria is important for adolescents: malaria was responsible for 13·7% (95% CI 11·1–16·6) of admissions in Malawian 10–16-year-olds, and in The Gambia malaria was the final diagnosis in 44·3% and 28·4% of admissions in 10–14-year-olds and 15–19-year-olds, respectively (40 of 69 cases in 15–19-year-olds were in pregnant young women; Nelson EAS, Chinese University of Hong Kong, Hong Kong, and Weber M, Department of Child and

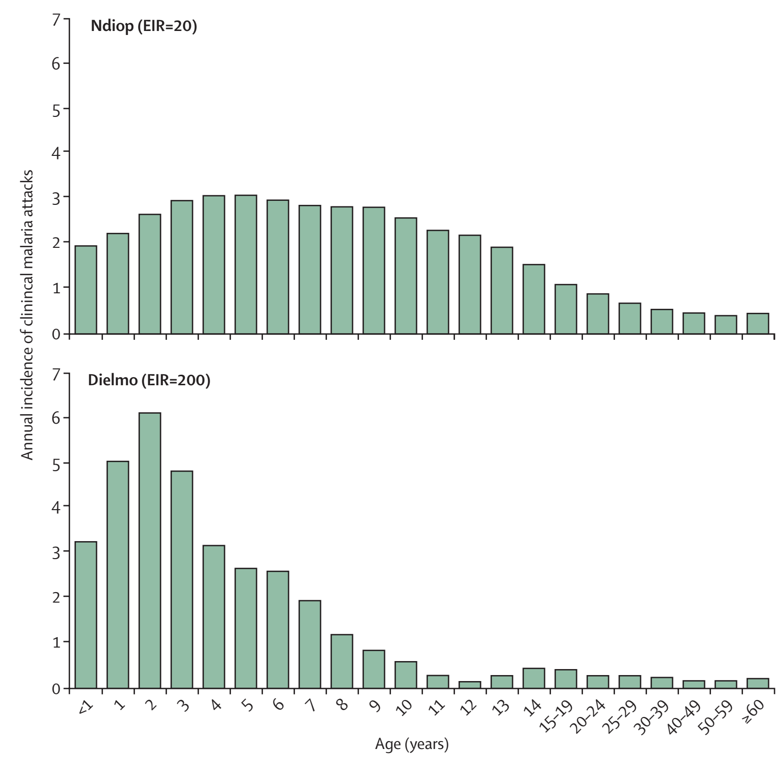

***Figure 1*: Annual incidence of malaria attacks in residents of two Senegalese villages with different *P falciparum* transmission**

EIR=entomological inoculation rate (infective bites per year). Adapted from Trape and Rogier,[6] with permission from Elsevier.

Adolescent Health and Development, WHO, personal communication).

Mortality

Table 3 summarises estimated population mortality rates in areas of stable transmission. Other studies address the importance of malaria relative to other diseases as a cause of death. In Guyana, where malaria was hyperendemic

Location	Adolescents			Infants		Young children		Older children		Adult
	Number	Incidence (episodes per year) (95% CI)†	Age (years)	Incidence (episodes per year)	Age (years)	Incidence (episodes per year)	Age (years)	Incidence (episodes per year)	Age (years)	Incidence (episodes per year)
Kenya[7]	262	0·22 (0·15–0·31)	10–14	2·6	0·5–1·0	0·58	3–4	0·24	5–9	..
Republic of the Congo[8]										
Daily survey	48	0·76 (0·01–4·04)	11–13	..	..	3·0	5–6	1·8	9–10	..
Weekly survey	53	1·18 (0·73–1·83)	11–13	..	..	5·2	5–6	2·0	9–10	..
Senegal[9]	14	0·21 (0·05–0·51)	11–14	6·8	1–2	5·6	3–6	0·87	7–10	..
Senegal[10]	41	0·13 (0·08–0·19)	10–19	..	..	2·1	4–5	0·77	6–9	0·13
Ghana[11] (high season)	248	0·61 (0·46–0·77)	12–20	..	..	..	..	..		..
Papua New Guinea[12]	355	0·28	10–19	0·78	0–1	1·96	2–4	0·78	5–9	0·16
Burma*[13]	47	0·19 (0·09–0·33)	10–14	..	..	0·64	2–4	0·47	5–9	0·09

*A rare area of apparently stable endemicity in southeast Asia. †95% CIs calculated from original data where available.

***Table 1:* Incidence of clinical malaria in adolescents in stable areas by country**

	Location	Incidence per 1000 per year*					
		<1 year	0–4 years	1–4 years	5–9 years	10–13 years	10–14 years
Admission for malaria[19]	Kinsasha, Zaire (DR Congo)	4·3	..	2·85	1·24	0·35	..
Severe malaria[20]	Brazzaville, Republic of the Congo	..	1·15	..	0·25	..	0·05
Cerebral malaria[21]	Brazzaville, Republic of the Congo	..	2·4	..	0·61	..	0·13

*Small numbers led to extremely wide confidence intervals in adolescents.

Table 2: **Incidence of severe disease in adolescents in areas of stable transmission**

Location	Adolescents		Infants (aged <1 year)	Young children		Older children	
	Mortality (per 1000 per year)	Age (years)	Mortality (per 1000 per year)	Mortality (per 1000 per year)	Age (years)	Mortality (per 1000 per year)	Age (years)
Zaire[19]	0·1	10–13	4·0	1·6	1–4	0·4	5–9
Republic of the Congo[20]	0	10–14	..	0·43	0–4	0·08	5–9
Republic of the Congo (cerebral malaria)[21]	0·01	10–14	..	0·58	0–4	0·05	5–9
Nigeria[24]	0·3	11–15	12·5	6·6	1–4	1·0	5–10
Papua New Guinea[14]	0·4	10–19	4·7	2·3	1–4	..	..

