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Distribution and Determinants of Dengue Fever, Cities of Jeddah and Makkah, Kingdom of Saudi Arabia, 2007 – 2013

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Introduction: Dengue fever (DF) is an infectious disease spread by the bite of the female mosquito, *Aedes aegypti*. It occurs mainly in urban, tropical cities and presents as a febrile illness, but in some patients (e.g., with co-morbidities), it can progress to death. Recently, outbreaks of DF have increased in the Kingdom of Saudi Arabia (KSA), especially in the port city of Jeddah and the holy city of Makkah. To better understand the rise in incidence rates (IRs) of DF, we analyzed DF cases reported to the Ministry of Health (MoH) from Jeddah and Makkah between 2007 – 2013.

Methods: Case reports from the KSA MoH for the years 2007 – 2013 included demographic, clinical, laboratory, and epidemiologic information. A growth factor was applied to census data obtained from the Central Department of Statistics and Information (CDSI) used to estimate population sizes. Yearly IRs were then calculated and stratified by nationality and gender.

Results: In the six-year study period >65% of all cases were from Jeddah. In each year the number of cases in Jeddah was higher than in Makkah except 2009. The IRs in those two cities varied significantly during the study period. In Jeddah, the IR of non-Saudis was generally greater than that of Saudis, and vice versa in Makkah. In both cities, the IR of males was greater than females. In both cities, individuals aged 15-45 years had the greatest number of cases.

Discussion: The IR of males was greater than that of females and the proportion of individuals aged 15-45 years was consistently greater in both Jeddah and Makkah. Active public health surveillance, developing a comprehensive education campaign, enhancing mosquito control, and conducting follow-up case-control studies to evaluate the effectiveness of public health prevention and control efforts seems appropriate.

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Chapter 1: Introduction

Dengue fever (DF) is an infectious disease spread by mosquitos that can cause high levels of morbidity and mortality (1). According to the World Health Organization (WHO), “dengue is the most common and widespread arthropod-borne viral infection in the world” and can be a self-limiting illness as well as proceed to severe disease, known as dengue hemorrhagic fever (DHF) (2). Before 1970, only nine countries recorded cases of DHF, but by the early 2000s, it spread in the Americas, Southeast Asia, the Eastern Mediterranean, and the Western Pacific (2).

The rate of DF has increased in the Kingdom of Saudi Arabia (KSA) in the port city of Jeddah and in the holy city of Makkah, approximately 50 miles away. In response to a 1994 outbreak, a passive surveillance system for DF was established in KSA; this mandated reporting and laboratory testing of suspected cases (3,4). Through public health surveillance, 289 confirmed cases were identified in Makkah in 1994, but only 26 cases were reported in the following five years (3). Between 1995 – 2003, 0 to 36 confirmed cases of DF were reported in Jeddah (5). There was a sharp rise in 2004 with 291 suspected DF cases, followed by 305 suspected cases in 2005 (5).

In 2006, in response to an epidemic (1,308 suspected cases) (5), KSA implemented an educational campaign as well as a mosquito chemical control program (5,6). While this public health campaign appeared to be effective (5), the mosquito control program was not implemented properly, and the epidemic increased in 2007 (6). According to a 2013 analysis, IRs of reported DF cases in KSA rose to 4,411, the greatest number of DF cases reported since the surveillance system began (6).

KSA faces challenges to effective prevention and control of DF through both its public health policy and practice. Although public health surveillance for DF was implemented in 1994, the public health response has not been modernized. One reason this has not taken place is that data have not been analyzed comprehensively. Multiple reports focusing on different years or locations exist (5–7) but no single report covers a broad span of years and provides updated information and insight into demographic and seasonal predictors of infection.

It is important to note that a case-control study was conducted on the 2007 confirmed cases (5), and while much information was gained from this analysis, the study had several limitations. First, only the 2007 cases were considered in the study, and the response rate for cases was only 53%, leaving the potential for selection bias (5). Second, only certain risk factors were studied, such as the presence of standing water as a condition that promotes mosquito breeding, while risk factors having to do with the use of clothing and nets as physical barriers and inappropriate or ineffective use of pesticides were not studied (5). So although this study is of high scientific rigor, many questions are still left unanswered about demographics and seasonal patterns of DF in KSA.

We determined the yearly IRs of DF in the cities of Jeddah and Makkah for the years 2007 through 2013 to identify at-risk groups and compare seasonal patterns. KSA must have updated analyses of DF surveillance data to inform ongoing public health response efforts. Although reports focus on different years or locations (5–7), no single report covers this timespan and provides stratified risk estimates by gender or nationality. We analyzed age and seasonal distributions and compared IRs in Jeddah and Makkah, cities with the greatest IRs of DF in KSA. The specific aims of this project are to:

- estimate the yearly IRs of DF for the cities of Jeddah and Makkah during the study period from 2007 – 2013;
- estimate the yearly IRs of DF for each city, by year and stratified by gender and nationality;
- estimate the proportions of DF, by age group and month, reported for each city; and
- perform a comparative analysis of results between Makkah and Jeddah.

DF incidence has increased in KSA, and infection control efforts have met challenges. KSA DF public health surveillance was developed in 1994 in response to an outbreak (3). Between 1995 and 2003, 0 to 36 confirmed cases of DF were identified yearly in Jeddah (5). However, there was a sharp rise in 2004 with 291 suspected cases, followed by 305 suspected cases in 2005 (5). In 2006, 1,308 suspected cases were identified with six deaths and a case fatality rate of 4.6 per 1,000 cases (5).

In early 2006, when deaths due to DF occurred, KSA developed public health education and chemical mosquito control campaigns (5), but the IRs still increased in 2007 (6). A recent case-control study focused on the cases reported in 2007 and revealed the effectivenss of some control measures (5) but did not provide a comprehensive assessment of knowledge, attitudes, and practices (8).

Definition of Terms

Aedes aegypti	The type of mosquito that carries the dengue virus. These mosquitos breed in tropical urban areas in standing water in manmade containers, and feed during the day.
CDC	Centers for Disease Control and Prevention in the United

	States.
DEN-1, -2, -3, and -4	The four isolates of the dengue virus.
DF	Dengue fever, or the flulike symptoms that present with dengue infection.
DHF	Dengue hemorrhagic fever, a rare but severe complication of dengue fever that can result in death.
Directorate General for Health in Makkah	This is the authoritative body that currently directs the dengue surveillance system in both Jeddah and Makkah.
DSS	Dengue shock syndrome, a rare but severe complication of dengue fever that can result in death.
The Hajj	An annual international Islamic pilgrimage to the holy city of Makkah.
IRs	Incidence rates, meaning the fraction of number of infections divided by number at risk during a defined time period.
Jeddah	A large commercial port city in KSA on the Red Sea located within 50 miles of Makkah. Visitors to Makkah enter KSA through Jeddah.
KSA	Kingdom of Saudi Arabia, a large middle-eastern country on the Arabian peninsula.
Makkah	The holy city of Makkah is the center of Islam. It is located in Saudi Arabia less than 50 miles from Jeddah, and is the destination of pilgrims for The Hajj and Umbra.

