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Distribution and Determinants of Malaria, Kingdom of Saudi Arabia, 2002 – 2011

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2015

## Abstract

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By Mai Jamdar

**Background:** Malaria is a leading cause of illness and death. Each year, 300 to 500 million cases of malaria are reported worldwide. Malaria occurs mostly in poor tropical and subtropical areas of the world. KSA is a non-endemic country, though the southwestern area is at high risk of imported malaria, with the greatest number of cases reported from Jizan and Asir regions. The aims of this study were to investigate the incidence rates (IRs) of reported cases of malaria from 2002 – 2011 stratified by administrative region and age, *Plasmodium* species, and mode of transmission in KSA; make recommendations for further investigation; and offer options for policy change.

**Methods:** We estimated the IRs and 95% confidence Intervals (CIs) using the number of cases per year over the total population per 100,000 individuals in the 13 KSA administrative regions from 2002 – 2011. We further investigated the proportion of malaria cases by age category, species (*Falciparum*, *Vivax*, *Quartan*, and *Oval*) and modes of transmission that included local, imported local (reported in one area of KSA but originally transmitted in another area of KSA), outside (imported from abroad), unclassified malaria parasite species, and illness by relapse or acquired by blood transfusion.

**Results:** The greatest IRs occurred in 2002 (12.1, 95%CI = 11.6 - 12.6) and 2007 (11.8, 95%CI = 11.4 - 12.2). We observed the greatest IR in Jazan out of all the regions. Tabuk, Jawf, and Eastern Region had consistently lower IRs than other regions. The proportion of infected persons was consistently much greater/higher for individuals > 15 years of age than those younger. In 2012, the proportion of malaria cases due to *P. falciparum* was much lower than that due to *P. vivax*. In addition, the results showed that a large proportion of malaria cases were imported.

**Conclusion:** The Kingdom is not endemic for malaria. The major source of reported malaria were imported cases from outside the Kingdom. Reports of local cases are very few currently, which reveals that control measures put in place have been effective in controlling the disease. However, testing is recommended for visitors who wish to travel to the KSA and pilgrims who wish to go there for religious purposes. It is also recommended that immigration into the country be regulated and that screenings occur before entry is allowed.

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## **Chapter 1 - Introduction**

### **Global Snapshot of Malaria**

Each year, 300 to 500 million cases of malaria are reported worldwide. Malaria occurs mostly in poor tropical and subtropical areas of the world. In many countries affected by the malaria pandemic, it is the leading cause of illness and death. Malaria imposes high costs to both individuals and governments and is considered a substantial public health threat in many areas.

In developed countries, travellers visiting friends and relatives (VFRs) constitute the most significant source of malaria importation due to their behavioral patterns. For behavioral and geographic reasons, they are at high risk for infection. It is known that partial immunity to malaria among VFRs who live outside malaria-endemic areas wanes with time; after 12 years away, they can find themselves with a more serious clinical presentation of malaria (1).

## **Places with the Highest Burden of Malaria**

In 2012, an estimated 627,000 people died of malaria—most were young children in sub-Saharan Africa (2). In 2007, 2,117 cases were reported in the Kingdom of Saudi Arabia (KSA), increasing to 2,696 in 20 (3). In other countries and regions, malaria is a less prominent cause of death, though it can cause substantial disease and have a negative economic impact, especially in the rural areas of South America and South Asia.

Yemen is an area with a high local rate of malaria transmission. In 2004, malaria caused 4.9 deaths per 100,000 and 43,000 disability-adjusted life-years lost. Up to 69% of the population live in areas of high transmission ( $\geq 1$  case/1000), with 99% of the confirmed infections attributed to *P. falciparum* and up to 20% of pediatric admissions (3).

## **Cost of Malaria**

The costs of malaria are a burden on individuals, families, communities, and governments. For individuals and families, costs include the purchase of drugs for treating malaria at home, expenses for travel to and treatment at dispensaries and clinics, lost days of work, absence from school and work, expenses for preventive measures, and expenses for burial in case of death. On the government side, costs include maintenance, supply and staffing of health facilities, the purchase of drugs and supplies, public health interventions against malaria (e.g., insecticide spraying or distribution of insecticide-treated bed nets), lost days of work with resulting loss of



income, and lost opportunities for joint economic ventures and tourism.

The global, direct costs of malaria—illness, treatment, and premature death—have been estimated to be at least US\$12 billion per year. Currently, KSA is classified as being in the pre-elimination/elimination phase of endemic malaria, despite the continued presence of the vectors *Anopheles stephensi*, *Anopheles fluviatilis*, *Anopheles serenity*, and *Anopheles superpictus*.

Every year, millions of pilgrims visit the holy cities of Mecca and Medina. In addition, KSA has a large population of immigrant workers. In both cases, many of these pilgrims and immigrant workers come from malaria-endemic countries such as Pakistan. Thus, imported cases of malaria represent a continuous public health threat to the KSA. This is attributable to international travel and a large expatriate population from malaria-endemic regions (3).

