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The prospect of malaria elimination in the Arabian Peninsula: A population genetic approach

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ABSTRACT

Background: In the Arabian Peninsula malaria control is progressing steadily, backed by adequate logistic and political support. As a result, transmission has been interrupted throughout the region, with exception of limited sites in Yemen and Saudi Arabia. Here we examined *Plasmodium falciparum* parasites in these sites to assess if the above success has limited diversity and gene flow.
Methods: We examined 108 *P. falciparum* isolates in three sites in Yemen (Taiz, Dhamar and Hodeidah) and 91 isolates from Saudi Arabia (Jazan). Nine microsatellites were analyzed for allelic diversity, multi-locus haplotype and inter-population differentiation.
Results: Diversity at each locus (unbiased heterozygosity [*H*]) was relatively lower in Yemen; (Hodeidah, $H = 0.615$, Taiz, $H = 0.66$, Dhamar, $H = 0.481$), compared to Saudi Arabia (Jazan, $H = 0.76$). Microsatellites were distributed widely and private alleles, detected in a single population, were rare.

Results: Pairwise comparisons revealed that parasites population in Dhamar was relatively distanced ($F_{ST} = 0.19$). However, Taiz (Yemen) ($F_{ST} = 0.065$) and Hodeidah ($F_{ST} = 0.107$) populations were closer to that in Jazan (Saudi Arabia). Nonetheless, parasites in the four sites can be considered as one population.
Conclusion: Although malaria risk in Saudi Arabia has been cut considerably, the extent of diversity and parasite genetic structure are indicative of a large population size. Elimination strategy should target demographic factors that favor parasite dispersal and flow of imported malaria.

1. Introduction

The Arabian Peninsula lies at the fringes of malaria endemicity, where disease transmission has passed through different phases of retraction as a result of sustained vector control. In Saudi Arabia, the largest country in the region, malaria was a major health problem in the middle of the last century and transmission was common throughout the country. However, systematic control program established in 1957 has resulted in elimination of the disease in the eastern and central regions; however, it remains sporadic in the western region and resilient in the South (Abdel-Hameed, 2003; Snow et al., 2013). Recent scale up of control efforts, lead by the Role Back Malaria Program (WHO), has reduced malaria risk considerably and limited local transmission to the south west region of Jazan (Abdel-Hameed, 2003) (Fig. 1). The success seen in Saudi Arabia and other countries in the region (Snow et al., 2013), has prompted a shift of strategy towards elimination, to achieve a malaria free peninsula, backed by health ministers of the Gulf Cooperation Council (GCC) (Meleigy, 2007). The elimination approach is based on vector control, improved surveillance and active case detection to define existing malaria foci (World Health Organisation, 2012).

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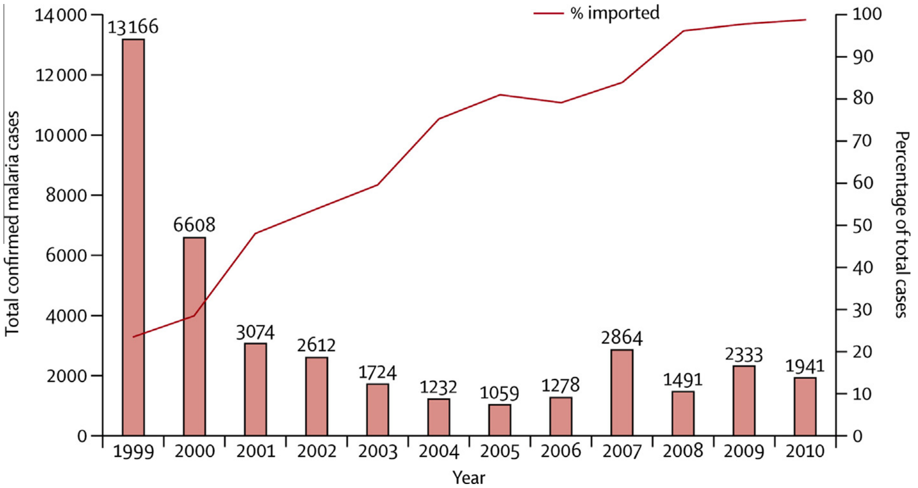

Fig. 1. Indigenous and imported malaria in Saudi Arabia, 1999–2010 (Cotter et al., 2013).