Makkah Mukarramah	The region in which both Jeddah and Makkah are located.
Ministry of Health	The federal body in KSA that regulates public health.
Umrah	A pilgrimage to the holy city of Makkah that takes place on a personal schedule, not during The Hajj.
WHO	World Health Organization, which provides international guidance for countries working to prevent and control dengue.

Chapter 2: Literature Review

Dengue fever (DF) is an infectious disease spread by mosquitos that causes high levels of morbidity and mortality (1). According to the World Health Organization (WHO), “dengue is the most common and widespread arthropod-borne viral infection in the world”, and can be a self-limiting illness as well as proceed to severe disease known as dengue hemorrhagic fever (2). The disease is currently prevalent in more than 100 countries, and DF is responsible for approximately 22,000 deaths annually, mostly among children (9). Every year, there are approximately 50 million new dengue infections, and half a million severe dengue cases (10). Once a patient is infected with DF from a mosquito, that person is also a carrier of DF and can serve as a reservoir infecting other mosquitos, thus spreading the disease (9). The incubation period between the mosquito bite and the development of symptoms is 4 to 10 days (9).

The mosquito that carries dengue is called *Aedes aegypti,* which lives largely in urban habitats and breeds mostly in man-made containers (9,11). The female mosquito is the primary vector for this disease, and because the mosquito is a daytime feeder, the peak biting periods are early mornings and before sunset (9). The mosquito can bite and infect multiple people during one feeding period (9). *Aedes aegypti* thrives in almost all temperate and tropical regions of the world, which are the regions with the highest incidences of dengue infection (9).

DF is a flu-like illness that does not generally progress to a severe state (9,11). Symptoms usually last from two to seven days and resolve (9,11). Less commonly, DF can progress to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (3,11), which are severe states of DF. Severe DF should be suspected when a high fever is accompanied by two or more of the following symptoms: severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands, or rash (9,11). The severe forms DHF and DSS have high case fatality rates (9,11). People with other comorbidities such as asthma are at higher risk for progressing to severe disease (12). Those with weakened immune systems are at higher risk of death from DF (12). The four antigenically related but distinct dengue virus serotypes are types 1–4 (DEN-1, DEN-2, DEN-3, and DEN-4), which can all cause DF-DHF (3); however, infection with one serotype confers temporary immunity against all other serotypes (10).

Control measures developed for DF mostly focus on vector control through water storage strategies, renovating housing conditions so as to discourage mosquito breeding (11,13), and spraying to kill DF-carrying mosquitos (5). Other control measures are wearing protective clothing and making sure skin is covered to prevent bites (14).

Before 1970, only nine countries had recorded cases of DHF, but by the early 2000s, it was increasing in incidence and had spread to the Americas, Southeast Asia, the Eastern Mediterranean, and the Western Pacific (2). DF has been a longtime public health problem in tropical regions of the world such as the Indian subcontinent, southern China, Southeast Asia, and Taiwan (11). However, since World War II, DF has also become a problem in Central and South America, the Pacific Islands, the Caribbean region and Mexico (11) (9).

More than 100,000,000 new cases of DF infections occur in the world every year (9). Approximately 500,000 of these involve severe to acute symptoms leading to hospitalization, and about 2.5% of those suffering from severe forms of dengue die (9).

Rates of DF have been rising, especially in tropical regions. In 2012, approximately 100,000 infections were reported in Indonesia. In 2007, 25,000 occurred in Cambodia, and that year, there was a 50% increase in the number of cases reported in Malaysia (15). These figures contrast with the ones reported in the period between 1996 and 2005, when the total number of cases reported to WHO ranged from 0.4 to 1.3 million annually (15).

Between 1870 and 1873, before the time when DF laboratory confirmation was possible, a dengue-like disease was described in the Arabian peninsula (3). The appearance of the disease in this era was identified in the cities of Aden, Makkah, Madina, and Jeddah (3). Previous epidemics of a dengue-like disease had already been identified in Asia and America, with an American epidemic taking place from 1779 – 1780 (3).

The KSA has undergone major changes in the recent past. Beginning in 1970, KSA embarked on the building of a modern economy and introduced a series of ongoing five-year development plans (16). With the help of oil revenues, the Saudi government has transformed the country from one with a predominantly nomadic society to one with an urbanized modern infrastructure.

The cities of Makkah and Jeddah are two products of this expansive urbanization. People often travel to and from these cities and the rural areas where they live, and thousands of foreigners from all over the world visit them. Because KSA is the spiritual home of Islam, almost two million international pilgrims travel each year to attend the Hajj in Makkah (6,17), flying in and out of the airport in Jeddah. Umra is a pilgrimage that does not need to take place during a certain time; throughout the year, Umra also attracts both internal and external pilgrims to Makkah (17).

For these reasons, Jeddah and Makkah are important cities in KSA to monitor for infectious disease. Both cities are located in the Makkah Mukarramah region of KSA (18). Jeddah, the second largest city in KSA, is located on the Red Sea and is a thriving port city noted for trade and industry (18). Makkah, the third largest city in KSA and capital of the Makkah province, is located in a narrow valley approximately 50 miles from Jeddah (7).

Jeddah and Makkah have a large numbers of visitors, creating opportunities for *Aedes aegypti* to reproduce and spread. Water tanks, washrooms, and sewage lines are some of the manmade items that facilitate the spread of *Aedes aegypti* (6). Aspects of Saudi culture may also contribute to the disease's spread. The vast majority of Saudi nationals use indoor or outdoor ablution areas to wash their feet and hands before praying five times a day. Thus, the presence of standing water is common, and the chance of mosquitoes breeding in these pools is high. Certain features of these cities' urban ecology may be responsible for the spread of *Aedes aegypti* mosquitoes and subsequent increase in the cases of dengue infection (5). The presence of stagnant water indoors creates a place for mosquito larvae to breed, and given that houses in Jeddah and Makkah have a steady supply of water, the presence of these conditions ensures constant reproduction of mosquitoes. In addition, a high number of construction sites in the city of Jeddah provide prime conditions for *Aedes aegypti* to reproduce (5), as these sites often have open water pools and areas of shelter for mosquitoes. In 2014, Arab News reported that "residents in the city, especially in south Jeddah, fear that the municipality has not realized the enormity of the health threat posed by the mosquito-breeding pools" (19). It is apparent that these manmade conditions and the presence of a warm climate in Makkah and Jeddah encourage the multiplication of *Aedes aegypti*.