As can be seen, continued vigilance is needed. Few studies exist concerning the prevalence of malaria in KSA. This study seeks to fill that gap by describing the trends of malaria in KSA from 2002 to 2012. The study examined the incidence rates of reported cases of malaria from 2002 – 2011 stratified by administrative region and age.

## Chapter 2 - Literature Review

### Introduction

Malaria is caused by a parasite *Plasmodium* transmitted through the bite of infected mosquitoes. As the parasite enters the human body, it multiplies in the liver and infects red blood cells. People who get malaria become sick with a flu-like illness, high fever, shaking, and chills. Four kinds of malaria parasites have long been known to infect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. They can be transmitted through blood transfusion, organ transplant, or shared needles or syringes contaminated with blood. Malaria is a life threatening condition if not treated, as it disrupts the blood supply to vital organs.

### Global Epidemiology

Malaria is a major international public health threat, causing an estimated 215 million infections worldwide with 655,000 deaths annually. Over the 20th century, *Plasmodium falciparum* – one of the four species of *Plasmodium* that causes malaria in human beings – rapidly expanded in Africa and spread worldwide (Figure 1).



Figure 1 Malaria-endemic Countries in the Eastern Hemisphere, Centers for Disease Control and Prevention. CDC Health Information for International Travel 2014. New York: Oxford University Press; 2014.

WHO stratified the population-at-risk-of-exposure by region to capture the endemicity of malaria between 1900 – 2002. The European region is the only group of countries to have shown a consistent decrease in populations-at-risk over this period. The American region (AMRO) remained approximately stable in terms of populations-at-risk. The African Regional Office (AFRO) area had a major increase of population-at-risk. The South East Asia Regional Office (SEARO) area (specifically India) also had a major increase. The Western Pacific region (WPRO) is not considered as a population-at-risk due to the marked reduction in the limits of transmission in China beginning in 1975. Increases in areas like the SEARO region have drawn greater international attention to risk exposure (4).

From January 1994 to June 2005, Al Tawfiq found 56 patients with imported malaria seen at Saudi Aramco Medical Services Organization: 28 males and 28 females with a mean age of 28.2 +/- 19.7 years. Saudis constituted 25% of the patients and the remaining 75% were non-Saudi. Most acquired the disease outside KSA; 21% acquired it in the Kingdom. The most frequently reported species were *Plasmodium vivax*, *Plasmodium falciparum*, and *Plasmodium malariae*. Of the cases acquired within other regions in KSA, 71.4% were secondary to *P. falciparum*. In terms of malaria acquisition in India, *P. falciparum* constitutes 71.4% and 91% in Pakistan. For Sudanese patients, *P. falciparum* constitutes 47% and *P. vivax* 53%. Most of the non-Saudi cases were

seen in the month of September, whereas 57% of the Saudi cases were seen in February and April (5).

Malaria cases and deaths grew rapidly from 1990 to 2010, reaching a peak of 232 million cases in 2003. Since 2004, child deaths from malaria in sub-Saharan Africa have decreased by 31.5%. Outside of Africa, malaria mortality has steadily decreased since 1990 (6).

It is essential to know the parasite responsible for malaria to control its endemicity. A 2007 study focused on generating a new map in Africa, America and Central and South East Asia (CSE Asia) for *Plasmodium falciparum* malaria endemicity. A total of 8,938 *P. falciparum* parasite rate surveys were identified using a variety of search strategies. Of these, 7,953 passed strict data fidelity tests for inclusion into a global database of falciparum parasite rate (PfPR) data, age-standardized to 2-10 years for endemicity mapping. A model-based geostatistical procedure was used to create a continuous surface of malaria endemicity within previously defined stable spatial limits of *P. falciparum* transmission. These procedures were implemented within a Bayesian statistical framework so that the uncertainty of these predictions could be evaluated robustly. The uncertainty was expressed as the probability of predicting correctly one of three endemicity classes previously stratified to be an informative guide for malaria control. Population at risk estimates, adjusted for the transmission-modifying effects of urbanization in Africa, were then derived with reference to human population surfaces in 2007. Of the 1.38 billion people at risk of stable *P. falciparum* malaria, 0.69 billion were found in Central and South East Asia, 0.66 billion in Africa, Yemen, and KSA and 0.04

billion in the Americas (4).

