Malaria elimination trend from a hypo-endemic unstable active focus in southern Iran: predisposing climatic factors

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Human malaria is the most important vector-borne infectious disease in Iran. It remains focally endemic being restricted to almost 20 counties in three oriental provinces. As a result of control measures applied since 1988, these counties appear to be on the verge of eliminating malaria. Malaria elimination strategy has thus become the new goal in Iran. Malaria due to *Plasmodium vivax*, whose transmission is particularly hard to interrupt, accounts for nearly 90% of the cases. This study was thus undertaken to show malaria elimination trend from a hypo-endemic unstable active focus in southern Iran and to examine the role of prevailing climatic factors. This focus is now under elimination phase (Stratum III or annual parasitic index <1/1000 person/year). All malaria-positive cases were identified with active and passive procedures from 2003 to 2011. Although all ages were infected, more than half of the patients were in the higher than 20-year age group and a clear majority (77%) of them identified in the warmer months (May–October) of the year were positive with *P. vivax* parasites. The rate of falciparum to mixed infections was highest (1%) in the penultimate year. Case finding was negatively related to precipitation rate both annually and over the 9-year period and positively to ambient temperature in each year. Despite progress in the scale-up of its elimination, transmission of malaria remains active. This should be tackled by proactive case detection in specific hotspots of the study focus.

Keywords: Malaria, Elimination, *Plasmodium*, Climate, Iran

Introduction

Human malaria is one of the world's most detrimental diseases which cause much morbidity and mortality particularly in tropical parts of the world.¹ It is one of the most important vector-borne infections in Iran caused by the protozoan species in the genus *Plasmodium* which produces intermittent febrile paroxysms every 48 or 72 hours marked with fever, chills, and sweats, the three cardinal symptoms of disease due to malaria parasites.²

Both *Plasmodium falciparum* and *Plasmodium vivax* occur sympatrically in Iran with the majority of malaria cases being due to *P. vivax*.^{3,4} Malaria transmission is unstable and year-round with two peaks in May–June (mainly due to *P. vivax*) and September–October with *P. falciparum* dominance.^{5,6} Since 2006, *P. falciparum* has accounted for <8% of reported malaria cases.⁷ In the year of 2002 in

Sistan-Baluchistan province, only 49% of the malaria cases were Iranians and the rest were non-Iranians, mainly from Afghanistan and Pakistan.⁸ Malaria due to *P. vivax* accounts for about 90% of the cases.⁹ *Anopheles stephensi* is the predominant vector. *An. culicifacies* plays an important role in malaria transmission in the southeast areas of Iran and another known vector species, *An. fluviatilis*, has been reported from the mountainous highland areas.¹⁰

The national key control intervention policies and strategies have involved four major issues: free distribution of insecticide-treated nets to all age groups, indoor residual spraying, free malaria diagnosis in the public sector and radical treatment of *P. vivax* cases following active and passive case detection using chloroquine (or primaquine in relapse cases for those with glucose-6-phosphate dehydrogenase deficiency, also known as Favism), and finally foci (including larviciding) and case investigation is undertaken.⁷

As a result of control measures initiated since 1988 in Iran, a considerable nationwide reduction (64%) of

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Figure 1 Sketch map of Iran showing the three southeast oriental provinces endemic for malaria and the location of study area.

cases has been reported by the national malaria control program during the last decade (2000–2009).⁷ Malaria is now under control with 96% of cases being effectively restricted to about 20 counties in the three southeast provinces of Sistan-Baluchistan, Hormozgan, and Kerman.^{7,11} This ‘refractory malaria region’ had an annual parasite index (API) of 8.74 and 4.83 per 1000 person year in 1997 and 2008, respectively.^{11,12} That is a reduction of 55.3% during a decade. The total numbers of indigenous and imported malaria cases in Iran in 2010 were 1847 and 1184 cases, respectively.¹³ Malaria elimination strategy by the year 2025 has thus become the new goal in Iran¹¹ where firstly most of its Palaearctic provinces already have substantial malaria-free areas, and secondly its Oriental provinces lie next to the malaria-endemic regions like India and Pakistan (Fig. 1). Malaria elimination was then adopted in 2005 so that processes

towards certification of the achievement of elimination could be initiated by the end of the decade.¹⁴

