Human malaria in the highlands of Yemen

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Between June 2008 and March 2009, a cross-sectional study of human malaria was carried out in four governorates of Yemen, two (Taiz and Hodiedah) representing the country's highlands and the others (Dhamar and Raymah) the country's coastal plains/foothills. The main aims were to determine the prevalences of *Plasmodium* infection among 455 febrile patients presenting for care at participating health facilities and to investigate the potential risk factors for such infection.

Malarial infection was detected in 78 (17.1%) of the investigated patients and was more likely to be detected among the febrile patients from the highlands than among those presenting in the coastal plains/foothills (22.6% v. 13.9%; $\chi^2=10.102$; $P=0.018$). Binary logistic-regression models identified low household income [odds ratio (OR)=13.52; 95% confidence interval (CI)=2.62–69.67; $P=0.002$], living in a household with access to a water pump (OR=4.18; CI=1.60–10.96; $P=0.004$) and living in a household near a stream (OR=4.43; CI=1.35–14.56; $P=0.014$) as significant risk factors for malarial infection in the highlands. Low household income was the only significant risk factor identified for such infection in the coastal plains and foothills (OR=8.20; CI=1.80–37.45; $P=0.007$).

It is unclear why febrile patients in the highlands of Yemen are much more likely to be found to have malarial infection than their counterparts from the coastal plains and foothills. Although it is possible that malarial transmission is relatively intense in the highlands, it seems more likely that, compared with those who live at lower altitudes, those who live in the highlands are less immune to malaria, and therefore more likely to develop febrile illness following malarial infection. Whatever the cause of the symptomatic malarial infection commonly found in the highlands of Yemen, it is a matter of serious concern that should be addressed in the national strategy to control malaria.

Human malaria is the most common vector-borne disease in Yemen, with an annual incidence of about 900,000 cases and approximately 60% of the total population considered to be at risk of the disease (WHO, 2009a). *Plasmodium falciparum* accounts for 95% of the cases and, although *Anopheles arabiensis* is the predominant vector, *An. culicifacies* plays an important role in malarial transmission in the coastal areas of Yemen and another known vector

species, *An. sergenti*, has been reported in the mountainous hinterland and highland areas (Anon., 2002; WHO, 2005; Alkadi *et al.*, 2006; Bin Mohanna *et al.*, 2007).

Within Yemen, the prevalence of human malaria varies from one governorate to another, apparently reflecting climatic differences. Mountainous areas (i.e. the central highland plateaux, at altitudes of 1500–2000 m above sea level) tend to have relatively low prevalences and malarial infection that is sporadic, particularly during malaria outbreaks (Anon., 2002, 2006). Land at altitudes of >2000 m and the

deserts are considered free of malaria whereas other areas are plagued with the disease and receive much attention from the National Malaria Control Programme (NMCP; Anon., 2002, 2006).

Globally, the transmission of the *Plasmodium* species responsible for human malaria, by *Anopheles* mosquitoes, is affected not only by a mix of natural determinants, such as temperature, rainfall, flood, wind speed and altitude (Snow *et al.*, 1998; Guthmann *et al.*, 2001; Al-Mansoob and Al-Mazzah, 2005; Hustache *et al.*, 2007), but also by several demographic, socio-economic and genetic determinants. For any at-risk individual, his or her ethnic group, level of education and occupation (or those of his or her parents/guardians), his or her genotype, level of acquired immunity, housing conditions, household's use of preventive measures (such as the home use of insecticides and/or bednets) and knowledge and attitude towards malaria, and (following treatment) the level of resistance to antimalarial drugs in the local parasites, may all affect his or her chances of developing symptomatic malaria (Bouma *et al.*, 1996; Incardona *et al.*, 2007; Al-Taïar *et al.*, 2009a; Baragatti *et al.*, 2009; Graves *et al.*, 2009; Tipmontree *et al.*, 2009).

Among the countries that lie within the World Health Organization's Eastern Mediterranean region, only Somalia and Afghanistan have higher levels of malarial transmission than Yemen (WHO, 2009a). Yemen is now the only country in the Arabian Peninsula that remains plagued with malaria, with considerable mortality and morbidity. Unfortunately, the country has been unstable for many years, suffering from civil wars, a deteriorating economy and severe depletion in water resources. The main aims of the present study were to determine and compare the prevalences of *Plasmodium* infection — and explore the potential risk factors for such infection — among febrile patients presenting for care at participating health facilities in highland and lowland areas of Yemen.