In 2009, 6,049 confirmed cases of malaria were reported by 27 European countries, compared to 5,912 in 2008. About 80% of these cases were reported by France, the United Kingdom, Italy, and Germany. The prevalence of confirmed malaria cases was higher among males and in people aged 25–44 years, which likely reflects population travel patterns rather than other risk factors. The number of imported malaria cases in Europe is higher during the summer holiday months (June–October) and peaks in September, with a lower incidence in January, possibly related to the winter holiday period (1). After 2009, an increase of imported malaria was noted in European and Mediterranean countries. This was associated with an increasing number of international travelers and an influx of immigrants from malaria-endemic countries. The presence of returned infected travellers as a source of the parasite as well as climate changes in Mediterranean countries may be factors in the reappearance of malaria in countries where it was previously eradicated. However, between 2001 and 2010, 45 countries in the European Region reported a decrease in imported cases, possibly due to under-reporting or the control of malarial activity, whereas in the Mediterranean region, malaria remains significant public health issue given the large number of imported cases (1).

The WHO estimates that in 2010, there were 219 million clinical cases of malaria with 660,000 deaths, mostly children in Africa.

### **Regional Epidemiology**

In terms of the Arabian Peninsula, malaria epidemics have occurred across

populated areas of most of the present day territories of KSA, specifically in the lowlands of Asir region, the southwestern province (7). Malaria outbreaks also occurred in Kuwait, Qatar, United Arab Emirates (UAE), Bahrain, Oman, and Yemen at the turn of the last century, where the extent of transmission was limited only by the availability of breeding sites for dominant vectors and the presence of human hosts (8).

Imported malaria, an infection acquired in an endemic area but diagnosed in a non-endemic country, is considered a public health threat that requires continuous monitoring (1). Malaria can be imported into a country via human hosts. When those who have malaria arrive in the destination countries, they can spread the disease to fellow travelers or residents who come into close contact with them by blood transfusion or sharing syringes. Cases of imported malaria have been diagnosed in many countries. For example, in Yemen hospitals, more than 80 cases were identified in less than a month. Some cases of imported and acquired infections were also discovered in Cairo and treated successfully. Deaths have resulted mainly from delayed diagnosis.

The most effective medicine for treating malaria is chloroquine. Patients that are diagnosed with imported and acquired malaria often test positive for either *P. falciparum* or *P. vivax*. Other medicines that have shown some success in the treatment of malaria are quinine, intramuscular artemether, and fansidar. Mild cases are treated by Quartem (9).

### **KSA Epidemiology**

KSA suffered its worst malaria epidemic in 1998. A total of 36,139 locally transmitted cases were recorded, with an incidence rate reaching 44/1,000 in malaria-

endemic regions in southern KSA. As a result, efforts were scaled up to control malaria (10). Figure 2 shows a map of the changes in incidence of autochthonous cases, the total number of cases, and the percentage of imported cases. Imported malaria cases have grown in proportion over the years to comprise an alarming 50% of the cases reported.

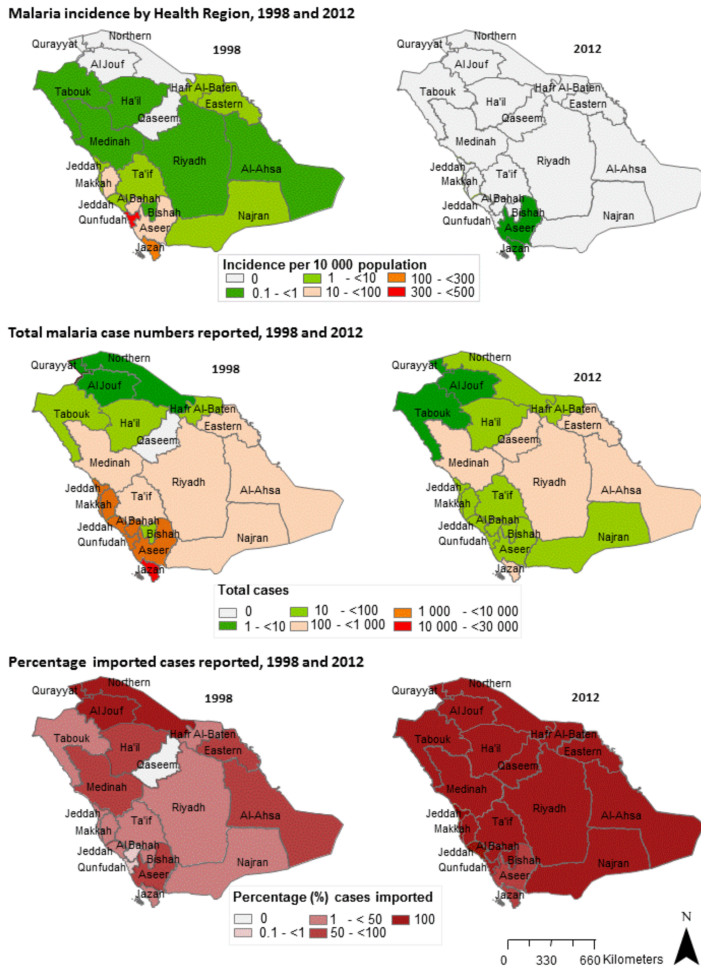


Figure 2 The Changes in Incidence Rate of Autochthonous Malaria Cases, Number of Reported Cases of Malaria and Percentage of Imported Malaria Cases, Kingdom of Saudi Arabia

In terms of geographic distribution, Coleman reports that the risk of imported malaria in KSA, a country known to be non-endemic, is limited to the southwestern part of the country, with the greatest number of cases reported from Jizan and Asir regions (11). Over 180 sites were sampled to detect malaria-carrying mosquitos between June 1999 and April 2001. A total of 7,085 larval and 754 adult female *Anopheles spp.* specimens were collected and seven species were identified in Asir region (12).

