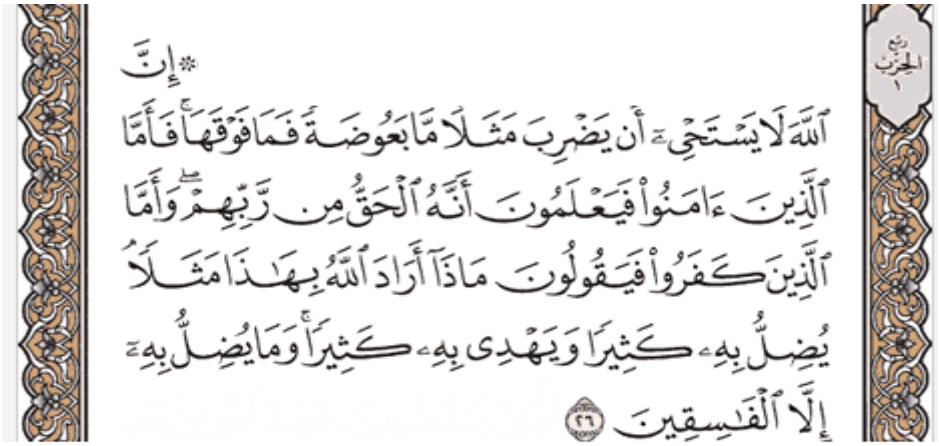
In the name of Allah, the Entirely Merciful, the Especially Merciful.



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Dengue Fever in Makkah, Kingdom of Saudi Arabia, 2008 – 2012

By

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Degree to be awarded: MPH

Global health

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Dengue Fever in Makkah, Kingdom of Saudi Arabia, 2008 – 2012

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Emory University

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An abstract of

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ABSTRACT

PURPOSE: Dengue fever is a reportable condition in the Kingdom of Saudi Arabia (KSA). Case-based information is collected by the Vector-Borne Disease Unit (VBDU) in the Ministry of Health (MOH). However, these case records have not been analyzed statistically beyond producing aggregated reports by year. Therefore, we analyzed dengue fever data collected by the VBDU from 2008 to 2012 to inform policymakers about the distribution and trends in Makkah city, especially because it hosts the Hajj, a yearly mass gathering.

METHODS: Using reported data from the VBDU, we calculated incidence rates and trends by nationality, age, and gender from 2008 –2012.

RESULTS: In 2008, the incidence rate of dengue fever was 6.2 per 100,000 (95%CI=5-7.5). This rate increased approximately 20-fold in 2009 to 110.6 (95%CI=105.4-115.9). The incidence rate then declined in 2010 to 62.95 (95%CI=58.1-66). In 2011 it declined further to 56.5 (95%CI=52.8-60.3) and in 2012 to 37.6 (95%CI=34.6-40.8). We observed significant increases in dengue fever incidence among males throughout the study period, as well as among those 25-44 years of age.

CONCLUSION: Dengue fever is endemic in Makkah city. There was an outbreak in 2009. We recommend improving the surveillance system to include the types of dengue fever (dengue hemorrhagic fever and dengue shock syndrome) plus outcomes (i.e., full recovery, recovery with complication, death). We also recommend using the revised WHO 2009 classification system. Additionally, dengue information should be available to the public to increase awareness. Finally, vector control efforts should be enhanced.

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Table of Contents

1. INTRODUCTION

Kingdom of Saudi Arabia

Kingdom of Saudi Arabia (KSA) is the biggest country in the Arabian Peninsula; it is the second-largest in the Arab world after Algeria. Located in Southwest Asia, it occupies an area about the size of the United States east of the Mississippi River (approximately 868,000 square miles). Around 27 million people, with 8.4 million foreign residents, its annual growth rate is 2.2% (Figure1-1)[1]. The median age is 25.7 years; for men it is 26.7 years and for women it is 24.4 years. The birth rate is 19.19 births per 1,000 people, and the death rate is 3.32 deaths per 1,000 people. The net migration rate is -0.64 migrant(s) per 1,000 people. The maternal mortality rate is 24 deaths per 100,000 live births, and the infant mortality rate is 15.61 deaths per 1,000 live births. The life expectancy at birth is 74.35 years, and the fertility rate is 2.26 children born per woman [2]. The majority of the population was nomadic until 1996; however, currently more than 95% of the population is settled, a result of rapid economic growth and consequent urbanization.

