Research

Severe malaria in children in Yemen: two site observational study

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Abstract

Objectives To assess the burden of malaria on health services, describe the clinical presentation of severe malaria in children, and identify factors associated with mortality by means of a prospective observational study.
Setting Two public hospitals in Taiz (mountain hinterland) and Hodeidah (coastal plain), Yemen.
Participants Children aged 6 months to 10 years.
Results Of 12 301 paediatric admissions, 2071 (17%) were for suspected severe malaria. The proportion of such admissions varied according to the season (from 1% to 40%). Falciparum malaria was confirmed in 1332 children; 808 had severe disease as defined by the World Health Organization. Main presentations were respiratory distress (322/808, 40%), severe anaemia (291/800, 37%), and cerebral malaria (60/808, 8%). Twenty two of 26 children who died had a neurological presentation. No deaths occurred in children with severe anaemia but no other signs of severity. In multivariate analysis, a Blantyre coma score ≤ 2, history of fits, female sex, and hyperlactataemia predicted mortality; severe anaemia, respiratory distress, and hyperparasitaemia were not significant predictors of mortality.
Conclusions Severe malaria puts a high burden on health services in Yemen. Although presentation is similar to African series, some important differences exist. Case fatality is higher in girls.

HELDUR NECTON/PANOS

Malaria accounts for many paediatric admissions

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Introduction

Malaria is not usually thought of as a major disease in the Middle East and the pattern is often assumed to be similar to that seen in southern Asia, where most disease is in adults infected with *Plasmodium vivax*. However, data from the World Health Organization suggest that after Afghanistan, Yemen has the highest incidence of malaria in the east Mediterranean region of WHO.[1]

Most studies on severe malaria in children have been undertaken in sub-Saharan Africa, and its presentation varies with the intensity of transmission.[2–6] Little is known of the pattern of malaria in Yemen, one of the most highly populated countries in the Middle East. Transmission is lower than in sites of previous studies of paediatric malaria in Africa, and immunity probably has less effect on the pattern of clinical infections. We carried out an observational study of the clinical pattern of malaria in two epidemiological settings: the coastal plain and the mountain hinterland. Transmission is not thought to occur in the inland plateau. We set out to determine the proportion of paediatric admissions in public hospitals that are due to severe malaria, to examine the presentation of severe malaria in a Middle Eastern

ELPS *This is the abridged version: the full version is on bmj.com*

Table 1 Clinical features on presentation of children with WHO defined severe malaria in two sites in Yemen. Values are numbers of children (percentage) unless stated otherwise

	Study site	
Clinical presentation	**Taiz**	**Hodeidah**
Severe malarial anaemia		
All ages*	221/604 (37)	70/196 (36)
<1 year old	39/81 (48)	16/22 (73)
1-4 years old	143/341 (42)	39/98 (40)
5-10 years old	39/182 (21)	15/76 (20)
Cerebral malaria		
All ages	42/604 (7)	18/204 (9)
<1 year old	1/81 (1)	1/22 (5)
1-4 years old	26/341 (8)	9/102 (9)
5-10 years old	15/182 (8)	8/80 (10)
Respiratory distress		
All ages	239/604 (40)	83/204 (41)
<1 year old	26/81 (32)	9/22 (41)
1-4 years old	118/341 (35)	40/102 (39)
5-10 years old	95/182 (52)	34/80 (43)
Prostration†		
All ages	233/562 (42)	91/186 (49)
<1 year old	36/80 (45)	13/21 (62)
1-4 years old	130/315 (41)	47/93 (51)
5-10 years old	67/167 (40)	31/72 (43)
Hypoglycaemia‡	51/601 (9)	15/190 (8)
Multiple convulsions	86/604 (14)	19/204 (9)
Impaired consciousness	31/604 (5)	21/204 (10)
Jaundice§	6/600 (1)	14/182 (8)
Bleeding	15/604 (3)	2/200 (1)
Hyperparasitaemia¶	116/601 (19)	35/200 (18)
Geometric mean (SD) parasite count	19845 (6.9)	6973 (9.8)

*Haemoglobin measurement missing for eight cases in Hodeidah.
†Excluding cerebral malaria.
‡Glucose values missing for three cases in Taiz and 14 in Hodeidah.
§Bilirubin value missing for four cases in Taiz and 22 in Hodeidah.
¶Parasitaemia results from the thin film missing for three cases in Taiz and four in Hodeidah.

context, and to explore the risk factors for death from malaria in this population.