Hajj visitors have not been diagnosed with malaria over the years, meaning they pose little threat (13). The Eastern Province has been free of locally-transmitted malaria cases since 1978 (14). Al-Tawfiq, in a retrospective study of the epidemiology of malaria in the Eastern Province, reported 56 cases of imported malaria from January 1994 to June 2005 (15). All cases were acquired outside of KSA and the most frequent species diagnosed were *P. vivax*, *P. falciparum* and *P. malariae* (1). In 2011, only 29 locally transmitted cases were reported in the country according to a report by the Saudi MoH, making the incidence <0.01 per 1,000, well below the WHO target rate of 5 per 1,000 when a country should be considered at risk. In 2012, 82 autochthonous cases were reported out of a total of 3,406 positive cases of malaria (11, 14).

### **Case Definition**

WHO has a recommend case definition for malaria, but it cannot be uniform because countries experience the disease differently. Other reasons for the non-uniformity of the case definition are variations in the local patterns of transmission and varied disease consequences. Suggested definitions are many and are based on clinical description, laboratory criteria for diagnosis, case classification for areas with or



without access to laboratory-based diagnosis, and surveillance data including routine monthly reporting of aggregated data of uncomplicated malaria and severe malaria, suspected and confirmed malaria deaths, and treatment failures.

WHO has a database for recording and analyzing case data that is useful for monitoring malaria trends. The database has information about age groups, gender, and their pregnancy status. It also includes other case detail, like uncomplicated malaria, severe malaria, referral, suspected death, presumptive malaria treatment failure, nature of the treatment taken, and the type of parasite.

Some health agencies have made an attempt to establish a surveillance system similar to WHO's. One example is the CDC's National Malaria Surveillance System (NMSS), which has a malaria case surveillance report with different sections such as demographics, clinical and laboratory information, travel information, and management methods including treatment and after treatment follow up (16).

KSA has integrated the WHO recommendations by creating a case report in Arabic that is uniform throughout the Kingdom. However, data analysis needs to be undertaken regularly to discover trends and patterns. With the changing rates of malaria, constant updates are necessary.

### **Malaria Surveillance in KSA**

Malaria is a notifiable disease in KSA, and diagnosis is predominantly based on microscopy. Most malaria cases are identified through passive case detection at health

facilities. Age distribution, seasonality, and spatial clustering should be included in malaria surveillance.

An active case surveillance of three cohorts of 6,750 individuals, where clinical tests and asymptomatic diagnoses were done on each cohort, identified 5,300 asymptomatic malaria cases. The existence of asymptomatic disease is not limited to KSA. Three similar studies carried out in the western Kenyan highlands in 2009 and 2010 revealed an increase in asymptomatic parasite prevalence from low to high transmission seasons. This asymptomatic increase was significantly greater for infants (<2 years) and adults ( $\geq 15$  years) (500% increase) than for children 2-14 years old (65% increase). The increase in incidence rates was significantly greater for children (700%) than that for adults (300%) (15).

New transmission hotspots were identified during the peak season through active surveillance, and this is an important observation with clear implications in the context of malaria elimination. Both mass parasite screening and active surveillance are essential for malaria transmission monitoring and control (15).

Using passive surveillance, KSA health centers and dispensaries are legally required to report suspected cases and blood film results to the MoH. Using active surveillance, home visits are made to every locality in a defined area at regular intervals (usually monthly during the transmission season) to inquire about febrile illness and test suspected persons for malaria (and treat if positive) (15). Since 1991, the protocol has been that all cases are reported within 24 hours to the local KSA malaria centers using a standard form that triggers a follow-up analysis to determine the probable source of

infection. Based on the concept that malaria cases tend to be clustered, case detection concentrates on other members of the affected household and neighbors (17).

KSA now faces the challenge of malaria elimination, and to this end, health officials need to implement strategies to enhance surveillance. An elimination campaign was started in collaboration with Arabisation of the Malaria Decision Support System Organization. Originally developed in collaboration with malaria programs in southern Africa, it includes tools that cover surveillance, intervention planning and monitoring, and entomological monitoring and survey development. It also incorporates the ability to generate maps and standard reports at the 'click of a button' (11). This can serve as an example for the KSA.