FIGURE 1.1. *Map of Saudi Arabia[3]*

Saudi Arabia is bordered by Yemen on the south; by Iraq, Kuwait, and Jordan on the north; by Oman on the southeast; by the Red Sea and Gulf of Aqaba on west; by the Arabian Gulf, Qatar, Oman and Emirates on the east (Figure 1-1)[3]. The capital city is Riyadh. Saudi Arabia is divided into 13 provinces. The provinces themselves are divided into 118 governorates, which contain the 13 provincial capitals, each one having a different status as a municipality ruled by a mayor.

Islam originated in Saudi Arabia, and the country is home to Islam's two holiest mosques, located in Makkah and Medina. The king's official title is the Custodian of the Two Holy Mosques. The Saudi state was founded in 1932 by King Abdul-Aziz bin Abdul-Rahman Al Saud after a 30 year campaign to unify most of the Arabian Peninsula. In 1992, the country's law required that the ruler should be one of his male descendants. So, in 2005, King Abdullah bin Abdul-Aziz ascended to the throne, where he remains today [2].

The weather is harsh, dry desert with great extremes in temperature. The temperature in the summer is high in most parts of the country, reaching as high as 50◦C. However, the winter season is cold in the north region, and it can drop to 10◦C. The terrain is varied and mostly barren and harsh, with sand deserts; there are a few man-made lakes but no permanent streams. The Rub Al-Khali, located in the south, is the largest sand desert in the world.[2]

Because the nation was built on Islamic values, protecting the Islamic way of life was the cornerstone of Saudi foreign policy under King Abdul-Aziz, and the country continues to be a strong advocate of peace, security and constructive collaboration throughout the world [4].

Saudi Arabia is the leading producer of oil and natural gas and holds more than 20% of the world's proven oil reserves; it is capable of making about 10 million barrels each day. Petroleum is considered the main resource of the country: it constitutes 80% of the total revenue, 45% of the Gross Domestic Product (GDP), and 90% of the export earnings. The economy has grown fast in the past two decades, even during periods of general downturn in the international economy.

Saudi Arabia is encouraging the growth of the private sector so that the economy is more varied and more Saudis will find employment. Foreign workers play an essential role in the Saudi economy. They number about 6 million and work all over Saudi Arabia. However, the government is struggling to reduce unemployment among its own nationals. As a result, Saudi officials are mostly focused on employing the large population of youth [2].

Saudi Arabia became a member of the World Trade Organization (WTO) in December 2005 after many years of negotiations and appeals for foreign investment. At that time, the government started forming six "economic cities" in different regions of the country and, since

that time, has been willing to spend $373 billion on social development and infrastructure projects to improve Saudi Arabia's economy. In 2011, the GDP at purchasing power parity (PPP) was $691.5 billion, and Saudi Arabia was ranked number 24 in the world. GDP-per capita (PPP) was $24,500, and Saudi Arabia was ranked 55th in the world. That year, budget revenues were $295.7 billion and expenditures were $214.3 billion. The inflation rate was 5%, making it 131st in the world.[5]

Makkah

Makkah is a city in the western region (called Hejaz) and is the capital of Makkah province. It is located in a narrow valley at a height of 277 m (909 ft.) above the sea, 75 km from Jeddah city. Its population is around 2 million according to the 2012 census. It is the third largest city in Saudi Arabia after Riyadh and Jeddah. It is the holiest city for all Muslims worldwide, and most Muslims wish to visit Makkah at least once in their lives. More than 15 million Muslims visit Makkah annually to perform Hajj and Omrah. Makkah is the birthplace of the Prophet Mohammed (peace be upon him). Muslims everywhere pray in the direction of the *kabaa* that is located inside the holy mosque in Makkah.

During the Hajj, several million Muslims of varying nationalities worship in unity. Every healthy, adult Muslim who is financially and physically capable of traveling to Makkah and can make preparations for the care of his or her dependents during the journey should perform the Hajj at least once. Omrah, the lesser pilgrimage, while not mandatory, is endorsed in the Qur'an.

Some pilgrims come from countries that have poor health prevention programs, even for those infectious diseases that can easily be prevented. As a result, infectious diseases can easily

be transmitted from all over the world to Makkah, and some of these infectious diseases are very dangerous.