There were inadequate data for confidence intervals.

Table 3: **Estimates of malarial mortality in adolescents in stable transmission areas by country**

before eradication between 1945 and 1951, malaria accounted for 4·2% of deaths in 11–14-year-olds compared with 13·0% of deaths in 6–10-year-olds, and 5·8% in those over 15 years.[25] Verbal necropsies in Papua New Guinea estimated that malaria accounted for 11·1% of all deaths in the 10–19-year age-group; 9·1% of death certificates implicated malaria in the 11–15-year age-group in Nigeria.[24,14] Unpublished hospital studies found malaria to be the cause in 6·3% (95% CI 0·7–20·8) of the adolescent deaths in Malawi, equal to respiratory or diarrhoeal illness, and 11·4 % (95% CI 3·2–26%) of deaths in The Gambia (Nelson EAS and Weber M, personal communication). In DR Congo, the in-hospital case fatality rate in malaria admissions was 31·8% in those aged under 1 year, 20·4% in 1–4-year-olds, 14·8% in 5–9-year-olds, and 13·5% (95% CI 8·2–20·5) in 10–13-year-olds.[19]

Snow and colleagues[18] developed a model to derive mortality estimates in stable areas of Africa for older groups by use of the 0–4 year age-group data as baseline. The estimated median mortality rate in the 10–14 year age group was 0·80 per 1000 compared with 2·17 per 1000 in 5–9-year-olds. Brooker and co-workers[17] estimated mortality rates of 0·41 per 1000 (IQR 0·27–1·62) in schoolchildren aged 10–20 years with malaria accounting for 9·1% of adolescent deaths overall.

Unstable transmission areas

Clinical illness

Most studies in regions of unstable transmission show clinical malaria at all ages (table 4). The wide variation in incidence between studies may be partly explained by large variations in transmission intensity over areas of unstable endemicity. The incidence in adolescents is often similar to that in younger age-groups and is sometimes higher.[26,32–34] By contrast with high-transmission areas, where *Plasmodium falciparum* pre-

Location	Adolescents			Infants and young children		Older children		Adults		Plasmodium proportions (95% CI) in adolescents	
	Number	Overall incidence (episodes per year) (95% CI)*	Age (years)	Incidence (episodes per year)	Age (years)	Incidence (episodes per year)	Age (years)	Incidence (episodes per year)	Age (years)	*P falciparium*	*P vivax*
Western Thailand[26]	86	1·0 (0·95–1·05)	12–15	0·76	4–8	1·03	9–11	0·75	>15	0·49 (0·37–0·62)	0·51 (0·38–0·63)
Philippines[27]	4585	0·026 (0·022–0·031)	11–19	0·026	0–4	0·023	5–10	0·015	>19	0·020 (0·016–0·024)	0·006 (0·004–0·009)
Brazil[28]	875	0·25 (0·22–0·28)	11–15	0·211	0–10	..	..	0·298	>15	..	..
Brazil[29]	40	1·08 (1·04–1·12)	11–15	0·31	0–10	..	..	1·27	>15	0·61 (0·40–0·80)	0·47 (0·27–0·68)
Brazil[30]	39	0·352 (0·22–0·52)	11–15	0·374	0–10	..	..	0·22	>15	..	..
Sri Lanka[31]	72	0·99 (0·96–1·02)	5–13	0·62	0–5	..	..	0·71	>15	..	..

*95% CIs calculated from original data.

Table 4: **Incidence of mild malaria attacks in areas of unstable transmission by country**