KSA did not begin formal DF surveillance until after DF virus was isolated in 1994 for the first time in the virology laboratory of Dr. Soliman Fakeeh Hospital in Jeddah (3). After this, physicians there were alerted to the possibility of an outbreak, and blood samples were collected from patients suspected of having DF (3). This surveillance was self-limited to the Jeddah region of KSA. The case definition of suspected cases was "fever with thrombocytopenia and or leucopenia, eye pain, generalized body aches, headache, and skin rash with or without bleeding" (3). Of the 673 suspected cases, serologic confirmation in the laboratory resulted in 289 confirmed cases (3). These cases were solely comprised of DEN-1 and DEN-2 types (3).

After the 1994 outbreak, KSA continued its surveillance of Jeddah for DF using the same process. This surveillance process identified 289 confirmed cases in 1994 but found only six in 1995, two in 1996, 15 in 1997, none in 1998, and 3 in 1999 (3), suggesting that 1994 was indeed an isolated outbreak. Throughout this time period, all cases identified were either DEN-1 or DEN-2, with the exception of one DEN-3 case in 1996 and 12 DEN-3 cases in 1997 (3). Of the 315 confirmed DF cases reported from 1994 – 1999, the greatest percentage (39.4%) occurred among those aged 21-30, with the next largest affected group those aged 31-40 (23.8%), and finally those aged 11-20 (18.7%) (3).

Between 1995 and 2003, between 0 and 36 confirmed cases of DF were identified yearly in Jeddah (5). However, there was a sharp rise in 2004 with 291 suspected cases, followed by 305 suspected cases in 2005 (5). In 2006, 1,308 suspected cases were identified with six deaths and a case fatality rate of 4.6 per 1,000 cases (5).

This alarming case fatality rate caused the KSA government to mount a public health response in the form of a health education campaign implemented through a joint effort of the Preventive Health Affairs agency, Jeddah Municipality; the Boys and Girls Education Department, Department of Religious Affairs; the Information Department at the Jeddah Governorate, and King Abdul-Aziz University (5). The goal of the campaign was “to strengthen community participation in the prevention and control of dengue fever and support preventive measures conducted by the MoH and other related governmental sectors” (5). The public received education about the causes of DF, how to prevent it, importance of early detection, and the management of suspected cases (5). In addition to the public education campaign, the government increased the budget allocation in Jeddah to fight the mosquito threat in 2006. In 2007, Makkah used 3,899 liters of mosquito larvicides and 17,975 liters of mosquito adulticides (6).

In 2007, public health officials in Jeddah confirmed another 244 cases and conducted a case-control study on risk factors for DF infection (5). The study found that outdoor risk factors for mosquito breeding, like the storage of uncovered water on balconies and the presence of stagnant water in drainage holes, were significantly associated with positive case status (OR = 4.934), but indoor risk factors for mosquito breeding were not associated with positive case status (5). Having been bitten on the legs and face was positively associated with case status, and results were statistically significant (5).

Having received face-to-face health information as part of the educational campaign was negatively associated with case status , but receipt of written information such as brochures was not associated with case status (5). In line with earlier results, cases were more likely to be adults than children (5). Peaks in incidence in July and December were explained by tracking the effects of increases in temperature on mosquito breeding patterns (5). Briefly, in a pattern demonstrated in Brazil, Thailand, and now KSA, increases in temperature have been shown to precede an increase in mosquito breeding, and in the month following, increases in DF incidence are then reported (5). The authors also noted the possible impact of the rainy season pattern in Jeddah (5).

DF incidence has increased recently in the KSA. Researchers calculated an incidence rate for DF in 2008 in the city of Makkah of 6.2 per 100,000, which increased dramatically in 2009 to 110.6 per 100,000 (7). In 2014, Aziz et al. reported on number of dengue cases from 2006 through 2013 in Jeddah and Makkah and found the highest number of reported cases in 2013, numbering 4,411 and resulting in eight deaths (6)

Currently, DF surveillance in Makkah region (where the cities of Jeddah and Makkah are located) is led by the Directorate General for Health in Makkah, which developed and now maintains the surveillance system (4). This is a passive surveillance system, so it depends upon the clinical presentation of the patient and the observation of disease identification by clinicians (4). Instructions provided by the Directorate cover all roles in the surveillance process (e.g., that of a hospital's infection control department and the public health department). The emergency and outpatient physicians play the most important roles (4), as they are the ones who apply the clinical case definition to patients and determine whether or not patients fit the definition and undergo testing (by blood sample) for DF (4). If these doctors are not aware of DF's presentation, cases will likely be missed.

Overall DF incidence has been increasing recently in the KSA in Jeddah and Makkah. Although KSA has been regularly tracking and analyzing DF cases nationally since the 1994 outbreak, focus has been on collecting case samples in Jeddah and Makkah, mainly because these are the most populous cities. Currently, for Jeddah and Makkah, sex-, age- and nationality -specific (Saudi vs. non-Saudi) incidence rates of dengue have not been calculated. The population of KSA is approximately 27 million, and 30% of those are non-Saudis, or foreigners whose home country is outside KSA. Hence, there is a need to calculate specific estimates for Saudis vs. non-Saudis. Also, the data have not been analyzed to determine high-risk months for DF infection in KSA. This section will review what is known about the incidence rates of DF by gender, age group, and ethnicity, and temporal patterns in DF infection in KSA.

The gender distribution of DF has been shown to be different in different populations. Therefore, the role of gender in incidence rates of dengue infections remains inconclusive and calls for further research. Some studies show higher incidence in males, some show higher incidence in females, and some show equal incidence rates (20). A study by Anker & Arima in six Asian countries found "an excess of males" in the adult case group (21), and another study in India found that males made up approximately 60% of the case group.

Little is known about the gender distribution of DF cases in KSA. Among the confirmed DF cases from the 2007 outbreak in Jeddah who were included in the case-control study, 65% (129) were male (5). A 2013 paper on DF incidence in Makkah reported a total of 4,187 confirmed cases from 2008 through 2012 and found that 73% were male (7). The authors calculated rates stratified by gender from 2008 through 2012 (7) and showed that the males had a higher incidence rate than females (7).