The Ministry of Health

In 1925, King Abdul Aziz established the Public Health Department in Makkah. A year later, the Public Health and Ambulance sector (PHA) was established in response to the health and environmental needs of the Kingdom. The PHA built hospitals and health centers across Saud Arabia to ensure acceptable standards for the practice of medicine and pharmacology.

The ritual of Hajj and Omrah increased the scope of the country's healthcare needs, so the government formed the Public Health Council. This council was the highest board in the Saudi Arabia, and supervised all aspects of healthcare, including all hospitals and primary healthcare centers. Their goals also included the development of skilled healthcare workers and control of the diseases and epidemics that were prevalent during that time.

Ultimately, it was essential to create a large-scale, specialized organization to carry out the Kingdom's health matters. To this end, the Ministry of Health (MOH) was established by royal decree in 1951. With the formation of the MOH, King Abdul Aziz's early vision of modern national healthcare facilities was well on its way to becoming a reality [6].

The MOH in the KSA consist of 30 branches, the Directorate-General of Parasitic and Infectious Diseases (DPID) being one of the main ones. DPID has five main departments and a National Program: the Infectious Diseases Department, the Department of Health Surveillance (at entry points), the Chest Diseases Department, the AIDS National Control Program and the Parasitic Diseases and Vector Control (PDVC) Department. Monitoring and upgrading the

applied preventive measures and arrangements is a continuous process implemented in collaboration with eight national scientific Committees:

- National Scientific Committee for Infectious Diseases,
- National Committee for Hepatitis Control,
- National Committee for TB Control,
- National Technical Committee for Vaccination,
- National Committee for certification of Poliomyelitis Eradication,
- National Committee for Khurma Hemorrhagic Fever,
- National Committee for Acute Flaccid Paralysis Cases, and
- Scientific Committee for AIDS national Control Program [7[7].

The vision of the Directorate General of Parasitic and Infectious Diseases is that Saudi Arabia "should always be a community free from severe infectious diseases," and that "the applied strategies and plans should always lead to progressive reductions in morbidity and mortality rates." The Directorate has three main objectives: the eradication or removal of severe communicable diseases, prevention and control of infectious and parasitic diseases, and prevention of communicable disease-related complications [7].

The Vector Control Department in the MOH in Riyadh has several branches in every region in KSA. One of its major branches is inside Makkah city. All programs associated with dengue fever operate at this level.

Dengue Fever

Dengue fever is a serious disease with many complications. It is a vector-born disease that is transmitted from person to person by mosquitos. According to the Centers for Disease

Control and Prevention (CDC), there are two species of mosquitos that transmit dengue fever, but the primary vector of dengue is *Aedes aegypti* [8]. This species, whose food source is human blood, lives mainly inside buildings in dark areas like closets and bathrooms. However, it can also be found in outdoor areas with standing water like construction sites and gardens [9].

Dengue fever has a wide range of presentations from mild to severe. On the mild side, it entails a low, self-limited fever, but severe cases can entail life-threating hemorrhagic shock. The incubation period of the dengue fever virus in humans ranges from three to 14 days.

This disease has a major impact on the health and economy of any population. In 2000, the estimated number of disability-adjusted life years (DALYs) lost to dengue was about 528 worldwide [10]. Dengue fever is treated by administering intravenous fluids and blood transfusions in severe cases. The treatment of dengue fever is only supportive, and there is no licensed vaccine or medication yet [11]. According to the World Health Organization (WHO), the incidence of this disease has increased around the globe. The number of people who are at risk of acquiring dengue is more than 2.5 billion, which is more than 40% of the world's population [12].

According to the WHO, dengue fever can be classified into dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS)[12]. Most DF cases are self-limited, but DHF and DSS cases are life-threating if not treated. The mortality rate from complications of dengue fever is 20% when untreated. However, it is less than 1% if recognized early and treated. [13]

Dengue fever is prevalent in tropical and subtropical areas. According to the CDC, there are about 100 million cases of DF, with 100,000 cases of DHF needing hospitalization every

year. The disease accounts for 22,000 losses of life each year in more than 100 countries, many of those children [9].

Many factors are associated with the transmission of this disease, including climate change, population growth, urbanization, travel, and poor vector control. All of these factors are present in Makkah city.