### **Risk Factors for Imported Malaria**

There are three major sources of imported malaria in KSA. First, KSA shares a southern border with a malaria endemic country, the Republic of Yemen, which is the major source of imported malaria cases. Second, KSA is home to the most important Islamic holy sites, which are visited by many millions of pilgrims from every country worldwide. Lastly, there exists a large expatriate work force in KSA, many originating from malaria endemic countries in the Middle East, Africa, and Asia (17).

### **Border with Yemen**

Imported malaria is a significant concern in many countries; for KSA, Yemen poses a public health threat. A clinical pilot study in Egypt, KSA, and Yemen revealed 16 imported malaria cases from Yemen in the Almaza Military Fever Hospital, Cairo, 53

imported malaria cases in the Saudi Hospital and also in Saber Hospital at Aden, Yemen. One imported case (6.3%) died by cerebral malaria due to delayed diagnosis in Yemen. Five imported cases (31.3%) had severe malaria. Four had severe malaria and one patient (5%) died by cerebral malaria in Aden (9). The study showed that malaria prevalence in KSA could rise quickly if no measures were put in place to stop the importation of malaria.

Malaria drug resistance is another issue in Yemen, which is a burden on the country itself and its neighbors. One study examined the genetic diversity of *Plasmodium falciparum* in Yemen and mutations of drug resistant genes to elucidate parasite structure and distribution of drug resistance genotypes in the region. This study found that a high diversity of *P. falciparum* in Yemen is indicative of a large parasite reservoir, which represents a challenge to control efforts (18).

Though malaria rates in KSA have dropped considerably, certain areas in the south, like Jazan, are at risk equal to those in Taiz and Hodeidah in Yemen. Because of the extent of the diversity of parasitic genes and genetic structure, the elimination strategy should target demographic factors that favor parasite dispersal and sources of imported malaria in places such as Yemen (19).

### **Hajj and Malaria**

The association between Hajj and the spread of malaria is less concerning. Hajj is the annual pilgrimage to Makkah and Medina; each year, over two million Muslims from around the world gather. It is the largest mass gathering in the world. Though the risk of infectious disease transmission is heightened, malaria is not spread from person

to person like a cold or the flu. Human-to-human transmission occurs when someone receives infected blood through a transfusion, organ transplant, or the shared use of contaminated needles or syringes. It also can be transmitted from a mother to her unborn infant before or during delivery (congenital malaria) (2).

One of the ritual practices of Hajj is shaving. Muslim men are required to shave their heads, and unclean blades can transmit bloodborne pathogens such as hepatitis B and C, malaria, and HIV. A study was conducted at Ajjad Hospital in Makkah during peak Hajj season (February to March of 2000) by Shah et al. to investigate the distribution of malarial parasites in Hajj pilgrims. In this study, random patients were selected and tested for malaria. The results showed a total of 19.2% positive identification of malarial parasite: 76% of patients were suffering from *Plasmodium falciparum* infections, while 24% had *Plasmodium vivax* infections. Of patients from Sudan and KSA, 50% had *P. vivax* malaria while those from the rest of the countries had only *P. falciparum* infections (20).

Malaria is not currently a high-priority issue during Hajj, according to the MoH, as there is no background of malaria prevalence during Hajj in Makkah region (21). The MoH has regulations and requirements for the Hajj and Umrah seasons that concern special risk groups: elderly people, those suffering from chronic diseases (heart diseases, kidney disease, respiratory diseases, nervous system disorders and diabetes) immunodeficient patients (congenital and acquired), pregnant women and children. Regulations require that pilgrims receive vaccinations for meningococcal meningitis ACW135, Wild Polio Virus (WPV), Yellow fever, Ebola Virus Disease (EVD) and routine

immunizations (22). However, malaria is not mentioned in these regulations, either because the incidence rates are negligible or the regulations were not properly formulated and enacted.

Both pilgrimage cities are located in Makkah region. A study of malaria incidence in that region supports the idea that malaria is not a major problem related to Hajj. A total of 318,000 malaria cases were analyzed to examine malaria patient nationality, and parasite type in Makkah region between 2008 and 2011. By age, 3.6% of cases were under 10 years of age, including two cases below 5 years. Non-Saudis comprised 95% of cases, with Pakistanis, Nigerians, and Indians accounting for 62%. *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium ovale* were the notable parasites (23). According to Memish, et al., the low frequency of malaria in Makkah suggests that KSA is in the consolidation phase of malaria eradication. The absence of local transmission is indicated by low frequency of malaria in children < 5 years of age, and the high frequency of malaria in non-Saudis is evidence of malaria importation. Health workers treating foreigners with febrile illness from Pakistan, Nigeria, and India should consider malaria a likely diagnosis (23).