SUBJECTS AND METHODS

Study Area and Subjects

The present, cross-sectional study was carried out between June 2008 and March 2009 (i.e. over one 'malaria season') in four governorates in Yemen, with two of the selected governorates (Taiz and Hodiedah) representing the country's coastal plains and foothills at altitudes of <2000 m above sea level and the other two governorates (Dhamar and Raymah) representing the highlands at altitudes of >2000 m. Together, Taiz and Hodiedah have a population of about 4 million whereas the combined population of Dhamar and Raymah is approximately 2 million.

The climate in Yemen differs depending on the region. In the coastal areas, the tropical monsoon in the summer, with two rainy seasons (February–April and July–September) and a mean temperature of 37.5°C, is replaced by dry, cooler weather, with a mean temperature of 24.0°C, in the winter. Relative humidity in such areas ranges between 70% and 90% and mean annual rainfall is about 200 mm. The highland areas receive much higher rainfall (a mean of 800 mm/year) and the climate is moderate in summer and cold in winter, with an annual mean temperature of about 20°C and relative humidity varying between 20% and 50%.

At a 5% level of significance and a 95% confidence level, the minimum number of febrile subjects required for the study was estimated at 246, assuming that the prevalence of malarial infection among the subjects was similar to the corresponding values previously reported in Yemen (Alkadi *et al.*, 2006; Al-Taïar *et al.*, 2006).

The study protocol was approved by the Ethical Committees of both the University of Malaya Medical Centre, in Kuala Lumpur, and Sana'a University's Faculty of Medicine, in Sana'a. Signed informed consent was obtained from each adult subject (i.e. a subject aged ≥15 years) and the parents/guardians of each child investigated.

Data Collection

Over the study period, malaria cases were detected through passive case detection (PCD). A fingerprick sample of blood was collected from each consenting febrile patient who presented at one of the participating health facilities in the study governorates. Thin and thick bloodsmears were prepared on clean glass slides, Giemsa-stained and checked for malarial parasites under a light microscope, at $\times 1000$. Each thick smear was checked, independently, by two expert microscopists and, for quality control, 25% of the thick smears were randomly selected and re-examined by a third microscopist who was unaware of the results of the earlier microscopy.

Data on the demographic and socio-economic characteristics of each subject were collected in face-to-face interviews (with the adult subjects and the parents/guardians of each child investigated), using a pre-tested standardized questionnaire. Information on the subject's household's antimalarial protection and malaria-control practices, history of malarial infection and water sources and on the materials used to build the subject's house was collected in the same interviews.

Statistical Analysis

The collected data were analysed using version 13 of the SPSS for Windows software package (SPSS Inc, Chicago, IL). Possible risk factors for malarial infection were initially explored in univariate analyses (weighted for sampling probability), with smear-positive malarial infection set as the dependent variable. The factors found significant were then checked in a binary logistic-regression model (ENTER) to confirm the significant predictors of malarial infection in febrile subjects. A P -value of <0.05 was considered indicative of a statistically significant difference.

RESULTS

Overall, 455 febrile subjects (207 males and 248 females) with a median age of 20 years

(interquartile range=8–32 years) participated in this study. Most (62.9%) of the male subjects but only 37.1% of female participants had received at least 6 years of formal education ($\chi^2=16.178$; $P<0.001$). Although about one-third of the subjects worked as farmers or government employees, the rest (students or housewives) were categorized as 'not working'.

Malarial parasites were detected in the bloodsmears of 78 (17.1%) of the subjects, with 75, two and one of the subjects found infected with *P. falciparum*, *P. vivax* and *P. malariae*, respectively (and no mixed infections observed). The percentage of febrile subjects found smear-positive for malarial parasites was significantly higher in the highland study areas than in the areas of coastal plain/foothills that were investigated (22.6% *v.* 13.9%; $\chi^2=10.102$; $P=0.018$).

In the univariate analyses (Table 1), which were run separately for the highland and coastal plain/foothill data, several potential risk factors for malarial infection (among febrile subjects) were identified. In the highlands, low household income (i.e. a monthly household income of less than 20,000 riyals or about U.S.\$85), the presence of a water pump within 250 m of the household, household water (i.e. rainwater and well water) collection, the presence of a stream within 250 m of the household, an age of >12 years, 'not working', and wearing 'short' clothes (i.e. clothes that leave most of the arms and legs exposed) were each significantly positively associated with malarial infection while using bed nets was negatively associated with such infection [i.e. the use of bednets reduced the risk of malarial infection being detected in febrile subjects, giving an odds ratio (OR) of 0.36, a corresponding 95% confidence interval (CI) of 0.16–0.80, and a P -value of 0.01]. Among the febrile subjects from coastal/foothill areas, male gender, low household income, the presence of a water pump and/or a stream within 250 m of the household, a household history of malarial infection, wearing