Case Definition

The MOH has a case definition for both suspected cases and confirmed cases. This definition has not been changed since 2004. For suspected cases, they have the following definition:

1. DF: Sudden high fever for five days, frontal headache, joins and muscle spasm with vomiting.
2. DHF: fever, platelets <100000, positive tourniquet test and hematocrit < 20%
3. DSS: same as above plus shock.

Confirmed cases are only diagnosed through laboratories by tissue culture, IgM, or PCR methods [14].

Procedures to Control and Report Dengue Fever

The reporting and control of dengue fever in Makkah each operate on different levels. The Vector Control Department receives notification about dengue fever cases from all hospitals in Makkah via a special form, gives a unique code for each case, and records the cases in their database. It follows the progress of specimen transfers from the hospital to the regional lab, and it receives the results from regional labs (IgM, IgG, Ns1, and PCR) and records them in their database. Then it sends the results back to hospitals as well as sending a vector exploration team

to investigate each individual case and implement preventive measures. After this, the Department records the results from the vector exploration team into the database. It archives all the notification cases and disseminates the data to Makkah Municipality, the MOH in Riyadh, hospitals and local schools.

The vector exploration teams identify the contacts for each case and follow them for the incubation duration, trying to locate their residence for the previous two weeks to identify the source of the infection and discover any unreported cases. The teams also educate the contacts about the disease: their symptoms and signs, and how to prevent the spread of the disease. At the houses of cases, they take a sample of the mosquitos. If there any positive results for Aedes Aegypti, the Makkah municipality will be notified to spray the house once a day for three days. The exploration teams also spray the rooms inside the case house, identify the types of mosquitos there, and perform sensitivity tests for different pesticides.

Hospitals are responsible for undertaking their own set of procedures concerning dengue fever. Any suspected case is assessed by the public health doctor on the hospital staff. The public health doctor, along with the treating doctor, fills out a special form and uses a unique code from the Vector Control Department. The form is then sent to the Vector Control Department in Makkah. The patient is isolated in a mosquito-free room to prevent the spread of the infection. The hospital takes 5ml blood to be sent to the regional lab. The results are then sent to the Vector Control Department by fax, and they notify the hospital.

2. SCIENTIFIC RATIONALE

During my 2012 practicum in the Surveillance Department in KSA, I noticed an increase in the number of dengue fever cases in Makkah City, especially among children. In one Makkah study, 24% of the cases occurred among children < 12 years of age [10]. Also, two of my relatives were diagnosed with dengue fever; they were admitted to the hospital. The cost of their care was very high. In addition, the number of cases in the general population continues to increase, even while the MOH invests an enormous amount of money for health education and vector control.

To reduce the number of dengue infections in Makkah, the KSA MOH must work to improve and enforce its prevention measures through multiple levels. To do this, it is very important to first understand the changing distribution of dengue infection over time and to identify high-risk groups. This epidemiologic information helps guide the development of proper policies. Dengue fever is a reportable condition and case-based information is collected by the VBDU in the KSA MOH. However, these case records have not been analyzed beyond the production of yearly aggregated reports. Therefore, I analyzed the dengue fever data in Makkah collected by the VBDU from 2008 to 2012 to inform policymakers about any conspicuous trends or at-risk population subgroups.

3. OBJECTIVES

1. Describe reported cases of dengue fever investigated by the VBDU from 2008 to 2012
2. Identify risk factors (e.g., age, outdoor exposure)
3. Identify “endemic channel”
4. Assess past public health interventions for effectiveness and efficiency
5. Make evidence-based recommendations for improved prevention and control
6. Publish the results in peer-reviewed literature

4. LITERATURE REVIEW

The dengue fever infection is common globally and is considered the most rapidly spreading mosquito-borne viral disease in the world [15]. An estimated 2.5 million people living in tropical and subtropical countries have been infected at least once with dengue virus. Almost 100 million people are infected annually, and there are around 500,000 hospital admissions in some years [16]. The incidence rate has increased 30 times due an increase in dengue's geographic spread to new countries, as well as population growth and urbanization [15]. In the Middle East, the first reported outbreak of dengue was in Egypt in 1799, and they have been confirmed throughout the Middle Eastern region since that time. The incidence of documented outbreaks continues to increase. Recent outbreaks of dengue have been documented in Pakistan, KSA, Sudan and Yemen (based on data from 2005 to 2006) [17].