In both the case-control study of the 2007 Jeddah cases and the study of cases in Makkah from 2008 through 2012, Saudis made up a larger percentage of confirmed cases than non-Saudis (5,7). The differences in percentages between studies is unusual. In the Jeddah study, of the 129 DF cases, about 51% were Saudi (5), while in the Makkah study, over 70% of confirmed cases were found to be Saudi (7).

These findings are contradictory to what would be expected, since non-Saudis generally have a lower socioeconomic status and should therefore be more likely to live in conditions where they would be exposed to mosquitos carrying DF (5), e.g., lower quality housing where there are more standing pools of water (5). In addition, non-Saudis are more likely to have outdoor occupations such as construction, which would put them at higher risk of being bitten by an infected mosquito (5).

In the Jeddah study, nationality was not found to be associated with case status (5), and in the Makkah study, Saudis had over twice the rate of non-Saudis of dengue infection (7). The authors attributed this difference to diagnostic bias, saying the discrepancy was due to Saudis having more access to treatment compared to non-Saudis. Health care in KSA is free for Saudis, and non-Saudis must pay. As a consequence, Saudis seek medical advice more often. Also, since DF is often self-limited, most non-Saudis will wait for it to resolve on its own rather than paying for medical care for a minor illness (7). Again, this problem is a side effect of a passive surveillance system. Currently, the precise distribution of DF among Saudis and non-Saudis is unknown.

Studies generally show that incidence rates of DF are highest among children, but the severe forms of DHF and DSS are not as common among children (10,22). However, in a study in Singapore where blood samples were taken from individuals and tested during a dengue outbreak, adults aged 45 and older were found to be more likely to have DF (23). This suggests that a passive surveillance system that relies on physician identification of suspected cases may not be ideal.

As described by WHO, local variations in DF transmission risk are caused by local differences in rainfall and temperature (9). Although monthly transmission patterns of DF in KSA are not known, studies of variations in the local population of *Aedes aegypti* have been conducted. In 2010, El-Badry & Al-Ali trapped mosquitos in Jeddah and Makkah during the period of July 2008 to June 2009 (24), subsequent to the 2007 Jeddah outbreak, and reported that a peak in the size of the population of *Aedes aegypti* was evident in April 2009. More recently, Alsheri reviewed confirmed dengue cases in Jeddah from 2004 through 2001 and examined associations between climatic factors and mosquito density as well as mosquito density and dengue fever cases in Jeddah (15). A positive correlation was found between climatic conditions such as temperature and humidity and the density of the mosquito population, and it was shown that when the density of the mosquito population decreased, the DF infection rate decreased (15). Consistent with the earlier observation of a high rates of *Aedes aegypti* in April 2009 (24), a peak was seen in July, with a climb beginning in April and dropping in August and September (15).

Chapter 3: Manuscript

Distribution and Determinants of Dengue Fever, Cities of Jeddah and Makkah, Kingdom of Saudi Arabia, 2007 – 2013

Abstract

Introduction: Dengue fever (DF) is an infectious disease spread by the bite of the female mosquito, *Aedes aegypti*. It occurs mainly in urban, tropical cities and presents as a febrile illness, but in some patients (e.g., with co-morbidities), it can progress to death. Recently, outbreaks of DF have increased in the Kingdom of Saudi Arabia (KSA), especially in the port city of Jeddah and the holy city of Makkah. To better understand the rise in incidence rates (IRs) of DF, we analyzed DF cases reported to the Ministry of Health (MoH) from Jeddah and Makkah between 2007 – 2013.

Methods: Case reports from the KSA MoH for the years 2007 – 2013 included demographic, clinical, laboratory, and epidemiologic information. A growth factor was applied to census data obtained from the Central Department of Statistics and Information (CDSI) used to estimate population sizes. Yearly IRs were then calculated and stratified by nationality and gender.

Results: In the six-year study period >65% of all cases were from Jeddah. In each year the number of cases in Jeddah was higher than in Makkah except 2009. The IRs in those two cities varied significantly during the study period. In Jeddah, the IR of non-Saudis was generally greater than that of Saudis, and vice versa in Makkah. In both cities, the IR of males was greater than females. In both cities, individuals aged 15-45 years had the greatest number of cases.

Discussion: The IR of males was greater than that of females and the proportion of individuals aged 15-45 years was consistently higher in both Jeddah and Makkah. Active public health surveillance, developing a comprehensive education campaign, enhancing mosquito control, and conducting follow-up case-control studies to evaluate the effectiveness of public health prevention and control efforts seems appropriate.

Introduction

Dengue fever (DF) is an infectious disease spread by the female mosquito *Aedes aegypti* mainly found in urban, tropical cities (1). Patients bitten with a DF-infected mosquito can get DF, a flu-like illness (9,11) that sometimes progresses to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (3,11), which are severe states of DF. Severe dengue should be suspected when a high fever is accompanied by two or more symptoms including severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands or rash (9,11). The severe forms DHF and DSS have high case fatality rates (9,11). Also, patients with other comorbidities such as asthma are at higher risk for progressing to severe disease (12).

Although DF has been described throughout history (3), it has recently become an international public health threat (1). According to the World Health Organization (WHO), "dengue is the most common and widespread arthropod-borne viral infection in the world" (2) and is currently prevalent in more than 100 countries. DF is responsible for approximately 22,000 deaths annually, mostly children (9). Recently, outbreaks of DF have increased in the Kingdom of Saudi Arabia (KSA), especially in the port city of Jeddah and the holy city of Makkah (3) It was not until a 1994 outbreak that dengue virus was first isolated in a KSA laboratory (3). Since its implementation, the surveillance system has tracked a subsequent outbreak in Jeddah that lasted from 2004 through 2007 (5) and detected a more recent outbreak in 2013, the largest yet, with 4,000 suspected cases and 8 deaths in the two cities (6). Makkah sees over 2 million pilgrims every year who fly in from outside KSA as part of the Hajj (17). To travel there, they fly to the airport in Jeddah. Because of the geographical location and the social movement in these two cities, surveillance efforts have focused mainly on these locations.

Although public health surveillance for DF has been in place in KSA since 1994, the public health response has not been modernized and the data have not been analyzed comprehensively. Monthly transmission patterns of DF in KSA are though unknown, studies of variations in the local population of *Aedes aegypti* have been conducted (24) (15). A positive correlation was found between climatic conditions such as temperature and humidity and the density of the mosquito population, and it was shown that when the density of the mosquito population decreased, DF infection rate decreased (15). Consistent with the earlier observation of a high rates of *Aedes aegypti* in April 2009 (24), a 2013 study found that counts of DF infections 2004 through 2008 in Jeddah demonstrated an annual peak in July, with a climb beginning in April and dropping abruptly in August and September (15). The data collected by the Directorates in Jeddah and Makkah were published before (5), but a comparative analysis has not been conducted, and incidence rates (IRs) for these two cities have not been estimated stratified by gender, age, and nationality.