Elimination refers to the persistent cessation of malaria transmission and the reduction to zero incidence of locally contracted infection or disease within the target population in a defined region, so that the only cases of malaria that might occur are through introduction of infections from outside the region.^{15,16} At any one point in time, a specific region could be either under intensified control (Stratum I or $API > 5/1000/\text{year}$), pre-elimination (Stratum II or $API = 1-5/1000/\text{year}$), elimination (Stratum III or $API < 1/1000/\text{year}$), or prevention from re-introduction phase (Stratum IV or $API = 0/1000/3 \text{ years}$).¹¹

In a study of possible ecological, geographic, and demographic parameters effective on the status and incidence of malaria in the capital city of Bandar Abbas, Hormozgan province, southern Iran, over a

5-year study period (1998–2002), the epidemiological trend of malaria in relation to the risk factors was investigated. It was found that the number of malaria-positive villages sharply declined to >50% by the end of the study period.¹⁷

The main aims of the present study were to show malaria elimination trend from a hypo-endemic unstable active focus in southern Iran and to explore the role of prevailing climatic factors over a 9-year study period.

Patients and Methods

Study area

The present cross-sectional study was carried out between April 2003 and April 2011 in Roudon county (27°28'N; 57°11'E) with an area of 3044.37 km² on the eastern part of Hormozgan province, southeast Iran. The population of Roudon was nearly 116 226 in 2010. The climate in this subtropical area is warm and humid with minimum and maximum temperatures of about 27.5 and 33°C, respectively (average 30.2°C) in malaria transmission seasons. Relative humidity in this area ranges between 25 and 65% and mean annual rainfall is about 150 mm. The risk of malaria transmission in this area prevails almost all the year round. Roudon is now under elimination phase (Stratum III or API <1/1000/year) since local transmission of malaria occurs actively in this region.¹⁸

Patients

Over the 9-year study period, case definition remained constant. It required parasitological confirmation (thick or thin blood films). Prior to admission, an informed consent was obtained from each adult (aged ≥16 years) patient or the parents/guardians of each child investigated. The sample size involved all parasitological confirmed cases during the above period of time. They were from all public health facilities within Roudon county. Their data were recorded in a few specific forms which were standardized and provided by the health staff in the Iranian capital, Tehran. These data were routinely collected by the local health staff and sent to the provincial and then the central authorities in Tehran. The present data were gathered from these specific forms in Roudon county health centers. All relevant data on status and incidence of malaria including such attributes of malaria patients as active (door to door search by mobile team of health care surveillance staff) and passive (self-motivated patient referral to local health centers, etc.) case detection, age group, indigenous versus imported cases, urban versus rural origin, country of original residence, gender distribution of positive cases, and species of parasites were gathered and then analyzed.

Diagnosis and Plasmodium detection

Finger prick samples of blood were obtained from each consenting patient who presented at one of the participating health centers in the study area. After the preparation of blood smears on clean microscope slides, the required information of patients and the results of microscopically examined blood films were recorded on the relevant forms by experienced technicians. Thick and thin blood films were counted as negative only after examination with an oil immersion lens at ×1000 magnification for at least 100 oil immersion fields by an expert microscopist. An external quality control was carried out under the supervision of the provincial health officers. A dataset of confirmed malaria cases from Roudon county was analyzed following collection through routine passive case detection (in all clinics of the region) during the 9-year study period.