In KSA, the first case of death from DHF was in Jeddah in 1993. Since then, KSA reported three main epidemics. The first was a DEN-2 epidemic in 1994 with 469 cases of dengue and 23 cases of DHF, two cases of dengue shock syndrome (DSS), and two deaths. The second was a DEN-1 epidemic in 2006 with 1,269 cases of dengue, 27 cases of DHF, 12 cases of DSS and six deaths Finally, KSA experienced a DEN-3 epidemic in 2008 with 775 cases of dengue, nine cases of DHF, four cases of DSS and four deaths.

Jeddah is a Hajj entry point, the largest commercial port in Saudi Arabia, and the largest city with the busiest airport in the western region. In this context, huge numbers of people come from high-burden dengue countries (e.g., Indonesia, Malaysia and Thailand), adding an additional burden to the dengue-affected countries of the area.

Dengue fever affect not only the health of a nation's citizens, but also have huge impact on a country's economy and social wellbeing. Worldwide, the estimated number of disability-adjusted life years (DALYs) lost to dengue in 2001 was 528 [18]. The number of cases reported yearly to WHO ranged from 0.4 to 1.3 million between 1996 and 2005 [19]. In one prospective study in Thailand, the yearly burden of dengue infection during a 5-year period was 465.3 DALYs per million, with non-hospitalized infected people with dengue illness at 44 DALYS per million [20]. In the Americas, studies on the cost of dengue infection [21] indicate that the general cost of a non-fatal outpatient case averaged around $514, and the cost of a non-fatal hospitalized case around $1,491. Generally, a hospitalized case of dengue infection costs three times what an outpatient case costs. If both types of care are considered together, the average cost of a dengue infection is $828.

Dengue viruses are members of the family *Flaviviridae,* which includes other medically significant vector-borne viruses (e.g., Yellow Fever virus, West Nile virus, Japanese Encephalitis virus, St. Louis Encephalitis virus, etc.). They occur as four distinct serotypes [22]. However, infection with one serotype does not provide immunity against the others. Moreover, secondary infections can be more severe than the primary infection [8].

Dengue viruses are enveloped, positive-strand RNA viruses consisting of three structural proteins: the envelope protein (E), the capsid protein (C), and membrane protein (M) [23]. Inside the cell, the RNA molecule is translated as a single polyprotein, which is transformed into three structural proteins (C, prM, and E) and seven nonstructural proteins: NS1, NS2A, NS2B,

NS3, NS4A, NS4B, and NS5 [24]. Patients with secondary dengue infection have high titer of NS1 proteins; however, patients have no titer of NS1 in the primary infection [22].

Dengue is transmitted to other people by the mosquitoes Aedes aegypti and Aedes albopictus, which are present all over the globe. However, *Aedes aegypti* is the principal mosquito vector of dengue viruses and yellow fever, the most significant arboviral human infections worldwide [25]. This mosquito is a tropical and subtropical species broadly spread around the world, typically between latitudes 35° N and 35° S. It lives with humans in their houses, feeds on their blood, and is dependent on water-holding containers in and around homes to finish its development. Studies prove that most female *Aedes aegypti* spend their lives inside or near the houses where they first appear as adults. So, it is people rather than mosquitoes who quickly transfer the virus within and between communities [26].

The mosquito lays dozens of eggs inside water containers, then the eggs hatch into larvae when water inundates them as a result of rain or the addition of water by people. After that, a larva will feed on organic matter to change to a pupa in seven days, and into a mosquito in two more days. The mosquito's entire life cycle ranges from 8 to 10 days at room temperature, depending on the amount of food it has. Moreover, the repopulation of mosquitos will continue to occur several months after their apparent elimination because mosquito eggs can withstand desiccation for many months. *Aedes aegypti* have preference for darker, cool places like closets enables the mosquito to live and bite indoors [8].

Environmental factors play an important role in the *Aedes aegypti* lifecycle. Higher temperatures will help the dengue virus replicate and be disseminated quickly inside the mosquitos in a process called the "extrinsic incubation period." As a result, in warmer

temperatures, there is more of a chance for humans to get infected [8]. Moreover, any change in weather correlates with a change in the dengue incidence rate. However, major epidemics can't be explained by these associations [27, 28]. A significant indicator of epidemics might be the interaction of the four different dengue serotypes. The level of people's previous exposure to each of the dengue serotypes may be a more critical cause of large epidemics than climatic change. Climate plays only minor role in the incidence of dengue fever [8, 28].