TABLE 1. *The results of the univariate analysis of potential risk factors for malarial infection among 168 febrile subjects from the highlands of Yemen and 287 febrile subjects from the country's coastal areas/foothills*

Variable	Highlands		Coastal areas/foothills	
	No. and (%) of subjects found smear-positive	Odds ratio and (95% confidence interval)	No. and (%) of subjects found smear-positive	Odds ratio and (95% confidence interval)
AGE (years)				
≤ 12	17 (15.9)	2.9 (1.36–6.0)*	28 (13.6)	1.04 (0.49–2.21)
> 12	21 (35.0)		11 (14.1)	
GENDER				
Male	22 (21.0)	0.78 (0.37–1.63)	26 (18.2)	2.06 (1.03–4.14)*
Female	16 (25.4)		14 (9.7)	
RESIDENCE				
Urban	5 (17.9)	1.42 (0.50–4.03)	8 (5.2)	5.78 (2.56–13.07)‡
Rural	33 (23.6)		32 (24.1)	
HOUSEHOLD INCOME				
High (≥20,000 riyals/month)	5 (8.3)	4.84 (1.78–13.19)‡	3 (2.9)	8.25 (2.48–27.49)‡
Low (<20,000 riyals/month)	33 (30.6)		37 (20.0)	
HOUSEHOLD SIZE				
One to five members	1 (6.7)	3.90 (0.49–30.76)	2 (3.2)	5.93 (1.39–25.41)*
More than five members	32 (21.8)		35 (16.5)	
EDUCATION				
At least 6 years in formal education	20 (23.5)	0.85 (0.41–1.77)	26 (15.2)	0.77 (0.38–1.54)
Other	17 (20.7)		14 (12.1)	
OCCUPATION				
Working	6 (10.9)	2.96 (1.15–7.64)*	17 (20.0)	0.51 (0.26–1.02)
Not working	29 (26.6)		23 (11.4)	
QUALITY OF HOUSING				
Good (made of stone or brick, with no large holes)	36 (22.8)	0.85 (0.17–4.17)	32 (13.1)	1.61 (0.69–3.80)
Bad	2 (20.0)		8 (19.5)	
TYPE OF ROOF				
Concrete	5 (14.7)	1.90 (0.68–5.29)	8 (9.1)	1.93 (0.85–4.37)
Wooden	33 (2.6)		32 (16.2)	
CLOTHES				
Long (covering arms and legs)	13 (14.9)	2.34 (1.09–5.02)*	12 (7.5)	3.52 (1.71–7.26)‡
Short	23 (29.1)		28 (22.2)	
INSECTICIDE SPRAYING				
BY GOVERNMENT?				
Yes	23 (26.1)	0.66 (0.32–1.38)	5 (9.6)	1.66 (0.62–4.47)
No	15 (19.0)		35 (15.0)	
BEDNETS				
Used	28 (30.1)	0.36 (0.16–0.80)	8 (13.8)	1.02 (0.44–2.35)
Not used	10 (13.3)		32 (14.0)	
WATER PUMP NEARBY?				
Yes	26 (34.7)	3.58 (1.66–7.74)‡	20 (33.9)	5.28 (2.60–10.72)‡
No	12 (12.9)		20 (8.8)	
WATER COLLECTED				
BY HOUSEHOLD?				
Yes	29 (33.0)	3.88 (1.70–8.84)‡	22 (17.1)	1.67 (0.84–3.30)

TABLE 1. *Continued*

Variable	Highlands		Coastal areas/foothills	
	No. and (%) of subjects found smear-positive	Odds ratio and (95% confidence interval)	No. and (%) of subjects found smear-positive	Odds ratio and (95% confidence interval)
No	9 (11.3)		17 (11.0)	
STREAM NEARBY?				
Yes	28 (28.9)	2.48 (1.11–5.51)*	19 (27.9)	3.62 (1.81–7.25)*
No	10 (14.1)		21 (9.7)	
INSECTICIDE USED BY HOUSEHOLD?				
Yes	11 (16.4)	1.86 (0.85–4.06)	8 (7.5)	2.69 (1.19–6.09)*
No	27 (26.7)		32 (17.9)	
HOUSEHOLD HISTORY OF MALARIAL INFECTION?				
Yes	24 (19.8)	0.58 (0.27–1.26)	34 (5.0)	4.89 (1.98–12.08)*
No	14 (29.8)		6 (20.5)	

*Significant association ($P < 0.05$).†Significant association ($P < 0.01$).