Data analysis

Estimates of annual residential population denominators in Roudon county over the study period came from respective national statistical collections. The data on personal attributes were extracted from the special malaria forms in health facility logs. Data on patient age, gender, place of residence (based on their *Plasmodium*-positive slide prevalence rate or SPR), and climatic attributes (precipitation and temperature) were compared using Student's *t*-tests. Data on climatic factors during the study period were obtained from the meteorological office of Hormozgan province. The spatial resolution of climatic data was one station per county while the temporal resolution was 24 times per day with minima and maxima being recorded once every 12 hours. The percentage annual total precipitation (%ATP) was calculated as annual precipitation times 100 divided by the total 9-year precipitation. The data collected in the first year of the study (2003) and those in the final year (2011) were compared on the basis of SPR using Chi-squared tests in the SPSS Info 16 software. Analyses were conducted on the 9-year data and on the annual trends. A *P* value of ≤0.05 was considered indicative of a statistically significant difference. Graphs were prepared using the Excel software package (Microsoft). The proposal for this study was initially approved for its design and statistical methods by the Shiraz University of Medical Sciences (SUMS), School of Health and Nutrition, Research Centre for Health Sciences, Scientific Board of Reviewers.

Results

Parasitological data

Over the 9-year study period, 398 individuals were confirmed positive by active and passive case detection as malaria patients in the study area of Roudon (Table 1). From March 2003 to the end of 2011,

105 996 blood slides were performed. Although disease abundance based on SPR was more prevalent among men than women, this difference between sexes was statistically insignificant ($P>0.05$). All age groups were, however, infected with *Plasmodium* species to varying degrees throughout each year. Slightly more than half of all the patients were in the higher than 20-year age group. The majority (84.9%) of malaria patients were locally contracted, and mostly (74%) came from the rural areas of Roudon county.

According to Fig. 2, the SPR as well as the percentage of vivax cases (% vivax) showed an overall descending trend over the 9-year period. Despite fluctuations in SPR trend, there was evidence of a slight decline in the last 2 years of the study period. A considerable reduction in total malaria cases from 130 in 2003 to 16 cases in 2011 (87.7% decline) was achieved in Roudon county. The maximal and minimal percentages of annual malaria cases belonged to the first and fifth year of the study period, respectively. Most of the malaria cases (68.34%) were aggregated in the first 3 years of study (2003–2005). In addition, a clear majority of these malaria patients (number 307 or 77.14%), who were identified in the warmer months of the year (May–October), were infected with vivax malaria parasites (Fig. 3). Two peaks of total percentage of malaria cases per year (percentage total number of patients or %TNP) in June and September were evident before the start of rainy season. The average annual parasitic index (API) in the study area was <1 (0.4) throughout this period. The annual blood exam rate (ABER) ranged from 24.4 in 2003 to 4.24 in 2011 with an average of 11.87. It steeply declined in concert with malaria metrics. The percentage rate of falciparum to mixed malaria cases (i.e. *P. falciparum* plus *P. vivax*) increased in the last years of the 9-year period and most of falciparum cases were from urban areas. The rate of falciparum to mixed infections was

highest (1%) in the penultimate year of the study period. The number of locally transmitted cases was 5.6 times higher than imported cases.

Climate data

The %ATP over the 9-year study period generally showed an irregular undulating trend with maxima and minima coinciding with low and high percentages of malaria patients, respectively (Fig. 2). The precipitation curve indicated most peaks of raining in the last 4 months of each year (Fig. 3). This figure showed that malaria occurred during the period of the year with no rainfall. There was a negative relationship between the %ATP and %TNP annually. The mean annual temperature remained almost constant over this study period (Fig. 2).

Discussion

There was an overall reduction in malaria disease cases over a 9-year period in the hypo-endemic unstable active focus of Roudon county, Hormozgan province, southern Iran. Three neighboring countries of Iran (Turkmenistan, Armenia, and United Arab Emirates) have been certified by the WHO Director General as having eliminated malaria.¹⁹ There appear to have been no previous reports on malaria elimination trend and its likely correlated climatic factors in this part of Iran.