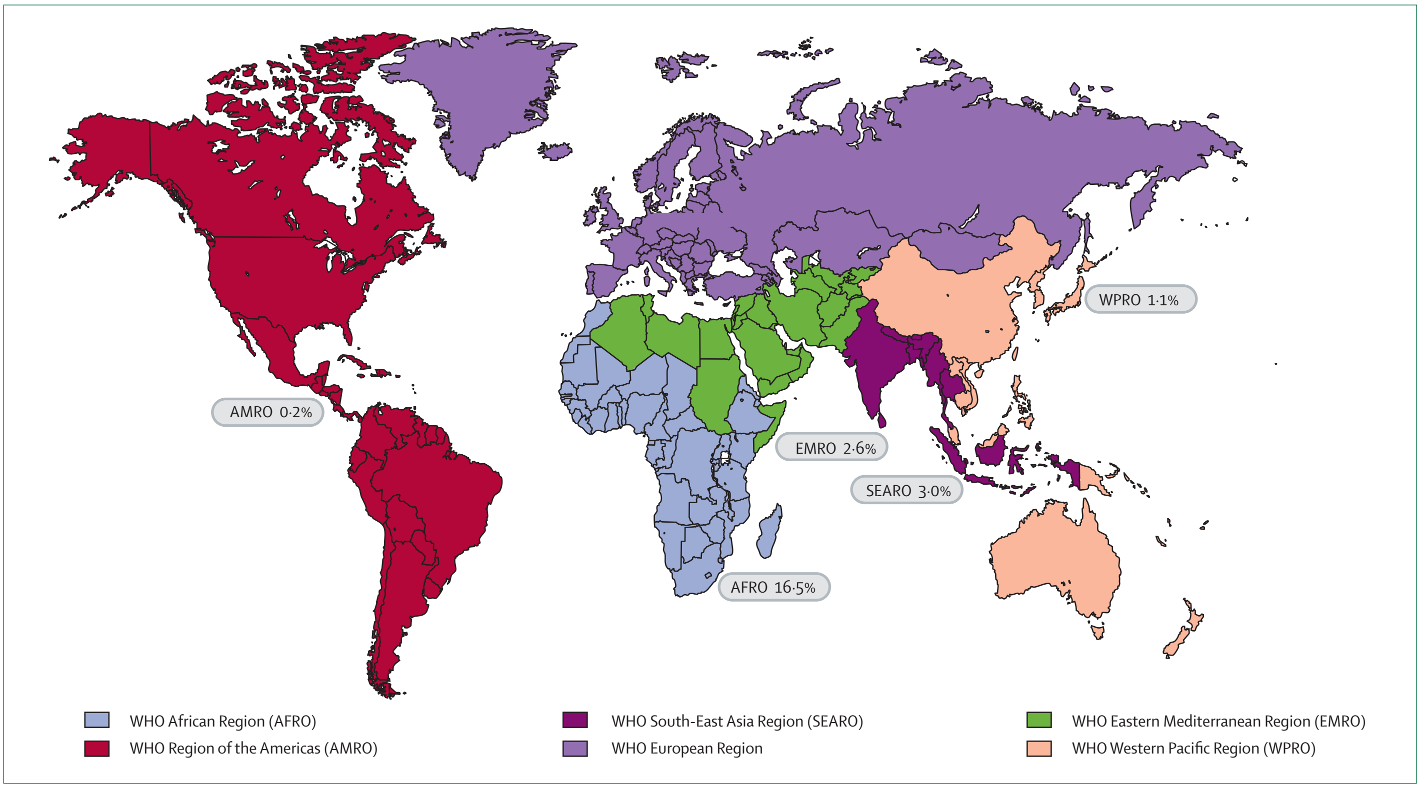

Figure 2: **Estimated proportion of adolescent deaths caused by malaria in each WHO region (WHO Global Programme on Evidence)**[4]

dominates, *Plasmodium vivax* is more important as a cause of clinical illness in the lower transmission areas of South America and southeast Asia.

Severe morbidity and mortality

Adolescents seem to have an equal or higher risk of severe disease compared with other age-groups. The peak age of admission with malaria in a study in KwaZulu Natal was in adolescents and young adults: case fatality rates were 14·6% over the age of 12 years.[35] Similar data have been reported in a hospital study from India.[36] In a low transmission area of Thailand, 4–9% of patients aged 11–19 years developed severe malaria annually.[37] Estimated annual incidence rates of severe malaria in an epidemic area of Vanuatu were 2·0 per 1000 in those aged 10–14 years compared with 1·17 and 1·01 in the 15–65 year and 5–9 year age groups, respectively.[38] Older adolescents and young adults made up the highest proportion of Burmese patients in a series of admissions with severe malaria: case fatality rates were significantly greater in those aged over 15 years than in those under 15 years (relative risk [RR] 2·8 [95% CI 1·03–4·4 4]).[39] In a reanalysis of a large Vietnamese study of severe malaria, case fatality rates were 5·9% (95% CI 1·7–14·0) in the 15–19 year age-group, compared with 11·0% and 14·9% in those aged 20–24 years and 25–29 years, respectively[40] (additional data courtesy of Day N, Mahidol University, Bangkok, Thailand and University of Oxford, UK, personal communication).

We found no good population mortality estimates for adolescents in areas of epidemic transmission. An Ethiopian study in the late 1950s estimated annual mortality rates of 0·144–0·372 per 1000 population. Although breakdowns by age-group were not reported, "most of the patients were between the ages of 5 and 20 years".[41]

Burden in pregnancy

Malaria in pregnancy is associated with maternal and fetal consequences that are particularly relevant to pregnant adolescent women because primigravidae are at highest risk;[42–46] in many malarious countries, over 50% of first pregnancies occur in teenagers. For example, in parts of Malawi, two thirds of primigravidae are adolescents, and in Niger, Zambia, and Kenya, over 70% of women with less than 7 years' education have had their first pregnancy by the age of 20 years.[47]

Stable transmission areas

In addition to the particular risk of adolescent primigravidae, youth alone may increase the likelihood of malaria in pregnancy. One Malawian study showed that parasitaemia at the first antenatal visit was more likely in those aged 12–19 years than in older mothers (62·6% *vs* 38·2%).[48,49] This effect remained, independent of gravidity, in a multivariate analysis (adjusted odds ratio [OR] 1·56 [95% CI 1·14–2·13]). By comparison, the ORs for first pregnancy and for not taking prophylaxis were 3·86 (95% CI 2·96–5·04) and 0·91 (95% CI 1·47–2·48), respectively. Parasitaemia at delivery was also more common in those aged under 20 years (OR 2·1 [95% CI 1·4–3·0]). Logistic regression analysis in another Malawian study showed maternal age and season to be more important than gravidity in determining the presence of parasitaemia.[50] An increased risk of malaria in those under 20 years (after adjustment for gravidity) was also shown in two different sites in Cameroon (OR 1·8 [95% CI 1·2–2·7] and 3·4 [95% CI 1·7–7·1]).[51] Similar findings occurred in an analysis of risk factors for malaria in pregnancy in Kenya (OR 1·45 [95% CI 1·16–1·83])[52] and Mozambique.[53] Although one might expect a greater risk for young adolescents (<15 years), we found no studies addressing this issue.