Aedes aegypti do not fly far, ranging no more than 100m outside of their emergence location. Although Aedes don't feed on non-human hosts, the control and eradication of this vector is hard. Many eradication efforts have failed for these reasons: vertical eradication was not sufficient and unmaintainable; outdoor space spraying was useless because the mosquito mainly lives indoors; and people's rejection of larviciding. Moreover, community educational messages have been mainly unsuccessful [29]. Today, it is very common to find more than 60% of households infested with Aedes larvae in several endemic regions [30, 31]. Though we can temporarily eradicate Aedes aegypti, the eradication cannot be sustained. So, the current goal is to control rather than eliminate vector populations [32].

Humans are the major host of dengue virus. Transmission of dengue can occur from one person to another after occupational exposure at any healthcare site, but it is most commonly transmitted by mosquitos. After the female *Aedes aegypti* ingests the blood of viraemic patients, the dengue virus grows inside its gut over 8-12 days. After that, the dengue virus will infect other people during the mosquito's subsequent feedings. The mosquito remains infective for the rest of its lifespan [26].

During the period of the slave trade (15th through 19th centuries), *Aedes aegypti* arose in Africa, then extended into Asia via commercial exchanges; it has spread worldwide with increased travel and trade in the past 50 years [33]. As an illustration, the trade in used automobile tires is believed to facilitate the dispersal of eggs and immature forms of *Aedes albopictus* vectors into new places [34].

Infection of dengue fever with any of the four dengue serotypes (called DENV-1, -2, -3, and -4) can result in different clinical presentations and severity. The clinical presentation can range from a mild, non-specific febrile syndrome to classic dengue fever (DF), and to the severe forms of the disease: dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [35]. About half of all dengue fever infections are asymptomatic [8]. Sometimes dengue fever presents as an undifferentiated fever, when a patient complains of a mild low-grade fever that mimics any other acute febrile disease. These patients do not meet case definition criteria for DF. So, in the majority of these patients, the diagnosis would remain unknown.

Those afflicted with DF are usually older children or adults, and they complain of having a high fever for two to seven days which is occasionally biphasic. Also, they complain of two or more of the following symptoms: severe headache, retro-orbital eye pain, myalgia, arthralgia, a diffuse erythematous maculopapular rash, and mild hemorrhagic presentation [8]. A tourniquet test may be positive in those patients. Patients with DF do not progress to plasma leaks or wide clinical hemorrhages [8]. There is usually a full recovery from the primary infection without any hospital admission or complication, especially among young children [8].

It is hard to distinguish a person with DHF/DSS from one with DF because the early clinical symptoms and signs are similar, and the course of infection is short [36]. There are three

phases of DHF: the Febrile Phase, the Critical (Plasma Leak) Phase, and the Convalescent (Reabsorption) Phase. The Febrile Phase usually occurs at the beginning of the infection, and it is similar to the presentation of common infections, except that the patients may present with hepatomegaly without jaundice later [8, 26]. Dengue viraemia is usually highest in the first three to five days from the onset of fever; however, it falls quickly to untraceable levels over subsequent days. The level of viraemia and fever frequently follow each other closely, and anti-dengue IgM anti-bodies increase as fever subsides [8].

The Critical (Plasma Leak) Phase starts when the fever subsides; the patient will be at high risk of developing the severe presentation of plasma leaks and hemorrhages. Thus, it is very critical to look for evidence of hemorrhage and plasma leaks into the pleural and abdominal cavities and, if found, to start appropriate treatments to replace intravascular losses and stabilize the patient [8]. Patients showing signs of increasing intravascular exhaustion or severe hemorrhage should be admitted to the intensive care unit immediately for monitoring and replacement. Once a patient complains of shock, he or she is considered to have DSS [8].

Dengue hemorrhagic fever (DHF) and shock (DSS) usually occur after a two- to seven-day febrile phase; however, clinical and laboratory-based alarm signs precede this complication [37]. It is critical to recognize dengue infection early and start treatment for those who develop DHF or DSS as soon as possible in order to reduce the case fatality rate to less than 1% of severe cases [26].