Methods

We conducted our study in Taiz—a densely populated province with a population of 2.4 million, typical of the mountainous hinterland—and in Hodeidah—a major city on the coastal plain. Focus group discussions and surveys in villages indicated that most children with severe febrile illness would visit hospital. We recruited study subjects from two hospitals that cover most of the paediatric beds in Taiz and Hodeidah city. We recruited children if they had a positive blood film for asexual forms of *P falciparum*; were between 6 months and 10 years old; and required admission to hospital. Cases were defined as severe if they met current WHO criteria for severe malaria in children (see bmj.com).[7] Severe malaria is treated with parenteral quinine in Yemen, and first line treatment for non-severe disease was chloroquine.

Two laboratory technicians at each site independently read the blood films for malaria, and we sent all blood films to Sana'a University for quality control. We measured parasitaemia, haemoglobin, blood glucose, creatinine, total serum bilirubin, and lactate in whole fresh venous blood.

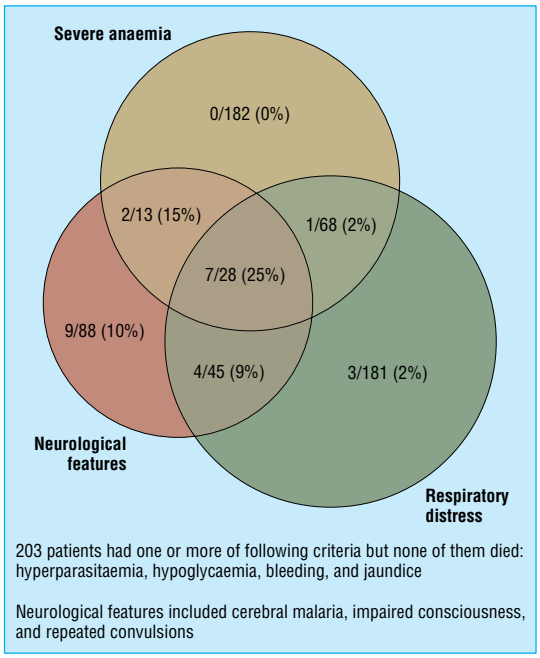
We calculated confidence intervals for case fatality and used unconditional logistic regression to investigate the risk factors for death. Data from clinical history, clinical examination, and laboratory tests were added sequentially to the model (see bmj.com for details of recruitment, laboratory methods, and statistical analysis).

Results

Between 19 November 2002 and 30 August 2004, 8068 children aged 6 months to 10 years were admitted to hospital in Taiz; 1358 (17%) were admitted for suspected severe malaria. In Hodeidah the total number of admissions was 4233; 713 (17%) were admitted with suspected severe malaria. The proportion of admissions for presumed malaria followed the transmission season and varied considerably over the year. In Taiz the proportion ranged from 7% in February and May to 38% in November and December, whereas in Hodeidah it ranged from 1% between July and September to 40% in February and March. Malaria was confirmed microscopically in 1049 children in Taiz and in 283 in Hodeidah. Six hundred and four of the cases in Taiz and 204 in Hodeidah satisfied WHO criteria for severe malaria.

Table 1 shows the features at presentation of children with WHO defined severe malaria. Severe anaemia with haemoglobin less than 50 g/litre was a common presentation at both sites: 37% (221/604) in Taiz and 36% (70/196) in Hodeidah. Mean haemoglobin concentrations were 61 (standard deviation 21) and 59 (21) g/litre. Young age was strongly associated with presentation with severe anaemia (χ^2 for trend $P<0.001$). Severely anaemic children had a median age of 2.0 (interquartile range 1.1-3.5) years, whereas those who were not anaemic had a median age of 3.5 (1.75-6) years ($P<0.001$).