The increasing HIV prevalence rates in female adolescents in many malarial transmission areas are also important. Parasitaemia seems to be more common in HIV-infected primigravidae than in non-infected women: 56·3% versus 36·5% (p=0·04) in one study, and 56·6% versus 43·6% in another study (OR in multivariate analysis 1·55 [95% CI 1·14–2·13]).[48,54]

Unstable transmission areas

Malaria in pregnancy has been studied in areas of southeast Asia, South America, and unstable areas of transmission in Africa.[55–58] Only one of these studies looked at age distribution and showed no relation between younger age and malaria infection.[58] Gravidity-specific effects seem to be less marked, although there was an increased risk of malaria in primigravidae compared with multigravidae in Thailand (RR 1·4 [95% CI 1·2–1·6]).[55]

Regional and global mortality

An overview of the global mortality of malaria in adolescents can be gained from data collated and analysed by the WHO Global Programme on Evidence (figure 2).[4] This report ranks malaria as the second most common cause of death in adolescence, accounting for 7·4% of all of the adolescent deaths globally reported to WHO each year (table 5). The burden is greater in the 10–14-year age-group, in which malaria is the most common cause of death, accounting for 14·1% of deaths from all causes; in this group, malaria is far more important overall than tuberculosis or HIV/AIDS. As the adolescent becomes older, malaria becomes less important, but is still a major cause of death. Unfortunately, these data do not distinguish pregnant adolescents. In addition, although the burden is estimated to be highest in Africa (82·8%), around 13% of the deaths occur in the southeast Asia region.

Identified risk factors and sex differences

A combination of biological, human, and vector factors determines the risk for acquiring malaria. Specific risk factors have only been identified for adolescents and young adult men in regions of unstable transmission. The comparatively higher incidence of malaria in young men, including adolescents, found in the Philippines, Thailand/Malaysian borders, and Brazil, and that of severe malaria in Vietnam, is generally ascribed to occupational exposure.[27–29,59–61] In one Brazilian study,[28] 11–15-year-olds were the most common female age-group affected by malaria, probably because they spent more time outdoors than older women.

Movement from non-endemic to transmission areas exposes naive populations to infection with high risk of severe disease and death. This is observed in displaced people, and the risk is highest in young children and pregnant women.[62,63] We found no data on mortality rates in adolescents in this setting. Many malaria workers recognised that adolescents may move to urban malaria-endemic areas to look for jobs, but no studies have addressed this issue.

In addition to behavioural factors, there is increasing evidence that the risk of acquiring malaria may change with sexual maturity. Studies in Kenya showed that, independent of age, high dehydroepiandrosterone sulphate concentrations in girls, a marker of pubertal development, were associated with decreased parasite densities and increased haemoglobin, suggesting that pubertal development might protect against malaria, independently of exposure and development of immunity.[64] Similarly, in young men, dehydro-

WHO region*	Adolescent deaths attributed to malaria (n)	Total adolescent deaths (n)	Proportion of adolescent malaria deaths by region	Proportion of all adolescent deaths caused by malaria	Malaria deaths by age (n)		Malaria deaths by sex (n)	
					10–14 years	15–19 years	Male	Female
WPRO	2437	226 142	2·0%	1·1%	407	2030	920	1517
SEARO	15 950	531 671	12·7%	3·0%	6600	9350	6536	9414
AMRO	185	105 775	0·01%	0·2%	37	148	126	59
AFRO	103 640	626 962	82·8%	16·5%	85 421	18 219	50 138	53 502
EMRO	2887	111 461	2·3%	2·6%	2361	536	1692	1205
Overall	125 113	1 679 415	100%	7·4%	94 827	30 286	59 412	65 701

*EURO region excluded (<5 deaths). WPRO=WHO Western Pacific Region; SEARO=WHO South-East Asia Region; AMRO=WHO Region of the Americas; AFRO=WHO African Region; EMRO=WHO Eastern Mediterranean Region; EURO=WHO European Region.

Table 5: **Annual adolescent malaria deaths estimated from WHO Global Programme on Evidence[4]**

epiandrosterone sulphate and testosterone were found to be independent predictors of resistance to *P falciparum* infection.[65]

Presentation and consequences of malaria in adolescence

Clinical presentation of malaria

The clinical presentation of uncomplicated malaria in adolescents seems to be similar to other age-groups, although adolescents may have a stronger correlation of fever to parasite density than do younger children.[15] A Senegalese study found no differences in symptoms, duration, or severity of symptoms between age-groups (including 41 adolescents).[10]

The pattern of severe malaria differs between adults and children; although cerebral malaria occurs in both, severe anaemia and respiratory distress predominate in children and renal failure is much more common in adults.[40,66–68] Whether these differences are because of an intrinsic effect of age, variation in background immunity, or differences in geographical strains is not known. Observations in low transmission areas of southeast Asia, where severe malaria occurs in both adults and children, suggest that there are true age-related differences in clinical manifestations between age-groups: although renal failure (a rare finding in African children) is occasionally seen in southeast Asian children, the severe renal failure of adult severe malaria is very uncommon.[37,69,70] In an area of low seasonal transmission in Senegal, the proportion of cerebral malaria cases rose and that of severe anaemia cases fell with increasing age up to age 16 years (table 6).[71] In Burkina Faso, the prevalence of anaemia as an indicator of severe malaria declined with increasing age in those aged 1–15 years, although the relation of cerebral malaria to age was less well defined.[72] Re-analysis of data from a severe malaria treatment trial in Vietnam suggests that renal failure was significantly less common (16% *vs* 28%; RR 0·54 [95% CI 0·31–0·95]) and that severe anaemia was more common (26% *vs* 12%; RR 1·97 [95% CI 1·22–3·18]) in 15–19-year-olds (n=68) than in 30–39-year-olds (n=350). Pregnant women were not included in this trial. Cerebral malaria was found with the same frequency in all age-groups[40] (data for re-analysis courtesy of Day N, personal communication).