### **Foreign Workers and Malaria**

A 2003 study was done to determine epidemiologic characteristics of imported malaria infections in Riyadh based on a retrospective analysis of laboratory records from the Central Laboratory (ref). The study concluded that there was no active malaria transmission in Riyadh; however, imported infections are still a significant health problem. A high index of suspicion should be maintained for those with a suggestive

travel history (24). This study suggests that tourists and job seekers are the source of imported malaria cases.

Another retrospective analysis supports this idea. It was conducted to investigate the epidemiology of imported malaria in the city of Buraidah in Qassim region from January 2010 to April 2013 and found that malaria occurred among expatriates, particularly those from the Indian subcontinent. The predominant species was *P. vivax*, and more than 50% of the cases presented with severe malaria (25).

### **Best Practices for Prevention**

Epidemics in the 1990s spurred the development of a national malaria control program and reinvigorated control efforts. Before the launch of the recent global goal of malaria eradication, countries on the Arabian Peninsula (Yemen, Oman, Qatar, Bahrain, Kuwait, Saudi Arabia and the United Arab Emirates as well as parts of southern Iraq and Jordan) kicked off a collaborative malaria-free initiative in 2005. This initiative was successful in reducing the malaria burden there, and today locally acquired clinical cases of malaria are reported only in KSA and Yemen. Yemen contributed to > 98% of the clinical burden (8).

According to WHO, malaria transmission can be reduced by directing efforts toward both the community and individuals. At the community level, prevention requires the reduction of malaria transmissions. At the individual level, it includes personal protection against mosquito bites, which represents the first line of defense for malaria prevention (21). A WHO Policy Advisory Committee conducts a yearly meeting on malaria control and prevention. The 2014 meeting covered areas such as maintaining

universal coverage of long-lasting insecticidal nets; combining indoor residual spraying with long-lasting insecticidal nets; the sound management of old long-lasting insecticidal nets; malaria diagnosis in low transmission settings; updates on vector control, the RTSS vaccine, the Malaria Treatment Guidelines, anti-malarial drug resistance and containment, and surveillance, monitoring and evaluation (21).

The WHO's key interventions to control and prevent malaria include prompt and effective treatment with artemisinin-based combination therapies, use of insecticidal nets by people at risk, and indoor residual spraying with insecticide to control the vector mosquitoes. Another method is antimalarial medicine for travellers (21).

Long-lasting insecticidal nets (LLINs) are the preferred form of Insecticide-Treated Nets (ITNs) for public health distribution programs. WHO recommends coverage for all at-risk persons in most settings. The most cost effective way to achieve this is through provision of free LLINs so that everyone sleeps under one every night (21).

### **Indoor Spraying**

Indoor residual spraying (IRS) with insecticides is a way of rapidly reducing malaria transmission. It is only possible to realize the full potential of this method when at least 80% of houses in targeted areas are sprayed. Indoor spraying is effective for 3–6 months, depending on the insecticide used and the type of surface on which it is sprayed.

DDT can work effectively for 9–12 months in some cases. Longer-lasting forms of existing IRS insecticides, as well as new classes of insecticides for use in IRS



programs, are under development (21).

WHO recommends intermittent preventive treatment with sulfadoxine-pyrimethamine for pregnant women living in high transmission areas at each scheduled antenatal visit after the first trimester. Similarly, for infants living in high-transmission areas of Africa, three doses of intermittent preventive treatment with sulfadoxine-pyrimethamine is recommended, delivered alongside routine vaccinations (21).

### **Malaria Prevention in KSA**

Early in the 1940s, several attempts were made to eliminate malaria on the peninsula, with varying degrees of success. Although malaria was not completely eradicated, these efforts did have the effect of shrinking the margins of malaria transmission across the peninsula.

The continued existence of imported malaria cases, which are a possible reservoir of infection, together with the occurrence of vector competent Anopheles species and changes in climatic conditions may induce the onset of autochthonous malaria cases in countries where malaria was previously eradicated. Surveillance, clinical management, laboratory diagnosis, entomological surveillance, vector control, and communication are necessary to prevent transmission and control the disease in the long term.

The recurrent presence of malaria necessitates more education efforts geared to travellers. Services for immigrants and travellers should be more readily available. Information about the distribution and seasonality of malaria should be discussed before travelers leave, and compliance with adequate chemoprophylaxis and adoption of

personal preventive measures should be improved. Vector control measures around the perimeter of airport should be implemented (1).

The initial steep decline in 1998, malaria cases occurred at the same time as the rapid increase of vector control measures. The malaria incidence rate (IR) in KSA continued to be low (from 0.01 - 0.1 per 1,000 population) until the adoption of artesunate plus sulfadoxine-pyrimethamine as the first-line treatment and the establishment of a regional partnership for a malaria-free Arabian Peninsula, both of which occurred in 2007 which decrease the incidence markedly. However, a high proportion of imported cases, the continued potential for autochthonous transmission, and an increased proportion of cases attributable to *Plasmodium vivax* are all considered risk factors that threaten the Kingdom.