However, imported malaria via asymptomatic travelers from malaria endemic areas, sustains a threat for possible resurgence of local transmission (Ismaeel et al., 2004; Cotter et al., 2013) (Fig. 1). The region attracts numerous numbers of skilled workers from Africa and Asia, where malaria is endemic. In addition, political instability has resulted in mass movement of people from the Horn of Africa (Somalia, Eritrea and Ethiopia) into Yemen and Saudi Arabia (Soucy, 2011). In Saudi Arabia, the proportion of imported malaria has increased from 23% to 99% of total detected cases (Cotter et al., 2013). Recent surveys in Saudi Arabia and Yemen revealed a high prevalence of drug resistance genotypes, and linked the source of some of them to Africa and Asia (Bin Dajem et al., 2012; Al-Farsi et al., 2012; Al-Hamidhi et al., 2013). The introduction of novel lineages into the region can enhance the parasite diversity and effective population size (*Ne*), as there is a direct relationship between the expected level of diversity and *Ne* (Awadalla et al., 2001). Consequently this can augment the ability of the parasite to evolve in the face of current control measures.

Current thoughts on malaria elimination focus on geospatial characteristics of targeted sites to locate and eliminate all infection (Kelly et al., 2013; Smith et al., 2013).Therefore, analysis of parasite diversity and population structure can provide valuable insight and guidance to control programs, by defining spatial structure of parasites in targeted foci, and how control strategies can disrupt the underlying dynamics and evolution of parasites (Chenet et al., 2012; Khaireh et al., 2013). For example, population genetic indices, extent of diversity and gene flow, can provide robust predictive markers to contracting parasite populations during the process of elimination.

The present study examined microsatellites and assessed diversity and population structure of *Plasmodium falciparum*, in Yemen and Saudi Arabia, which represent the relic of malaria in the Arabian Peninsula. In Saudi Arabia considerable reduction in disease morbidity and parasite rate were achieved in the past two decades (Snow et al., 2013). Analysis of microsatellites, which are fast-evolving markers, can reveal genetic variation imposed by recent demographic changes. Such analysis will help in guiding control efforts to epidemiological target that can disrupt the parasite structure, and break the cycle of transmission.

2. Materials and methods

2.1. Study sites

One hundred and eight finger-prick blood samples, from microscopy-confirmed malaria cases, were collected between June 2008 and March 2009, in three localities in Yemen (Dhamar, Hodeidah and Taiz). Dhamar (Latitude: 14°32′33″N, Longitude: 44°24′18″E) is a highland (2407 m above sea) where transmission occurs throughout the year. Hodeidah (Latitude: 14°48′08″N; Longitude: 42°57′04″E) is a coastal area where malaria transmission occurs in winter and Taiz (Latitude: 13°34′44″N, Longitude: 44°01′19″E) is a mountainous area (1311 m above sea) and transmission occurs in summer (Al-Mekhlafi et al., 2011). The risk of malaria in Yemen ranges between 1 and >100 per 1000 individuals, depending on local transmission indices (World Health Organisation, 2011). *P. falciparum* is the main malaria parasite and *Anopheles arabiensis*, *Anopheles sergenti* and *Anopheles culicifacies* are the main mosquito vectors (Snow et al., 2013).

Chloroquine resistance (CQR) is common in the highland and lowland areas in Taiz (Alkadi et al., 2006) and Hodeidah (Al-Shamahy et al., 2007). However, resistance to sulpadoxine–pyrimethamine (SP) is rare in Yemen (Al-Mekhlafi et al., 2011; Mubjer et al., 2011). Currently SP is used in combination with artesunate (AS) as first-line treatment of uncomplicated falciparum malaria. In addition, artemether–lumefantrine (AL) is used as a second-line therapy for treatment failure (World Health Organisation, 2012).

In Saudi Arabia, 91 samples were collected from microscopically confirmed *P. falciparum* infection from 11 hospitals and health clinics belonging to 9 different sites in Jazan, in 2008 (Bin Dajem et al., 2012). Jazan region, southwest Saudi Arabia is an area with multiple active transmission sites. The main mosquito vectors are *A. arabiensis* and *A. sergenti* (World Health Organisation, 2011; Khater et al., 2013). Nearly 96% of the cases are caused by *P. falciparum* (Snow et al., 2013). However, the risk of malaria is limited approx. 1 per 1000 individuals (World Health Organisation, 2011). Malaria transmission occurs during the rainy season between November and March. *P. falciparum* was considered as chloroquine-susceptible. However, early signs of chloroquine resistance emerged in the late 1990s and the prevalence of mutations associated with CQR escalated in the region (Bin Dajem et al., 2012). This prompted a change of treatment policy to artemisinin-based combination therapies (ACTs) (Lynch et al., 2008).

Ethical clearance was obtained from Faculty of Medicine, Sana'a University, Yemen, and Ethics Committee at King Khalid University, Abha, Saudi Arabia. Informed consent was obtained from each participant before enrolment in the study.

2.2. Microsatellites

Microsatellites are useful genetic markers that allow detecting genetic structures at recent divergence times (Anderson et al.,