	0–3 years (n=52)	4–7 years (n=48)	8–15 years (n=61)
Severe anaemia	73·1%	52·1%	26·2%
Cerebral malaria	15·4%	41·7%	70·5%
Hyperparasitaemia (>5%)	30·8%	37·5%	27·9%
Acidosis	25·0%	28·0%	14·7%
Hypoglycaemia	15·4%	14·9%	6·6%
Jaundice	3·8%	12·5%	13·1%
Renal failure	0%	4·2%	3·3%
Case fatality rate	7·7%	12·5%	11·5%

Percentages show proportion with disease. Data from Imbert et al.[71]

Table 6: **Pattern of clinical presentation in children and adolescents with severe malaria in Senegal**

Physical sequelae of malaria

Anaemia and nutrition

The prevalence of anaemia is estimated to be 27% in adolescents in low-income countries.[73] Malaria is associated with anaemia across a wide range of age-groups including adolescent men and women, although the contribution of malaria to anaemia is uncertain. Some studies suggest an association between malaria and anaemia in adolescents, although others have found no correlation.[7,74] Improved malaria control in Kenya, leading to decreased population parasite carriage, was associated with significant increases in haemoglobin concentration in both sexes aged 10–14 years and 15–19 years.[75] In male adolescents in early puberty, there is a correlation between mean parasite density over a 16-week period and reduced growth measured by body mass index.[76]

Neurological sequelae

Neurological sequelae occur in 7–12% of children soon after recovery from cerebral malaria; long-term sequelae are less common.[65,77,78] Neurological sequelae are rare in adults, and when described, often have been associated with mefloquine treatment.[79] There are few formal data on adolescents, although most clinicians consider sequelae to be rare in adolescents (reported in only one of 43 [2·3%] Senegalese 8–15-year-olds with cerebral malaria,[71] and in none of 68 Vietnamese 15–19-year-olds[40]).

Social and economic consequences of malaria

Between 0·16% and 2·1% of all schooldays are estimated to be lost because of malaria in Africa, which accounts for 2–8% of all absenteeism.[17] This equates to approximately 0·2–1 day lost per schoolchild per year. Published surveys are small and many surveys include schoolchildren from the age of 5 or 7 years. One comprehensive study in the Republic of the Congo estimated that 0·34–2·3 days were lost per 1000 days in children aged 11–13 years. Malaria accounted for 1·4–3·7% of causes of absence in this age-group (2·7–8·3% in all school age-groups).[8] Unpublished data quoted in reference 11 suggested that adolescent schoolboys lost 1·2–1·8 days per year from school. The frequency of absence could vary substantially across the transmission season.[80]

The problem could be greater in epidemics and areas of unstable transmission, although data are limited. During a Kenyan epidemic, school absenteeism ranged from 17·6% to 54·4%, and although slightly higher in younger children, seemed to have a more detrimental effect on younger adolescents.[81] In rural Sri Lanka, 2·7% of school days were lost because of malaria in children aged 5–13 years (on average, 3·8 days per child per year), with substantial seasonal variation; in high-transmission months, just under 10% of all schooldays were lost because of malaria.[31] A high frequency of malaria attacks in Sri Lanka has been shown to be associated with reduced performance in mathematics.[82] Thai adolescents aged 12–15 years had one clinical attack of malaria per year, with a loss of 2–3 days of schooling.[26]

We found only one study of the economic consequences of malaria in adolescents. 3·7% of working days were lost because of malaria in 14–17-year-olds during 1 year in Sri Lanka compared with 4% from all other medical causes. The 31 adolescents lost 141 working days during 1 year at an estimated cost of US$106 in total (the average annual household income was US$258).[31]

Consequences of malaria in pregnancy

Malaria in pregnancy is associated with severe maternal anaemia and low birthweight, and, in areas of unstable transmission, severe maternal illness and abortion or stillbirth.[42–45] In addition to their higher risk as primigravidae, adolescent mothers might generally be at increased risk for anaemia compared with other mothers.[83] Some studies, although not all, suggest that anaemia is more common, more severe, and has higher mortality in antenatal adolescents than in older mothers.[84,85] Malaria may not be controlled or treated well in adolescent pregnancy.[45,86] Young adolescents who become pregnant are often less well educated and from lower socioeconomic groups. They are less likely to use antenatal services and hence less likely to receive education or prophylaxis. In 1050 pregnancies in 12–14-year-old Nigerian mothers, 32·9% with planned and 71·5% with unplanned hospital deliveries had malaria parasites at delivery.[87]

Adolescents might also be at a higher risk of death if they contract malaria in pregnancy. In a Mozambique study of maternal deaths, malaria was reported as the cause of death in 27% of adolescents (RR 2·07 [95% CI 1·26–3·41]) compared with older mothers.[88] 37·8% of malaria-related maternal deaths occurred in adolescents, although adolescents only made up 18·8% of the maternal population. Most deaths were associated with severe anaemia. The malaria-related mortality rate for adolescents was 1 per 1000 per year (approximately double that in the 20–29-year age-group). Unplanned hospital deliveries and poor antenatal care were major risk factors.[88,89]