*P. vivax* is very drug resistant and causes serious illnesses that in most cases are fatal. In response, KSA has implemented strategies for the eradication of malaria imported via travelers or foreign workers (26).

There were just 82 autochthonous cases in 2012, a 99.8% reduction from 1998. This was a result of the adoption in 2007 of artesunate plus sulfadoxine-pyrimethamine as a first line treatment and the establishment of a regional partnership for a malaria-free Arabian Peninsula (26).

The strategies of the Saudi MoH are consistent with WHO recommendations. They include focal spraying (combating larvae in breeding sites in places where transmission is likely), spraying houses with a long-lasting insecticide, especially in places where malaria is likely to prevail, using mechanical techniques for combating

malaria at the breeding sites of mosquitoes, distributing mosquito nets sprayed with the insecticide to vulnerable people, and encouraging health awareness programs (14).

Currently, KSA mainly focuses on the above mentioned techniques together with management of infection through rapid confirmed diagnosis and treatment, individual case follow up and reactive surveillance with appropriate treatment and vector control, and active case detection at borders with screening and treatment (17).

### **Challenges of Malaria Elimination**

There are several challenges related to malaria surveillance, monitoring, and evaluation in KSA. First, there has been a decline in the sensitivity of malaria case detection, and it has been impossible to monitor the efficacy of anti-malarial drugs using WHO standard procedures (27). Imported malaria cases are mainly from immigrant workers from the Indian subcontinent and the eastern part of Africa. As a result, most parasites have been exposed to antimalarial drugs prior to entry into the country. Therefore, there must be more knowledge about the pattern of resistance to these drugs outside of the country, which will result in better management of the disease (28).

Furthermore, random screening of *Plasmodium falciparum* strains indicated that chloroquine (CQ) resistance *in vitro* became increasingly common in the Jazan region of southwestern KSA between 1986 and 1998 ( $\chi^2$  for trend = 50.027;  $p < 0.001$ ). This worrisome trend and the emergence of a micro-epidemic in 1997 and 1998 prompted an assessment of the therapeutic efficacy of CQ against uncomplicated *P. falciparum* malaria in the area. The in-vivo testing of sensitivity to CQ was carried out in 291 clinically manifest, microscopically positive cases of *P. falciparum* malaria. Most of

these patients (88%) were successfully treated with a single standard regimen of CQ therapy. The other 36 patients (12%) showed early treatment failure or a poor response to the CQ, although all of these were then successfully treated with a single standard dose of sulfadoxine-pyrimethamine (Fansidar) as a replacement therapy. Those unsuccessfully treated with CQ were generally younger ( $t = 2.625$ ;  $P = 0.01$ ) and tended to have higher body temperatures ( $t = -2.62$ ;  $P = 0.012$ ) and higher levels of parasitaemia at initial presentation ( $p > 0.000$ ) than those who responded well to the drug. However, CQ will be kept as the first-line drug for the foreseeable future and failure of CQ efficacy must be carefully monitored in the area (29).

A second challenge in terms of the elimination effort is the unstable security situation in the border areas with Yemen. Yemen currently is suffering from the struggle between many competing groups divided along regional, tribal, and sectarian lines. In addition, KSA and Iran are competing for influence in Yemen, with Tehran supporting the Houthis, based in northern Yemen, and Riyadh supporting the Hadi government. The Saudis back the Hadi government against the Houthis, which Riyadh sees as Iranian proxies. In 2009, the Saudis conducted air strikes against the Houthis and then designated them a terrorist organization in 2014. The unstable political and security situation between the countries has affected the elimination of malaria as well as the surveillance system for monitoring and evaluation (30). Turmoil in the border area has led to the freezing of vector control operations and surveillance, especially the mobile teams (27).

Third, many of the expatriate health workers at malaria stations have been

replaced with less experienced graduates from KSA, and this turnover has been a challenge to malaria control efforts. The MoH began to replace foreigner workers with Saudi nationals as part of a government policy to reduce the dependency on foreign workers and decrease the Saudi unemployment rate. Around 20% of the Saudi public health sector's workforce is comprised of Saudis. The dependence on foreign doctors and nurses is even higher in the private health care sector. However, due to limited space in the field and budget, the MoH has replaced experts with new graduates without allotting sufficient time for training. This affects the consistency of many programs including the elimination and surveillance of reportable disease such as malaria.

Finally, there is a lack of reporting by the private sector. Not all private sector facilities follow the policies and procedures of reporting infectious diseases; this is an additional challenge to the malaria elimination program in KSA.