To better understand the rise of DF cases and inform ongoing public health surveillance efforts, we determined the annual IR of DF for the cities of Jeddah and Makkah during the period of 2007 – 2013, estimated the DF IR in each city stratified by gender and ethnicity, and analyzed distribution of cases of DF by age category and month.

Methods

This is a descriptive analysis of surveillance data of confirmed dengue cases detected by KSA's surveillance system in Jeddah and Makkah from 2007 through 2013. We estimated the IR of DF in each city over the study period. The IRs were stratified by nationality and gender. In addition, we estimated the proportion of cases distributed in different age categories and months of reporting.

Data were obtained from laboratory-confirmed cases of dengue that were detected in KSA's surveillance system from 2007 through 2013. The case database consists of the following variables: laboratory reported number of cases in Jeddah and Makkah and total cases stratified by gender, nationality, and age category.

The DF surveillance system of Makkah region includes data on the cities of Jeddah and Makkah and was developed by the Directorate General for Health in Makkah (4). The surveillance teams in Jeddah and Makkah who were involved in laboratory confirmation sent reports of confirmed DF cases to the KSA Directorate of Communicable Disease Control in the MoH. These case reports include demographic information such as gender, nationality, age, the city from which the cases originated, and the month in which the cases were reported. Population data were obtained from the census reports compiled by the Health Information Center and Biostatistics Department in the General Directorate of Health Affairs of Jeddah and Makkah.

IRs were estimated using the number of new cases of DF per year over the total population per 10,000 individuals. Ideally, the formula requires the population at risk in the denominator. Since the prevalence of dengue is relatively rare, the population at risk is almost close to the total population, so the total population was used in the denominator to estimate the IR.

To investigate the trend of IR by gender, population data for men and women were only available in the 2010 census. In order to estimate the population data for other years, we first estimated the growth factor in each year based on the projected data in population level as reported by the Central Department of Statistics and Information (CDSI). Assuming the same growth factor for both men and women, using the data from 2010, we estimated the size of the population by gender in other years.

To estimate the proportion of cases by age category, we used the following age group categories: ≤14, 15 – 45 years, and >45 years, the same categories used by the MoH. We further estimated the proportion of cases by month based on when the cases were reported.

Microsoft Excel 2011 (Microsoft, Seattle, WA) was used to perform data analysis and produce the figures (25).

Ethical Considerations

This analysis was determined to be IRB-exempt because it was an analysis of secondary data and all data were de-identified prior to analysis. Prior to data collection, all portions of the study were reviewed by Emory's IRB and determined to meet the criteria for exemption.

Results

Overall, 18,772 confirmed DF cases were reported, out of which 67% were from Jeddah (Table 1). Yearly IRs varied between the two cities. The IR per 10,000 was <1 in Jeddah in 2007 and in Makkah in 2008. The IR was >10 in Jeddah in 2013 and in Makkah in 2009. In 2009, Makkah's DF IR was more than twice that of Jeddah's.

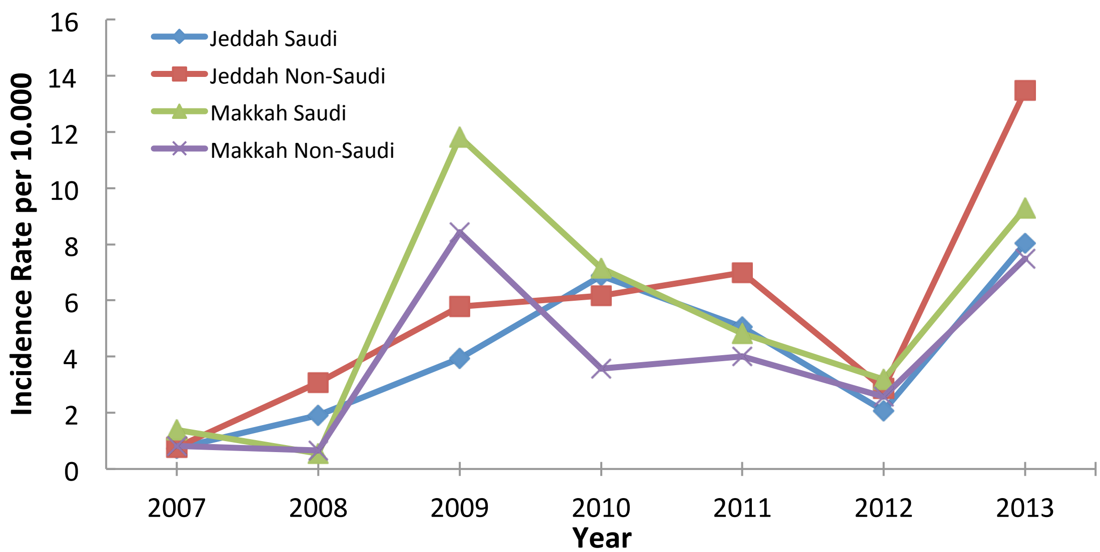
Table 1. Reported Cases of Dengue Fever and Incidence Rates, by Year, Cities of Jeddah and Makkah, Kingdom of Saudi Arabia, 2007 – 2013

Year	Jeddah			Makkah		
	#	IR°	95% CI*	#	IR°	95% CI*
2007	243	0.75	0.66 - 0.85	182	1.16	1.00 - 1.33
2008	807	2.44	2.28 - 2.61	95	0.59	0.47 - 0.71
2009	1,606	4.79	4.56 - 5.03	1,697	10.45	9.96 - 10.95
2010	2,244	6.55	6.28 - 6.82	949	5.72	5.36 - 6.08
2011	2,348	6.08	5.83 - 6.33	867	4.48	4.18 - 4.78
2012	991	2.49	2.33 - 2.64	584	2.93	2.69 - 3.16
2013	4,411	10.74	10.42 - 11.05	1,748	8.51	8.11 - 8.91
Total	**12,650**			**6,122**		

°IR = incidence rate per 10,000 population
*CI = confidence interval

DF IRs by nationality were statistically significant in both cities over the study period with the exception of the year 2007 (for Jeddah) and 2008 (for Makkah) (Figure 1). In Jeddah, the IRs in Non-Saudis were generally greater than that of Saudis, but vice versa in Makkah.