Knowledge and health-seeking behaviour

The limited data available suggest substantial variation in adolescents' awareness and knowledge of malaria. In all age-groups, education improves knowledge of malaria and those in employment are generally more knowledgeable about malaria.[90,91] Adolescents' recognition of the importance of mosquitoes in malarial transmission varies substantially from less than 10% in Ghana and India,[92,93] to 59% in Zimbabwe.[94] 48% of Zimbabwean and 36% of Nigerian adolescents knew about preventative measures; bednets and environmental measures were mentioned by 21% and 16%, respectively, in Zimbabwe, but bednets were only mentioned by 2% in Nigeria.[94,95] Knowledge in Sudanese secondary school students (mean age 18·5 years) was generally much better, with awareness of the symptoms of malaria; 83% recognised that malaria was more serious in the pregnant woman. Bednets were acknowledged to be protective in over 90% of cases.[96]

The importance of understanding cultural beliefs about malaria in the investigation of health-seeking behaviour has been emphasised for all age-groups.[97] Some evidence from the Philippines and Africa suggests that those aged over 15 years are much less likely to attend health facilities for malarial illnesses and to use western medication than those aged under 15 years, but no specific data on adolescents were available.[98,99] In Papua New Guinea, the likelihood of adolescent men (but not women) presenting to a health centre with malaria decreased with the distance from the health facility. This was thought to indicate a lower priority assigned to health by male adolescents.[100]

Malaria interventions

Prevention of malaria in non-pregnant adolescents

There are very limited data on the prevention of malaria in male and non-pregnant female adolescents. Although adolescents have been included in studies of bednets,[101] detailed data are limited. One study examined the effect of insecticide-treated nets in non-pregnant adolescent girls and showed a reduction in anaemia in 12 and 13-year-olds (OR 0·38 [95% CI 0·21–0·69]) but not in older adolescents; no effect on malaria episodes or morbidity was shown in any age-group.[102] Studies in Africa, South America, and Asia have shown benefit across a wide range of age-groups that included adolescents.[103–108]

Chemoprophylaxis in adolescent schoolchildren in Africa has generally shown a short-term benefit with a reduction in episodes of infection documented in several studies.[11,104,109] In Thailand, chemoprophylaxis reduced the incidence of clinical malaria in 5–16-year-olds.[110] However, long-term programmes have generally been less successful;[111] most studies were done before the development of antimalarial drug resistance. There is currently little evidence to support the use of chemoprophylaxis in adolescents in endemic regions.

Treatment of malaria in non-pregnant adolescents

No specific recommendations for the management of malaria could be found in a wide variety of national and international guidelines. Only children and adults were distinguished, although adolescent age-groups were mentioned in discussion of antimalarial doses.[1,112–114] Adolescents are not mentioned in documents that deal with the pattern of severe and complicated malaria in children and adults.[115]

Although there is no evidence that treatment of malaria in adolescents in health facilities should be any different from adults or children, school-based programmes have been used successfully for the treatment of helminths and schistosomiasis. Two studies have found malaria diagnosis and treatment in school to be practical and effective. In Tanzania, schoolteachers successfully administered antimalarial treatment according to algorithms; 75% of children were subsequently shown to have a positive malaria slide.[116] In Malawi, introduction of teacher-based dispensing of antimalarials for students aged 5–18 years in one district was associated with a reduction in overall and malaria-specific mortality from 2·2 to 1·4 deaths and from 1·28 to 0·44 deaths per 1000 student-years, respectively.[117] Approaches to community-based treatment or prevention could potentially expose young adolescent girls to toxic drugs if they are in the early stages of pregnancy, and this must be considered when planning such programmes.

Prevention of malaria in pregnant adolescents

Chemoprophylaxis or intermittent preventive treatment

The most important effective interventions in adolescents are in pregnancy. Chemoprophylaxis and intermittent preventive treatment (IPT) have been extensively studied in pregnancy (panel 2).[46] Many studies do not distinguish adolescents, but do analyse first and second pregnancies separately, which often occur in adolescence. A Cochrane review of predominantly African studies showed that chemoprophylaxis or IPT significantly reduces fever episodes and lowers antenatal parasitaemia in all pregnancies.[118,119] In first and second pregnancies (most relevant to adolescents), parasitaemia is significantly reduced in most studies with protective efficacies of up to 85%.[118] Intervention in primigravidae also seems to reduce maternal anaemia. In one trial, the risk of severe anaemia was reduced from 23·7% to 14·5% (protective efficacy 39% [95% CI 22–52%]).[120] In the only specific study of IPT in adolescent mothers, parasitaemia at delivery and placental malaria were significantly reduced (RR 2·22 [95% CI 1·07–4·60] and 4·87 [95% CI 1·58–15·0], respectively).[121]

The Cochrane analysis showed little effect on most indicators of fetal health in pregnancy overall.[118] However, in first and second pregnancy subgroup analyses, perinatal mortality was reduced (RR 0·73 [95% CI 0·50–0·99]). Placental malaria was less common (RR 0·56 [95% CI 0·41–0·76]). Moreover, mean birthweight was significantly higher (seven studies; difference 122 g, [95% CI 81–164]) and the prevalence of low birthweight was significantly reduced (five studies; RR 0·49 [95% CI 0·36–0·65]).[118]