The oriental provinces of Iran appear to be on the verge of eliminating malaria in the coming years. There is an urgency to do this. It is a highly focal and locally transmitted disease.¹ Apart from the year of 2005 which unexpectedly showed a surge in relation to the previous year, the number of malaria cases exhibited a dramatic descending trend (80% decline) in Roudon area over the 9-year study period. There was, however, an increase in ABER that year. This ‘surge’ was due to having tested more people in 2005, since there was a peak of precipitation in 2004. Among the main reasons pertaining to increase in malaria disease cases, the peak in %ATP in 2004 and the following extensive establishment of *Anopheles* larval breeding habitats for mosquito vectors transmitting the malaria parasites in the region, optimal temperature, and humidity, and so increasing vector abundance, high rise in the number of malaria cases from neighboring malariogenic areas, and setbacks or suspension of vector control measures could be implicated.

According to the data presented above, the ABER steeply declined in concert with malaria metrics. A logical explanation for the observed decline in malaria cases was that there were simply fewer people being tested at the local clinics. This meant logically that of course there were fewer people being confirmed even if malaria transmission was unchanged. The SPR indicated what fraction of those who were tested were

Table 1 Some of the major attributes reported on malaria patients from Roudon county between 2003 and 2011

Attribute	Category	No. (%)
Sex	Male	234 (58.8)
	Female	164 (41.2)
Age group (years)	≥ 20	204 (51.3)
	<19	121 (30.4)
	<9	73 (18.3)
Residence	Urban	104 (26.1)
	Rural	294 (73.9)
Origin	Indigenous	338 (84.9)
	Imported	60 (15.1)
Detection method	Active	169 (42.5)
	Passive	229 (57.5)
Parasite species	<i>Plasmodium vivax</i>	385 (96.7)
	<i>Plasmodium falciparum</i>	10 (2.5)
	Mixed (vivax and falciparum)	3 (0.8)

Figure 2 Nine-year trends in reported malaria cases of Roudon (Hormozgan province, Iran) from 2003 to 2011, represented as the *Plasmodium*-positive slide prevalence rate (SPR), percentage of vivax malaria cases (% vivax), annual parasitic index (API), annual blood exam rate (ABER), and percentage of falciparum to mixed infections (%F/M). For comparison with the above named parameters, the climatic factors including percentage annual total precipitation (%ATP) in mm and mean annual temperature (MAT) in °C were also depicted.

infected with malaria parasites. That could thus be a better measure of whether malaria prevalence was actually declining. It was possible to have SPR stay constant even if malaria was truly declining if the population being tested was shifting in concert with transmission rates, but this would have required very good data on who was being tested over time. Unless such clarifying data were available, the conclusion would be that there is evidence of a slight decline in the last 2 years of the study period.

The negligible difference in malaria disease abundance based on SPR between sexes (more prevalent among men than women) was similarly reported at the countrywide level.¹⁸ In most studies, including the present one, gender appeared to have little effect on the incidence of malaria.¹⁷ In various districts of the adjacent Sistan-Baluchistan province and in Minab and Bandar-Abbas districts of Hormozgan province, however, some researchers found men to be much more affected than women, respectively.^{20,21}

Figure 3 Annual trends of percentage annual total precipitation (%ATP) in mm and percentage total number of patients (%TNP) who were infected with malaria parasites over the 9-year study period in the county of Roudon, Hormozgan province, Iran.