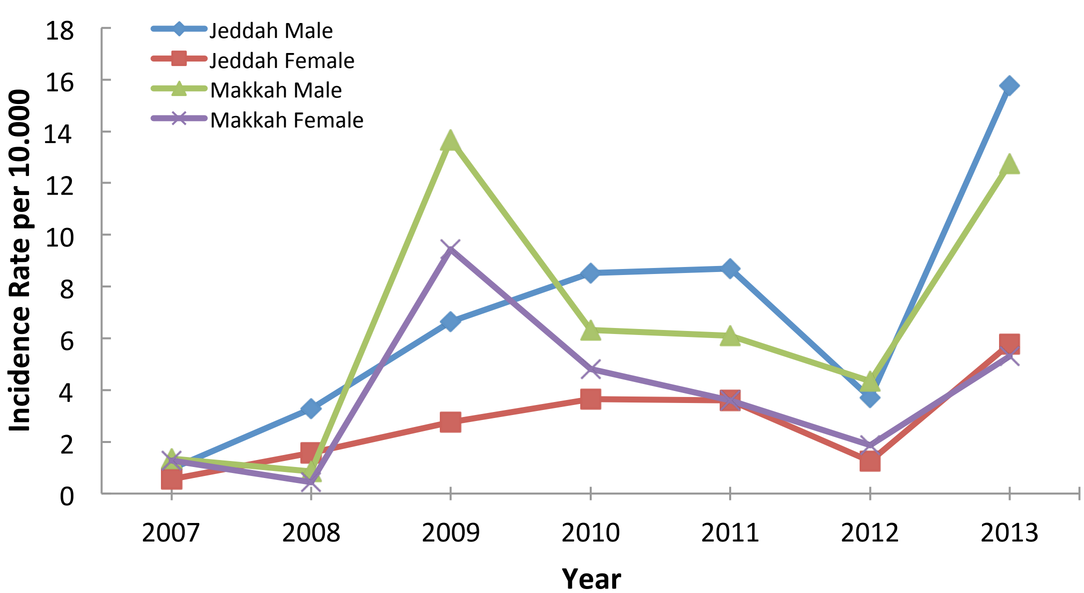
Figure 1. Incidence Rates of Reported Cases of Dengue Fever, by Nationality, Cities of Jeddah and Makkah, Kingdom of Saudi Arabia, 2007 — 2013



The yearly IRs of DF were consistently higher in males than in females for both cities (Figure 2).

Age-specific proportions were similar between Jeddah and Makkah (Figures 3). Over 60% of DF cases were among those aged 15 – 45 years old.

Figure 2. Incidence Rate of Reported Dengue Fever, by Gender, Cities of Makkah and Jeddah, Kingdom of Saudi Arabia, 2007 — 2013



The trend of proportion of cases by month in both cities ware similar (Figure 4). Over the study period, less than 5% of the cases were reported in both cities during the month of September to December. The proportion of reported DF cases was much higher during April to June in each city, with the highest proportion in May.

Figure 3. Proportion of Reported Dengue Cases in the Cities of Jeddah and Makkah, by Age and Year, 2007 – 2013

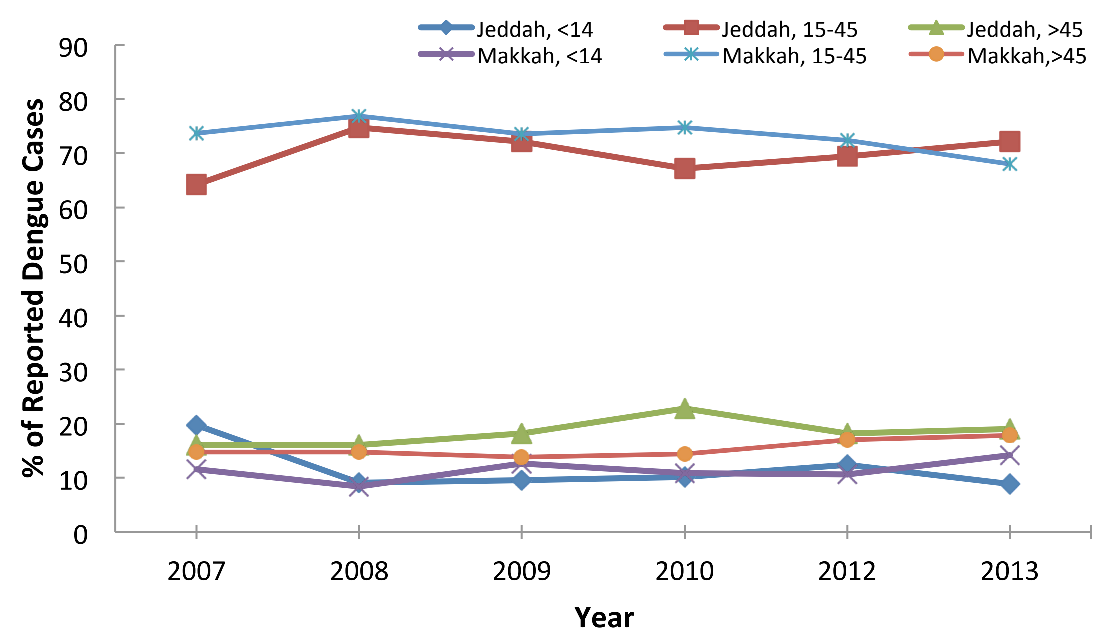
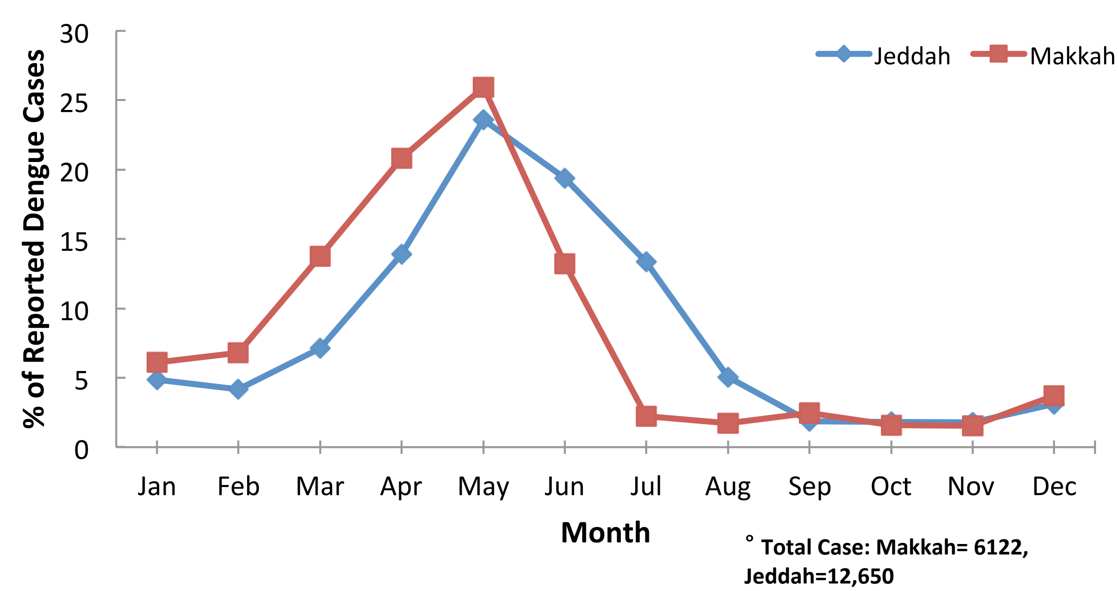