Although IPT is clearly indicated for the pregnant adolescent, there are practical difficulties in delivering such interventions.[122,123] The interaction between HIV and malaria means that more frequent dosing with sulphadoxine-pyrimethamine is necessary for HIV-positive women in Africa;[124,125] patterns of parasite resistance will determine the effectiveness of IPT or prophylaxis.[49] Outside Africa, different patterns of drug resistance and malarial transmission mean that the results of predominantly African trials cannot be extrapolated. Multidrug resistance is some areas of southeast Asia means there is no suitable routine drug for prophylaxis, and because impregnated bednets are only partly effective, the only approach in such areas could be the early diagnosis and treatment of pregnant adolescents with malaria.[126]

Adolescents are a difficult group to reach. Pregnant adolescents may be less likely than their non-pregnant peers to visit health centres, particularly if they are unmarried; some studies suggest that take-up of prophylaxis is lower in younger age groups.[86,127–129] The practical consequences of these difficulties in reaching adolescents is illustrated by the quality of antenatal care recorded in 615 adolescents in Malawi:[86] morbidity and low birthweight were common, and 73·3% of adolescents were illiterate. Over half of the girls in one hospital received only one dose of IPT instead of the standard two doses; peripheral parasitaemia was as high at delivery as it was at the time of the first visit, indicating inadequate malaria control.[86]

Panel 2: Prevention of malaria in pregnancy

Chemoprophylaxis
Regular administration of an antimalarial drug, often weekly, throughout pregnancy.

Intermittent presumptive treatment
Full curative doses of an antimalarial drug (usually sulphadoxine-pyrimethamine) given throughout pregnancy, usually two or three times in second and third trimester.

Bednets in pregnancy

The evidence for a beneficial effect of bednets in pregnancy is varied. Some studies in Africa have shown widespread benefit with convincing reductions in malarial parasitaemia, malarial anaemia, and low birthweight, whereas others have found no benefit.[130–132] The combination of IPT and bednets was found to be particularly effective in reducing anaemia in primigravidae in one study.[133] These studies have also shown that compliance was worst in adolescents (74%). In a low-transmission area of Thailand, the incidence of anaemia in 341 pregnant women was reduced in both treated and untreated bednet groups (in the treated bednet group compared with no net, RR 2·00 [95% CI 1·18–3·42]).[134]

Nutritional supplementation

The interaction of malaria infection, nutritional deficiencies, and anaemia is complex but important in adolescent pregnancy. Initial studies suggested that the supplementation of antimalarial drugs with folate and iron in teenage primigravidae led to increased maternal and fetal growth. Increased maternal growth was correlated with the haematocrit level measured at 28 weeks.[83] However, susceptibility to malaria after intravenous iron supplementation in pregnant women has been reported,[135] and in a retrospective study in Papua New Guinea,[136] intravenous iron resulted in little overall benefit in mean haemoglobin concentrations, but increased the risk of perinatal malaria in primigravidae (OR 5·46 [95% CI 2·20–13·53]). Confounding factors could have affected these interpretations. Oral iron supplementation in Gambian multigravidae with sickle-cell trait was associated with lower haemoglobin concentrations, lower birthweights, and increased placental malaria.[137] Whether iron supplementation to reduce the risk of iron-deficiency anaemia alters maternal susceptibility to malaria has not been studied in adolescent pregnancy, but in view of the consequences of malaria in this group, there is a need for further investigation.

Education and health promotion

In some rural settings, schoolchildren are the most educated members of the community and have a potentially important role in improving health; however, measuring the success of interventions is difficult (figure 3). There are relatively few data on malaria education in adolescents. Studies in India and Nigeria have shown that education aimed at adolescents can improve knowledge about malaria.[93,138] 3 months of health-education classes in a Kenyan school increased the awareness of malaria and knowledge of the importance of control measures in schoolchildren aged 7–18 years. This translated into a practical health improvement: a 25% decrease in the incidence of malaria compared with a 5% increase in the control group.[139]

In Kenya, adolescents aged 12–15 years were involved in follow-on education of the community in a bednet programme (figure 4). Adolescents' comprehension of the specific bednet messages improved, both immediately after teaching and 3 months later. Mothers were aware of the education programme, but only 30% could subsequently remember specific messages.[140] By contrast, adolescents were the one group that did not participate in community educational activities in a successful South American health-education community intervention about malaria.[141]

In view of the number of adolescent mothers, educating them not only about their own health but also about their children's health is important. There is good evidence that early diagnosis and treatment of malarial symptoms depend on recognition, mainly by women; older mothers have significantly better knowledge about the manifestation of malaria in children.[142,143] Education of the adolescent age-groups would therefore be of substantial potential benefit.[144]

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Figure 3: **Adolescents returning after malaria education in Uganda**

Discussion

Most attention in malaria has focused on the young African child because of the huge burden of disease and mortality in this age group. Finding good quality data on the incidence of disease in adolescents is not easy: few published studies specifically investigate malaria in adolescents, and younger adolescents are often not separated from children. However, although the burden of disease and mortality is clearly far less than that in younger children, we have presented evidence that from the perspective of the adolescent, malaria is a significant problem. Malaria seems to be a common cause of clinical illness, an important cause of hospital admissions, and a preventable cause of death in adolescents. This was true even in areas of stable transmission that traditionally might have been expected to have low burdens of malaria in those over the age of 10 years.