Only 42 (7%) cases in Taiz and 18 (9%) in Hodeidah satisfied WHO criteria for cerebral malaria (Blantyre coma score ≤ 2). Children with cerebral



Number of deaths in children with severe malaria by clinical pattern on presentation in two sites in Yemen

Table 2 Risk factors for case-fatality for malaria in univariate analysis adjusted for age. Values are numbers (percentage) unless stated otherwise

Variable	Prevalence	Mortality	Odds ratio (95% CI)	P value
Sex				
Male	484/808 (60)	9/484 (2)	1	0.006
Female	324/808 (40)	17/324 (5)	3.0 (1.3 to 6.9)	
Clinical history				
No of reported fits:				
<2	674/808 (83)	12/674 (2)	1	
≥2	134/808 (17)	14/134 (10)	6.3 (2.8 to 14.1)	<0.001
Reported history of coma	167/808 (21)	21/167 (13)	18.9 (6.6 to 54.2)	<0.001
Clinical examination				
Abnormal respiratory rhythm	76/808 (9)	11/76 (15)	8.3 (3.5 to 19.5)	<0.001
Respiratory grunting:				
No grunting	747/808 (93)	19/747 (3)		
Every breath	61/808 (8)	7/61 (12)	5.2 (2.1 to 13.2)	<0.001
Jaundice	106/808 (13)	7/106 (7)	2.5 (1.03 to 6.2)	0.03
Dehydration*:				
None	579/808 (72)	15/579 (3)	1	0.05
Some	178/808 (22)	7/178 (4)	1.53 (0.6 to 3.9)	
Severe	51/808 (6)	4/51 (8)	3.2 (1.02 to 10.3)	
Cold periphery	148/808 (18)	9/148 (6)	2.4 (1.04 to 5.5)	0.03
Prostration without CM	324/808 (40)	7/324 (2)	4.6 (0.88 to 46.2)	0.05
Blantyre coma score:				
>4 (normal)	686/808 (85)	7/686 (1)	1	
3-4	61/808 (8)	2/61 (3)	3.3 (0.7 to 16.5)	<0.001
≤2†	61/808 (8)	17/61 (28)	39 (13.5 to 115.3)	
Witnessed fitting	50/808 (6)	10/50 (20)	11.3 (4.7 to 27.0)	<0.001
Posturing	20/808 (3)	8/20 (40)	27.6 (9.4 to 81.2)	<0.001
Abnormal pupil size	21/808 (3)	9/21 (43)	33.6 (11.2 to 100.6)	<0.001
Abnormal pupil reaction	22/808 (3)	8/22 (36)	23.8 (8.2 to 69.0)	<0.001
Abnormal doll's eye	13/808 (2)	7/13 (54)	51.3 (13.4 to 196.1)	<0.001
Laboratory data				
Creatinine:				
<88 μmol/l	722/789 (92)	18/722 (3)	1	
≥88 μmol/l	67/789 (94)	8/67 (12)	5.7 (2.3 to 14.2)	<0.001
White blood cell count:				
<10 000×10^9/l	519/807 (64)	11/519 (2)	1	
≥10 000×10^9/l	288/807 (36)	15/288 (5)	2.6 (1.2 to 5.8)	0.01
Lactate:				
≤5 mmol/l	340/460 (74)	5/340 (2)	1	
>5 mmol/l	120/460 (26)	11/120 (9)	6.9 (2.2 to 21.0)	<0.001
Bilirubin‡:				
<50 μmol/l	762/782 (97)	25/762 (3)	1	
≥50 μmol/l	20/782 (3)	1/20 (5)	1.5 (0.2 to 11.8)	0.7

*χ^2 test for trend (P<0.05).
†In one patient the score changed from 2 to 3 after giving 50% dextrose.
‡Bilirubin results missing for four cases in Taiz and 22 in Hodeidah.

malaria were older than children with severe anaemia (median age 3.3 (1.6-5.3) *v* 2 (1.1-3.5) years). Respiratory distress was seen in about 40% of cases at both sites. Only five patients with respiratory distress had radiological evidence of chest infection.