## Chapter 3 – Manuscript

**Background:** Malaria is a leading cause of illness and death. Each year, 300 to 500 million cases of malaria are reported worldwide. Malaria occurs mostly in poor tropical and subtropical areas of the world. KSA is a non-endemic country, though the southwestern area is at high risk of imported malaria, with the greatest number of cases reported from Jizan and Asir regions. The aims of this study were to investigate the incidence rates (IRs) of reported cases of malaria from 2002 – 2011 stratified by administrative region and age, *Plasmodium* species, and mode of transmission in KSA; make recommendations for further investigation; and offer options for policy change.

**Methods:** We estimated the IRs and 95% confidence Intervals (CIs) using the number of cases per year over the total population per 100,000 individuals in the 13 KSA administrative regions from 2002 – 2011. We further investigated the proportion of malaria cases by age category, species (*Falciparum*, *Vivax*, *Quartan*, and *Oval*) and modes of transmission that included local, imported local (reported in one area of KSA but originally transmitted in another area of KSA), outside (imported from abroad), unclassified malaria parasite species, and illness by relapse or acquired by blood transfusion.

**Results:** The greatest IRs occurred in 2002 (12.1, 95%CI = 11.6 - 12.6) and 2007 (11.8, 95%CI = 11.4 - 12.2). We observed the greatest IR in Jazan out of all the regions. Tabuk, Jawf, and Eastern Region had consistently lower IRs than other regions. The proportion of infected persons was consistently much greater for individuals > 15 years of age than those younger. In 2012, the proportion of malaria cases due to *P. falciparum* was much lower than that due to *P. vivax*. In addition, the results showed that a large proportion of malaria cases were imported.

**Conclusion:** The Kingdom is not endemic for malaria. The major source of reported malaria were imported cases from outside the Kingdom. Reports of local cases are very few currently, which reveals that control measures put in place have been effective in controlling the disease. However, testing is recommended for visitors who wish to travel to the KSA and pilgrims who wish to go there for religious purposes. It is also recommended that immigration into the country be regulated and that screenings occur before entry is allowed.

### Introduction

Each year, 300 to 500 million cases of malaria are reported worldwide. Malaria occurs mostly in poor tropical and subtropical areas of the world. In many countries affected by the malaria pandemic, it is the leading cause of illness and death. Malaria imposes high costs to both individuals and governments and is considered a substantial public health threat in many areas. KSA suffered its worst malaria epidemic in 1998. A total of 36,139 locally transmitted cases were recorded, with an incidence rate (IR) reaching 44/1,000 in malaria-endemic regions in southern KSA. As a result, efforts were

scaled up to control malaria (10). However, imported malaria cases have grown in proportion over the years to comprise an alarming 50% of the cases reported. The major risk factors that contribute to malaria are related to sharing a border with Yemen, which is an endemic country, and the influx of Hajj pilgrims and foreigner workers.

## Methods

This is a 10-year retrospective study (2002 – 2011) that investigates the incidence rates (IRs) of malaria using data reported to the KSA MoH. We estimated the IRs for the total population and the 13 KSA administrative regions of KSA. We further investigated the proportion of malaria cases by age category, species of malaria (*Falciparum*, *Vivax*, *Quartan*, and *Oval*), and modes of transmission that included local, imported local (reported in one area of KSA but originally transmitted in another area of KSA), outside (imported from abroad), unclassified malaria parasite species, and illness by relapse or acquired by blood transfusion.

We used Microsoft Excel 2011 (Microsoft, Seattle, WA) to perform statistical analyses. The IRB of the Saudi MoH and Emory University determined this study to be exempt from human subjects review.

## Results

The malaria IR for the total population per 100,000 population from 2002 – 2011 was greatest in 2002 (12.1, 95%CI = 11.6 - 12.6) and 2007 (11.8, 95%CI = 11.4 - 12.2) (Table 1). Of all the regions, we observed the greatest IR in Jazan (Table 2). Tabuk, Jawf and Eastern Region had consistently lower IRs than other regions. The proportion of infected persons was consistently much higher for individuals > 15 years of age than those in younger age categories (Figure 3). In 2012, the proportion of malaria cases due to *P. falciparum* was much lower than that due to *P. vivax* (Figure 4). In addition, the trend showed that the proportion of malaria cases in KSA was due to importation (Figure 5).



**Table 1. Reported Cases of Malaria and Incidence Rates, by Year, Kingdom of Saudi Arabia, 2002 – 2011**

Year	#	IR°	95% CI
2002	2,583	12.1	11.6 - 12.6
2003	340	1.5	1.3 - 1.7
2004	1,229	5.4	5.1 - 5.7
2005	1,058	4.6	4.3 - 4.9
2006	1,278	5.4	5.1 - 5.7
2007	2,862	11.8	11.4 - 12.2
2008	1,491	6	5.7 - 6.3
2009	2,337	9.2	8.8 - 9.6
2010	1,934	7.1	6.8 - 7.4
2011	2,787	10	9.6 - 10.4
Total	17,897		

°IR = incidence rate per 100,000 population

\*CI = confidence interval