‘short’ clothes, belonging to a household with six or more members, living in a household that did not use insecticides, and residing in a rural area were each significantly positively associated with malarial infection.

In the binary logistic-regression models, low household income, household access to a water pump and the presence of a stream within 250 m of the household were identified as the significant predictors of malarial infection among febrile subjects from the highlands (Table 2) whereas only one corresponding predictor — low household income (OR=8.20; CI=1.80–37.45; $P=0.007$) — was identified for the febrile subjects from lower altitudes.

DISCUSSION

Yemen is the most populous country in the Arabian Peninsula, with about half of the total population living below the poverty line (World Bank, 2010). Although the United Arab Emirates was declared a malaria-free country in early 2007 (WHO, 2008) and Oman and Saudi Arabia have achieved substantial achievement in controlling malaria, Yemen (like Afghanistan, Djibouti, Pakistan, Somalia and Sudan) has failed to achieve a consistent decrease in the incidence of malaria (WHO, 2009a). The present results confirm that malaria remains a public-health problem in Yemen, apparently accounting for 17.1% of all episodes of

TABLE 2. *The significant results of the binary logistic-regression analysis of potential risk factors for malarial infection among 168 febrile subjects from the highlands of Yemen*

Variable	Parameter estimate (B) and (S.E.)	Odds ratio and (95% confidence interval)	P
Constant	–2.965 (0.556)	—	0.000
Low household income	2.604 (0.837)	13.52 (2.62–69.67)	0.002
Water pump nearby	1.431 (0.491)	4.18 (1.60–10.96)	0.004
Stream nearby	1.487 (0.607)	4.43 (1.35–14.56)	0.014

febrile illness (at least, all such episodes for which treatment was sought) in the study areas. The present observations are similar to those made, in different governorates of Yemen, over the last decade (Al-Maktari *et al.*, 2003; Alkadi *et al.*, 2006). Al-Taïar *et al.* (2006) reported that 17% (2071/12,301) of the paediatric admissions in two public hospitals in Yemen (one in Taiz governorate and the other in Hodeidah) were the result of severe malaria. In southern Yemen, Bin Mohanna *et al.* (2007) found that about 13% of the asymptomatic children who they investigated in primary schools had malarial infections; given that children are unlikely to attend school when they have clinical malaria, the prevalence of malarial infection among children of primary-school age who live in southern Yemen is probably higher than 13%.

In the present study, as in previous reports on malaria in Yemen (Alkadi *et al.*, 2006; Bin Mohanna *et al.*, 2007), *P. falciparum* was by far the most common *Plasmodium* species detected (accounting for 96.2% of the malarial infections observed).

Yemen has unique topography, climate and socio-economic structure. The endemicity of malaria ranges from malaria-free areas (mostly mountain plateaux and arid slopes from the highlands to the desert) to areas of coastal plain and foothills where the disease is holo- or hyper-endemic (Anon., 2002). Not surprisingly, the activities of the NMCP are mainly concentrated in the areas that have long been considered the most malarious (i.e. the coastal plains and foothills). The main observation made in the present study — that, compared with such a subject from the ‘malarious’ coastal plains/ foothills, a treatment-seeking febrile subject from the highlands was almost twice as likely to be smear-positive for malarial parasites — was surprising. Human malaria does, however, occur in other areas at altitudes of 2200–2600 m — in Ethiopia (Ghebreyesus *et al.*, 2000), Kenya (Hay *et al.*, 2002), Argentina (Burgos *et al.*, 1994), Rwanda (Van Lieshout *et al.*, 2004),

Afghanistan (Abdur Rab *et al.*, 2003) and Pakistan (Bouma *et al.*, 1996) — and global warming may be increasing the incidence of such ‘highland malaria’ (Burgos *et al.*, 1994; Bouma *et al.*, 1996; Bryan *et al.*, 1996; Rogers and Randolph, 2000; Sutherst, 2004).

In Yemen, climate variability and change combined with demographic and socio-economic factors (such as population increase, social instability and poverty) may all aggravate the problem posed by malaria (D. Kumetat, unpubl. obs.). Over the last decade, the temperatures and rainfall on the Arabian Peninsula have been unusually high, with severe floods in Yemen, Saudi Arabia and Oman. Such conditions are not only likely to favour mosquito breeding — perhaps explaining the epidemics and high incidences of malaria and dengue fever recently observed in Yemen (Al-Mansoob and Al-Mazzah, 2005; WHO, 2009b) — but may also allow mosquito vectors to move up to altitudes that were once too cool for their survival.