Figure 4. Proportion of Reported Dengue Cases in the Cities of Jeddah and Makkah, by Month, 2007 – 2013



Discussion

More than 65% of all reported DF cases during 2007–2013 were in Jeddah. In each year the number of cases in Jeddah was higher than in Makkah except in 2009, when the DF IR in Makkah was more than twice that observed in Jeddah. In both cities, the IRs varied significantly during the study period. In Jeddah, the IR of non-Saudis was greater than that of Saudis, and vice versa in Makkah. The IR of males was greater than that of females in both cities. The greatest proportion of reported DF cases occurred among individuals aged 15-45 years, and the highest proportion of reported DF cases was observed in the month of May. The proportion was lowest (<5%) from September to December in both cities.

The main limitation of this study concerns the passive surveillance system. First, diagnostic bias might be responsible for underreporting of DF cases for non-Saudis who generally have a lower socioeconomic status and are therefore more likely to be living in conditions where they would be exposed to mosquitos carrying DF. In addition, non-Saudis do not have the health coverage that citizens do; health care is free for Saudis, which encourages them to seek medical advice more frequently than non-Saudis.

Additionally, a suspected case in the passive surveillance system must present to a physician who should diagnose using the proper clinical case definition. When this does not occur, no blood sample is taken, and consequently there is no laboratory confirmation. Even among Saudis, this process could be responsible for an underreporting of infections, especially if patients do not present to the health care system. Another limitation is that population data by gender were not available for the cities of Jeddah and Makkah. We estimated this data using a growth factor based on census data obtained from the CDSI and assumed the same growth factor for both males and females.

Currently, surveillance case definitions are not emphasized in clinical practice outside of Makkah and Jeddah, and cases are reported at low rates in the surveillance system each year from all parts of KSA. This suggests that there may be severe underreporting from these other localities, possibly due to the historical emphasis on surveillance in Jeddah and Makkah because of their large populations. Ideally, surveillance efforts should not be limited to these two high-incidence locations. Without a comprehensive surveillance system, it is impossible to know if cases in other locations are being missed.

To address the under-coverage of non-Saudis, the MoH should offer free care to those presenting with flu symptoms, thus removing access barriers and increasing the likelihood that non-Saudi DF cases will be detected by the surveillance system. Moreover, active surveillance can be implemented during the high incidence months starting from February until July. Regardless of how these efforts are implemented, there is a strong need to improve the coverage of the surveillance system to provide more accurate estimates. These estimates are clearly necessary to better inform the KSA government as it continues to develop its dengue prevention and control strategy.

We would recommend active surveillance, updating the clinical case definition, improving the sensitivity of the surveillance programs, developing a comprehensive education campaign, enhancing mosquito control, and conducting follow-up case-control studies to evaluate the effectiveness of dengue fever prevention and control efforts.

Chapter 4: Conclusions and Recommendation

Conclusions

More than 65% of all reported DF cases during 2007–2013 were from Jeddah. In each year the number of cases in Jeddah was higher than in Makkah, except in 2009, when the DF IR in Makkah was more than twice that observed in Jeddah. In both cities, the IRs varied significantly during the study period. In Jeddah, the IR of non-Saudis was greater than that of Saudis, but vice versa in Makkah. The IR of males was greater than that of females in both cities. The greatest proportion of reported DF cases occurred among individuals from 15-45 years of age, the highest proportion of reported DF cases was observed in the month of May, and the lowest propotion (<5%) was observed from September to December in both cities.

Recommendations

KSA has been struggling with its public health response to dengue since the first outbreak in 1994. The magnitude of the outbreak is what prompted the establishment of a laboratory that could isolate the dengue virus and the development of the surveillance system (3). This surveillance process, which identified 289 confirmed cases in Makkah in 1994, found only 26 cases in the 5 years that followed (3). Between 1995 and 2003, between 0 and 36 confirmed cases of dengue infection were identified yearly in Jeddah (5). When there was a sharp rise in 2004 with 291 suspected cases, KSA did not have a public health response prepared. When the rate rose in 2006 to 1,308 suspected cases and six dengue-related deaths (5), KSA mounted an educational campaign, and later, implemented an extensive chemical mosquito control effort as part of its prevention program (5).

Currently, KSA's public health response to dengue infection continues to be criticized. Although the door-to-door campaign was especially successful (5), the government currently emphasizes its chemical mosquito control program (6), the limitations of which are discussed extensively in a 2014 update on dengue in KSA (6). The authors describe how in 2006, the KSA government, alarmed by the high 2004 and 2005 rates, substantially increased the mosquito control budget to seven billion Saudi Riyals (6). Nevertheless, rates climbed in 2007, and "it is assumed that this unexpected failure could partially be due to contracting out the mosquito control work to private companies that lacked in terms of precise mosquito control knowledge, use of appropriate science-based strategies, and perhaps efficient professional supervision" (6). The authors elaborate on how often the wrong types of insecticide are used by private contractors, sometimes in doses that actually confer human health risks, and how poorly planned application of insecticides can actually cause targets to become resistant (6).

The authors go on to strongly recommend that a public health education campaign be mounted while the chemical application program be reconsidered and reformed (6). In fact, the interventions that are most effective, such as eliminating standing water in the home, must be done by the residents themselves, and so a public education program is necessary (6). The authors also point out a downside of not conducting a public education campaign: less access to homes for mosquito assessment and control. They write that, as a cultural practice, permission to enter people's homes is given by the male head of the family. Permission is refused when people are afraid of police or immigration authorities, so researchers and spray teams are sometimes denied entry, “often an impediment in the crucial requirement of mosquito population assessment and dengue control process” (6). Health education officers have “relatively easier access to the homes,” and researchers and control personnel can follow them (6).