The Convalescent (Reabsorption) Phase starts after the Critical Phase ends, when the plasma leak halts and reabsorption starts. Usually the patient will start to feel better in this phase, and hematocrit levels return to normal with an increase in the urine output. This phase is

characterized by the presence of the unique Convalescence Rash of Dengue (i.e., a confluent pruritic, petechial rash with multiple small, round shapes of unaffected skin). However, there are complications that occur. For example, fluid overload may happen from the use of hypotonic intravenous fluids or from the use of isotonic intravenous fluids.

There is no cure for dengue infections, and its management is dependent mainly on the use of supportive care, including the administration of isotonic intravenous fluids or colloids, and close observation of vital signs and hemodynamic status, fluid balance, and hematologic factors [8]. Clinical research can offer vital data for management guidelines to prevent leakage, hemorrhage, or both [38-42]. In one study, administering Ringer's lactate was sufficient to resuscitate infants with severe dengue fever [42].

There are three chief risk factor categories for dengue hemorrhagic fever. The first category encompasses individual risk factors (e.g., age, sex, nutritional status, secondary infection and host response). The second category is epidemiologic risk factors (e.g., high vector density, hyperendemicity and viral circulation). The third category is viral factors (e.g., strain virulence and viral serotype) [43]. Although secondary infection is a risk factor for severe dengue, severe dengue infection cases have been documented in association with primary infections [44-47]. The duration between infections may also be of significance. For example, a higher case fatality rate was documented in Cuba after an interval of 20 years when a dengue type 2 disease followed a dengue type 1 disease, compared to the case fatality rate after an interval of four years between diseases [46].

Thrombocytopenia almost always exists in any patients with dengue fever. This is due to bone marrow suppression plus an increase in the peripheral destruction of platelets during the

early febrile phase and early convalescent phase of dengue infection. The thrombocytopenia can be as low as 5,000 cells per μL in some cases. However, platelet numbers usually return to normal in the recovery phase [48-50].

In 1974, a WHO committee established case classification guidelines based on information from different studies of the disease spectrum in children in Thailand in the 1960s [35, 51]. However, the WHO discovered that this classification system was not globally applicable for suitable clinical management. So, the WHO Dengue Scientific Working Group recommended additional research for optimized medical management [52]. In the 1997 guidelines, the dengue infection was divided into DF, DHF (Grades 1 and 2) and DSS (DHF Grades 3 and 4) classifications [53]. The case definition of DF depends mainly on laboratory confirmation .

This classification system has many limitations. First, it originated from clinical data from Thai children. So, it is not globally applicable, especially for older children [54]. Moreover, the 1997 case definitions depended on the tourniquet test, and that test doesn't differentiate between DF and DHF and between dengue and other febrile illnesses [53, 55, 56]. Furthermore, those using the 1997 guidelines missed the detection of severe dengue in many patients, especially adults [57]. As a result, new classifications were developed by the WHO that would take observed disease severity into account [53, 58-60].