Clearly there are flaws in some of the data presented here. Direct comparison of incidence rates in different studies is difficult because of considerable variation in definitions of malaria incidence and prevalence. The accuracy of quoted incidence rates must therefore be treated with caution; the difficulties of accurate estimates are particularly illustrated by the variation in rates in the three Brazilian studies (table 3), all done in the same province. The WHO Global Programme on Evidence mortality data are modelled on the basis of reports by individual countries, and the tendency to over-diagnose malaria in endemic areas is well recognised: fever is often attributed to malaria without confirmation by microscopy or exclusion of other causes of fever. Nevertheless, despite these concerns, our review shows that malaria needs to be considered seriously by adolescent health programmes, and that the needs of adolescents should be considered by malaria control programmes.

The risk of malaria in pregnancy and its consequences is one of the most important areas identified. Adolescents are at risk as primigravidae and there is some evidence that the pregnant adolescent could be at even higher risk than older primigravidae. This might be compounded by limited access or use of antenatal care for this age-group. The severe consequences of malaria in pregnancy, both for the mother and for the baby, mean that prevention and treatment of malaria should be an extremely important component of antenatal services for pregnant adolescents (and other age-groups) in malarious areas.

There is no evidence of important specific clinical features of malaria in adolescents. The manifestations of severe malaria are most like those of adults, although severe anaemia may be more prominent. Malaria is likely to contribute to the problem of anaemia in adolescence, but the extent of its contribution is uncertain and much more research is needed, particularly for young adolescent boys. Malaria is responsible for loss of schooling because of ill health: the extent of the problem varies according to geographical region, and is greater in areas of unstable transmission.

Specific risk factors for the acquisition of malaria were not identified in areas of stable transmission. However, in areas of unstable transmission, occupational risks, particularly related to forestry work, are clearly important in young male adolescents, who may be at greater risk than younger children. A better understanding of risk factors and behaviour might allow specific education and prevention campaigns. We are similarly ignorant about adolescents' perception and knowledge of malaria and what they do when they become ill. Further research would be extremely useful.

In view of the burden of malaria in this age-group, effective preventive measures are clearly important. There is some evidence that high bednet coverage can reduce the incidence of uncomplicated malaria in non-pregnant adolescents in areas of both stable and unstable transmission, although the benefit is less clear in South America. No study has assessed the effect of bednets on severe disease or mortality in adolescents and this is a potentially important area for further research.

Chemoprophylaxis has been shown to be effective in reducing the incidence of clinical malaria, but no effect on mortality has been shown in adolescents, and most studies were done before antimalarial resistance became a major problem; the options for a cheap and effective prophylactic drug are currently limited in most parts of the world. A review has shown that costs of prophylaxis would be prohibitive, and that prompt presumptive treatment would be far more cost-effective.[145] Furthermore, the difficulties in sustaining chemoprophylaxis programmes mean that chemoprophylaxis is only useful for non-pregnant


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Figure 4: **Adolescents in a bednet programme in Tanzania**

adolescents from regions of low malaria prevalence who are travelling to malaria-endemic areas.

The severe consequences of malaria in adolescent pregnancy make this a crucial area for adolescent health services to consider. Bednets seem to offer benefits to both mother and fetus, although there are few specific data in adolescents. There are substantial differences between different trials, most likely related to malaria transmission intensity and immunity, but the influence of HIV seroprevalence needs to be explored further. Chemoprophylaxis or IPT reduces episodes of malaria and maternal anaemia, and may increase birthweight, particularly in first (or second) pregnancies; major efforts should be made to ensure that all adolescent primigravidae receive chemoprophylaxis or IPT. The mode of delivery and drug used will depend on local conditions and the spread of antimalarial resistance; increased HIV seroprevalence could make treatment more difficult. Further research into understanding the factors that influence the use of antenatal services by pregnant adolescent girls would be very helpful. Much more work is also needed on the potential importance of the interactions between malaria and nutrition in young pregnant women and the role of supplementation.

Finally, firm evidence of the benefit of health-education programmes for adolescents is scarce, despite the importance of these interventions both in terms of adolescents' health and their position within the community. WHO has recognised the potential role of adolescents and schoolchildren in the dissemination of information on malaria to their communities, and other national groups have stressed the importance of this group in malaria-control programmes.[146,147] The education of students in the school setting has the potential to

Panel 3: Priority areas for research

- Researchers should be encouraged to include adolescents as a separately defined group in malaria studies
- Improving use and uptake of preventive measures by the pregnant adolescent
- Understanding health-seeking behaviour of adolescents with malaria and how to improve access to treatment
- Interaction of malaria with anaemia and nutrition (including adolescent men)

benefit the individual by reducing the number of days lost from schooling caused by malaria, and could lead to a substantial benefit to the community.[148] The approach to treating malaria in schools could be an extremely practical way of ensuring prompt treatment of adolescents, who otherwise might not access health care; therefore, confirmation of its effectiveness is important.

Conclusions

This review has examined all aspects of malaria in adolescence. Although the burden of malaria is far lower than in younger children in areas of stable transmission, malaria should be one of the highest priorities in adolescent health care; in particular, young pregnant women are at high risk and require special attention in all malaria endemic areas. This review has also shown the relative paucity of good data on many aspects of malaria in adolescents. Researchers should be encouraged to include and report on adolescents as a separately defined group in malaria studies (panel 3).

Conflicts of interest

We declare that we have no conflicts of interest

Search strategy and selection criteria

These are described in detail in the Methods section on page 780.

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