In a letter to the editor responding to this article, authors from India added some further recommendations for KSA to consider in its public health response, mainly concentrating on physical safeguards (14). The authors recommend that the public education campaign include the instruction that people should “be advised to cover their arms and legs during day-time as well as in the evenings if they are out of their homes” (14). The authors further emphasize that although clothing worn outdoors in KSA is formal and provides almost full-body coverage, most people are inside during the day, and when inside, both men and women dress informally and are more exposed (14). It is important for school children not to wear skirts or shorts all day, and for fashion designers to develop fashionable, indoor daytime clothing that covers the skin and is also promoted by celebrities (14). The authors also observe that local outbreaks take place in and around hospitals, so they recommend the use of insecticide-treated bed nets both day and night for the bedridden (14).

Public Health and Policy Implications

The main implications of these findings should inform both public health practice and policy in KSA. First, in terms of public health practice, an upgrade to the surveillance system should be considered. Throughout the year, all physicians should be trained to recognize the clinical case definition of dengue and to engage the surveillance system if needed for blood samples and laboratory confirmation. Ideally, surveillance efforts should not be limited to the two high-incidence locations of Jeddah and Makkah. Without a comprehensive surveillance system, it is impossible to know if cases in other locations are being missed.

Next, components of an active surveillance system need to be designed and put in place. These components could be activated during the high-incidence months starting in February (in Makkah) and March (in Jeddah) and ending in September.

For instance, teams of public health workers could visit hospitals during high-incidence months and review records for missed cases that meet the clinical case definition, which is available on the internet in Arabic (4). To address the under-coverage of non-Saudis, the MoH should offer free care to those presenting with flu symptoms, thus removing access barriers and increasing the likelihood that non-Saudi DF cases will be detected by the surveillance system.

Regardless of how these efforts are implemented, there is a strong need to improve the surveillance system's coverage in order to provide more accurate estimates. These estimates are clearly necessary to better inform the KSA government as it continues to develop its dengue prevention and control strategy.

From a public health policy standpoint, it appears that the fastest, safest, and most effective way to immediately mobilize against dengue in KSA is through a comprehensive, widespread, grassroots public health education campaign (8). As noted in the study of Jeddah's DF cases in 2007, in-person contact, not merely dropping off brochures, is necessary in KSA for effective public health education (5). As noted in a recent update, most efforts for dengue control rely on individual, not government, actions, so even as the KSA government supports a chemical control program, the public health education campaign component is a necessary complement to ultimately achieve dengue prevention and control (6,8). In fact, researchers asserted that the inappropriate use of chemical control coupled with a lack of public education were what stymied the efforts of the KSA government to control the outbreak in 2006 – 2007 (6).

In addition to the need for implementation of health education, it is clear from the assessment by Aziz and colleagues that reform is necessary in the chemical mosquito control program in the KSA (6). Aziz et al. suggest that heavier regulation of private contractors is necessary to achieve proper mosquito control. This ultimately requires another public health education campaign of sorts, this one aimed at private contractors hired to spray for *Aedes aegypti,* that could be built into a governmental certification program. The KSA government could develop optimal recommendations for mosquito control in Makkah and Jeddah and certify private contractors based on these guidelines. Only after this education and certification should this group have access to the large budget appropriated by the KSA government for such services (6).

According to the literature, it seems that although the KSA government and its residents are at least somewhat attuned to mosquito prevention and control approaches, the use of clothing and nets as protective barriers has not been written about extensively. In fact, Aziz and colleagues neglected to describe how to use clothing and nets in the daytime and indoors to prevent transmission, which prompted a letter of response from those with experience in India. Public health policy in KSA needs to add these components to the education campaigns. The existence of outbreaks in and near hospitals needs to be verified before the use of nets in hospitals can be recommended.

Recommendations for Future Research

In terms of research, the next step would be to better understand the risk factors for dengue infection in KSA, and to benchmark the effectiveness of the current public health response. This could be done in the form of a case-control study similar in design to the one conducted in Jeddah on cases in 2007. This one could use more recent cases (such as those occurring in 2013, which are included in this analysis), and asking about exposures that were overlooked in the previous study. In addition, questions could be asked that gauge the knowledge gain and effectiveness of the educational campaign and the current level of public knowledge about prevention and control measures (8). This information would be extremely helpful in guiding the KSA government in upgrading its current surveillance system and making improvements to the effectiveness of its public health response to dengue.

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Appendix.

Table 1. Reported Cases of Dengue Fever and Incidence Rates, by Nationality, City of Jeddah, Kingdom of Saudi Arabia, 2007 – 2013

Year	Saudi			Non-Saudi			p-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2007	129	0.74	0.61 - 0.87	114	0.77	0.63 - 0.91	0.78
2008	340	1.91	1.71 - 2.11	467	3.07	2.79 - 3.35	<0.05
2009	713	3.94	3.65 - 4.23	893	5.79	5.41 - 6.17	<0.05
2010	1,272	6.88	6.50 - 7.26	972	6.16	5.78 - 6.55	<0.05
2011	997	5.05	4.74 -5.36	1,320	6.99	6.61 - 7.37	<0.05
2012	419	2.08	1.88 - 2.27	568	2.88	2.65 - 3.12	<0.05
2013	1,656	8.03	7.64 - 8.42	2,755	13.47	12.96 - 13.97	<0.05
Total	**5,526**			**7,089**			

°IR = incidence rate per 10,000 population
*CI = confidence interval

Table 2. Reported Cases of Dengue Fever and Incidence Rates, by Nationality, City of Makkah, Kingdom of Saudi Arabia, 2007 – 2013

Year	Saudi			Non-Saudi			p-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2007	130	1.39	1.15 - 1.63	52	0.83	0.60 - 1.05	<0.05
2008	53	0.55	0.41 - 0.70	42	0.65	0.46 - 0.85	0.43
2009	1,147	11.82	11.13 - 12.5	550	8.42	7.72 - 9.13	<0.05
2010	710	7.16	6.63 - 7.68	239	3.58	3.13 - 4.04	<0.05
2011	533	4.83	4.42 - 5.24	334	4.01	3.58 - 4.44	<0.05
2012	360	3.19	2.86 - 3.52	224	2.58	2.24 - 2.92	<0.05
2013	1,072	9.3	8.74 - 9.86	676	7.49	6.93 - 8.06	<0.05
Total	**4,005**			**2,117**			

°IR = incidence rate per 10,000 population
*CI = confidence interval