In the present study, poverty (represented by low household income) was found to be associated significantly with malarial infection in febrile subjects, whether the subjects lived in the highlands or at lower altitudes. A similar poverty-malaria link has been observed in Africa and South-east Asia (Panvisavas, 2001; WHO, 2002; Worrall *et al.*, 2005). Malaria can almost be considered to be a symptom of poverty because it mostly affects the poorest people in Africa and Asia. Poor families are unlikely to have access to healthcare services and do not have the capacity to afford relatively expensive drugs or even to provide healthy housing conditions for their members (Panvisavas, 2001; WHO, 2006). A poverty-malaria link may also explain why a lack of income-generating employment appears to be a risk factor for detectable malarial infection in highland Yemen (present study) and among Kenyan adults (Coldren *et al.*, 2006).

The collection of water and living close to a stream and/or a water pump were identified as significant risk factors for malarial

infection in the present study. The people who live in rural Yemen use uncovered tanks, cement cisterns and smaller containers to store water and the evidence of similar water-storage practices can also be seen in the major cities, such as those in the Hodeidah (coastal plains) and Taiz (foothills) governorates (unpubl. obs.). There are relatively few streams in Raymah governorate and water pumps are relatively rare in Dhamar governorate but dozens of dams, for agricultural irrigation and also for groundwater recharge, have been constructed by the government in all four of the study governorates. Water storage, streams, dams and the puddles left around water pumps may all provide breeding sites for mosquitoes and therefore, potentially, support the transmission of malarial parasites to humans (Ghebreyesus *et al.*, 1999; Klinkenberg *et al.*, 2004; Al-Taïar *et al.*, 2009a).

The high temperatures and humidity that occur in the coastal plains and foothills of Yemen lead to the boys and men in rural communities wearing light clothes that leave the arms and legs exposed to the sun and (both outside and inside the houses that are made of mud, wood and straw, with many gaps through which mosquitoes can move) to mosquito bites. (Girls and women in Yemen — a predominantly Muslim country — are expected to keep their legs and arms covered.) Poorly constructed housing and the wearing of clothes that leave most of each arm and leg exposed have been previously identified as significant risk factors for malaria in studies in Yemen (Al-Taïar *et al.*, 2006) and Sri Lanka (Konradsen *et al.*, 2003).

Knowledge, attitude and practices (KAP) towards malaria play important roles in malaria transmission. In Yemen, the KAP towards malaria are often vague, with common misconceptions about transmission, improper prevention and control practices, and delays in treatment seeking (Al-Taïar *et al.*, 2009b). In the present study, the use of bednets was found to be

a protective factor against malaria whereas not using insecticides was identified as a significant risk factor. Al-Taïar *et al.* (2009a) showed that regular insecticide spraying gave significant protection against malaria in Yemen. Occupation and level of parental education were not significantly associated with malarial infection in the present study, perhaps because most of the subjects were housewives or students and parental education showed relatively little variation. In both the Congo (Carme *et al.*, 1994) and Mali (Safeukui-Noubissi *et al.*, 2004), malaria appeared to be significantly affected by maternal education and occupation.

The present results must be treated with some caution, as they do not allow the prevalences of either malarial infection or symptomatic malaria in any of the study governorates to be estimated. The present data come from passive case detection among febrile patients presenting for treatment. Parasitaemic but asymptomatic individuals, who may be common in areas of high transmission — where many people can develop protective immunity against symptoms during malarial infection (Branch *et al.*, 2005; Erhart *et al.*, 2007) — are unlikely to have been detected in the present study. Moreover, there may be other common causes of fever in Yemen and those causes may not be homogeneously distributed throughout the country. The percentage of febrile patients found smear-positive for malaria may be affected more by the local incidence of febrile illnesses other than malaria as by the local level of malarial transmission or the local incidence of symptomatic malaria. Although it is possible that, within Yemen, malarial transmission is relatively intense in the highlands, it seems more likely that, compared with those who live at lower altitudes, those who live in the highlands are less immune to malaria, and therefore more likely to develop febrile illness following malarial infection.

Despite the limitations of the present study, the discovery that many febrile subjects in the highlands of Yemen have

malarial infection is still a matter of serious concern (especially as *P. falciparum* predominates). The community-wide active detection of malarial infections in the people who live in the highlands of Yemen is now recommended, so that the burden of malaria in these areas can be accurately assessed, the geographical variation in malaria risk across Yemen can be mapped, and effective methods of malaria control can be implemented and, perhaps, focused on high-risk communities.

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