Twenty six children died in hospital. The case fatality rate was 3.2% (95% confidence interval 2.1% to 4.7%). Table 2 shows risk factors for mortality at presentation. The age of children who died was similar to those who survived, but mortality was significantly higher in girls than boys (5.2% *v* 1.9%; odds ratio 3.0; 95% confidence interval 1.3 to 6.9). Most deaths were in children with neurological features at presentation (figure). No deaths occurred in children with severe anaemia alone, and the mortality rate in children presenting with respiratory distress alone was less than 2%. Four factors were associated independently with mortality in logistic regression: Blantyre coma scale ≤2 (7.2; 1.8 to 28.9), history of coma (8.0; 2.1 to 30.6), female sex (4.6; 1.3 to 16.2), and hyperlactataemia (6.1; 1.8 to 20.2). All children who died had severe malaria according to revised WHO criteria, although some deaths would have been missed using previous versions.[8]

Discussion

We found that in Yemen severe paediatric malaria is a substantial burden to the health services, both on the coastal plain and in the inland mountains. In the peak malaria season, around 40% of paediatric admissions were for clinically diagnosed malaria, and more than half of the cases satisfied current WHO criteria for severe falciparum malaria. This proportion of admissions is comparable to many sites in Africa during the peak season.

Although the clinical pattern of malaria in Yemen was similar to that seen in Africa, we found some

What is already known on this topic

Severe anaemia, cerebral malaria, and respiratory distress are associated with poor outcome in paediatric malaria in Africa

Little is known about severe malaria in the Middle East

What this paper adds

Severe malaria is a common reason for paediatric admissions in Yemen and most deaths are associated with neurological features

Female sex is a risk factor for mortality from malaria in Yemen; reasons for this are not clear

important differences. More than half of the children with WHO defined severe malaria in both sites were anaemic. Severe anaemia was associated with young age, whereas the peak for cerebral malaria was at a later age; this pattern is similar to that found in many African sites.[9–11] Transmission is probably lower in Yemen than in most of Africa, and adults do not seem to acquire appreciable immunity to malaria; this supports the view that age and not immunity is the key determinant of this difference. About 40% of patients at each site had respiratory distress; this is a higher proportion than is found in African countries.[9 10 12 13] Chloroquine was first line treatment for non-severe disease at the time of our study and this may have contributed to the high proportion of children with severe anaemia—sentinel site data suggest that chloroquine has up to a 50% parasitological failure rate within 14 days.

None of the children in our study with severe anaemia but no other signs of severity died; blood is readily available (usually within an hour) and indirect evidence suggests that when this is the case this form of severe malaria seldom causes death.[14] In contrast to some studies in Africa, where respiratory distress without neurological signs was a strong predictor of mortality,[15 16] almost all deaths in our study were in children with cerebral malaria or other neurological signs at presentation. Mild respiratory signs are common in less severe malaria,[17] and children with respiratory distress in Yemen may be referred for care earlier than in some African settings; in addition blood and fluid resuscitation may be used more widely in Yemen. As in other studies, we found no association between the outcome and the level of parasitaemia. One important difference between our study in Yemen and studies in Africa is that female sex was a significant predictor for death in univariate and multivariate analyses, although all measured risk factors were distributed evenly between both sexes. Since this difference has not been found elsewhere it is probably not due to biological differences between the sexes. It could be due to differences in background immunity between male and female children—boys may have more contact with the vector for various cultural reasons including the clothing they wear and the time they spend outdoors. Another possible cause is that for cultural reasons boys and girls present at different times; health education is needed if this reflects a delay in the presentation of girls.

Although hospital studies are no substitute for epidemiological studies in the community and can underestimate the burden of malaria, our study demonstrates a considerable burden of severe malaria in children in Yemen. Malaria control should be a priority in Yemen and lessons could be learnt from other areas of highly seasonal malaria.

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