Although all ages were susceptible to the disease, most of the *Plasmodium*-positive cases were in the higher than 20-year age group reflecting firstly that the disease is endemic in this area and secondly indicating that little if any acquired immunity was present.²² One reason for the latter indicator could be that patients in endemic areas are exposed to multiple species and strains of *Plasmodium*, and so any strain-specific immunity would be intermittent, discrete, and/or inefficient. *P. vivax* presents extensive polymorphism.^{23–26} The fact that parasite strains can functionally down-regulate some immune cell types and up-regulate others means that parasite modulation of the host immune response is critical to the final outcome of infection.²⁷ Another scenario postulates that progressive and repeated exposure to malaria antigens is vital to stimulate an effective immune response, perhaps associated with a maturation of the response with increasing age.²²

The majority of malaria cases belonged to *P. vivax* during 2003–2011, which descended from 128 to 15 cases (88.3% decline). This was partly due to the decline in the number of refugees from Pakistan and Afghanistan and partly due to the strengthening of the health system through improvements in diagnostic and therapeutic services. Despite dramatic declines in the burden of vivax malaria, the data presented here confirmed that the percentage of falciparum to vivax cases increased towards the final years of the study period and most of the falciparum cases were from urban areas which corroborated the studies by others.¹⁷ Using serological tests, it has been shown that antibodies against *P. falciparum* antigen were

more prevalent in the older age group, while such prevalence with *P. vivax* antigen was dispersed in all age groups.²¹

The elimination of *P. vivax* through treatment could be harder than the elimination of *P. falciparum* due to the formation of dormant hypnozoite stages in the liver of vivax malaria patients which could relapse in later months or years.²⁸ These cryptic parasitic stages provide an important reservoir for novel infections since they are subpatent (i.e. below threshold densities detectable by microscopy, $\sim 1 \times 10^8$ parasites)²³ with very low parasitaemia during convalescence, which perfectly evade the conventional measures of malaria control and elimination. In-depth research is thus required to unravel the mysteries surrounding the biology of *P. vivax* hypnozoites.

The malaria disease profile in Roudon has changed in relation to the original domicile of patients over the 9-year study period. The gradual return of Afghan immigrants back to their homeland has been instrumental to the steep decline in malaria disease cases in recent years.^{29,30} This is very important since, following elimination, the loss of herd immunity and the relatively high basic reproductive rate of the *Plasmodium* species implies that outbreaks after an imported infection might expand swiftly over a very short period of time.¹⁵ This situation could be further complicated if simultaneous co-infection with other blood-dwelling pathogens occurred.³¹

The malaria profile in Roudon did not follow the national pattern in relation to the age groups. This disparity could be due to the local transmission of

sporozoites from infectious *Anopheles* mosquitoes. It is essential to note that the age distribution of malaria disease cases and, maybe, its clinical outcome will vary as the total level of parasite transmission descends.¹⁵

The disease trend over the study period has also changed in relation to the place of residence, and most of the malaria disease cases were directed to rural areas with most people as cattle keepers. Up to three quarters of all malaria disease cases were distributed in rural areas of Roudon which reflected that the infection was locally transmitted among residents. It was concluded that malaria disease profile in Roudon has mostly achieved a locally developed event. Despite the dramatic decline in the overall number of malaria cases, the number of locally contracted disease cases (autochthonous cases) has thus increased over the study period.

The challenges, risks, and benefits of malaria elimination have recently been addressed by Professor Feachem and colleagues.^{32,33} Since malaria transmission in the elimination phase is not homogeneous and the reductions in malaria cases spatio-temporally may not be achieved uniformly (i.e. maybe aggregated), the burden of malaria and its transmission could be concentrated in some specific 'hotspots' where, due to local ecology or behavior, effective control measures have been rendered inefficient.³⁴ The implementation of malaria elimination strategies presents new challenges which include the intensive vigilance of health authorities particularly under conditions of chloroquine and DDT resistance, rising rate of imported malaria from adjacent areas and relapse of some cases.³⁵ Health officers who embark on elimination policies should ensure to meet the expected results as excessive optimism could lead to a serious control problem after the failure of possibly disastrous elimination efforts. They must be certain that any elimination activity will not end up in a hard-to-control scenario. Proactive case detection (or screening people for parasitaemia at regular intervals) and treatment in malaria hotspots is essential to tackle elimination.

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