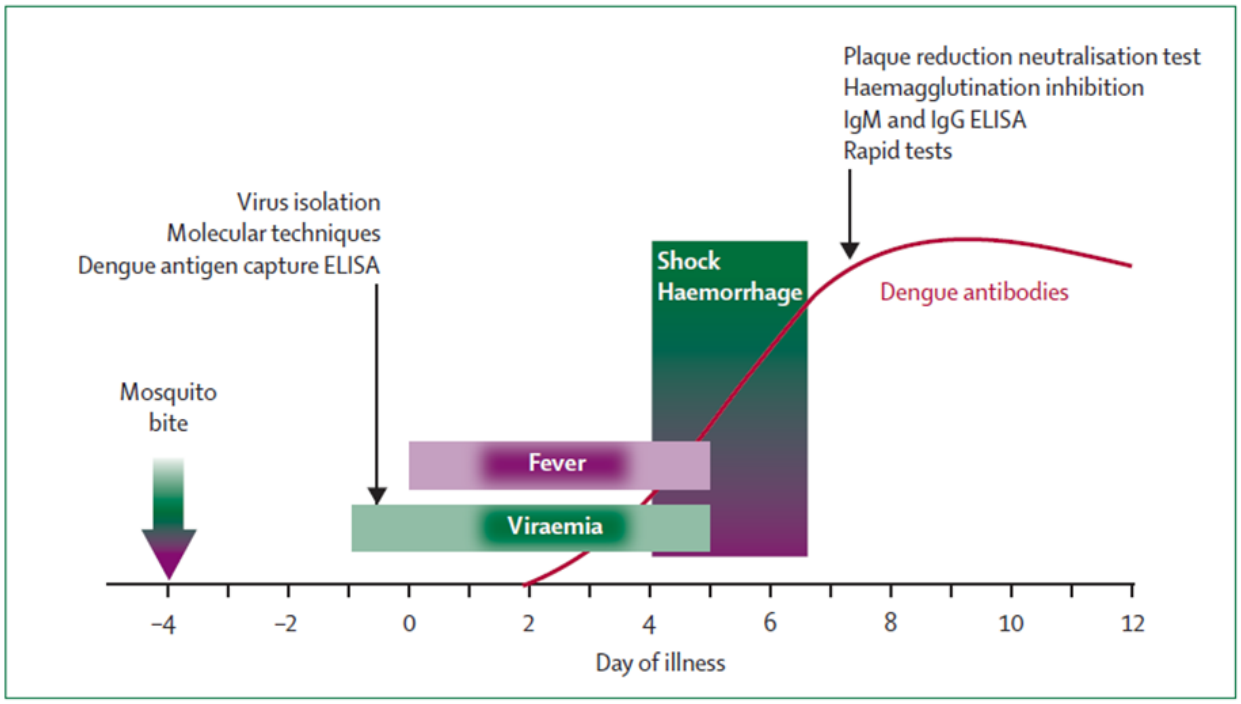
An international Dengue Control (DENCO) study was initiated to assess the limitations of the 1997 classification and create new classifications that would better reflect clinical severity

[61, 62]. In this study, 22% of patients with shock didn't meet all the criteria for DF. As a consequence, this study formed the basis of the new 2009 WHO classification system [60].

The 2009 WHO classification categorized dengue according to its levels of severity: dengue without danger signs; dengue with danger signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure) [26]. This new classification is more sensitive (92% sensitivity) than the 1997 classification (39% sensitivity)[62, 63]. Moreover, in dengue clinical trials, the new classification was helpful in the triage and management of dengue, as well as for reporting during surveillance and for endpoint outcome assessment [15, 52]. The question is, does this newest classification scheme need additional modifications or not [60]? The VBDU uses the 1997 WHO classification system for case definitions in their written protocol. However, they don't use the 1997 WHO classification properly, reporting any case with lab confirmation as dengue fever regardless of the type of dengue disease.

There are two stages in the diagnosis of dengue infection. Stage one includes fever and viraemia associated with NS1 antigens in blood, and stage two includes a post-febrile period that lasts a few weeks when IgM and IgG antibodies are in excess [64]. In the primary infection, viraemia corresponds with the fever (Figure 4-1). In the secondary infection, the duration of viraemia can be around 3 days, while presence of NS1 antigens in blood lasts longer [64]. So, antibodies like IgM are present after viraemia ends or the fever declines.

FIGURE 4.1: Course of Dengue Infection and the Timing of Diagnosis [64]. Published with permission of Timothy Endy, Syracuse University, Syracuse, NY, USA



The onset of DF is acute, and patients generally seek medical advice early, usually within two days. So diagnosis at this stage is possible only by detecting RNA or dengue protein in the blood. However, the serological diagnosis will most likely be negative until the end of the fever. As a result, the patient must be asked to come back again for a second blood sample once the fever has subsided. In patients with DHF/DSS, the IgM-capture serological test will be positive, but tests to detect dengue RNA or dengue proteins most likely will be negative [64].

Commercial dengue serological tests have quality control problems in most countries. In one study, a commercial dengue IgM-capture, the ELISA test, had a high rate of false-positive results [65]. Therefore, an inexpensive, rapid, sensitive, and specific test is needed to diagnose dengue early in the febrile stage. BioRad is marketing a dengue group-specific NS1 monoclonal antibody in an ELISA format to detect dengue NS1 antigens in the blood. This test has an established 85% sensitivity [66]. NS1 can be used in an ELISA-based format as an alternative to

viral antigens to diagnose the primary infection and accurately identify primary and secondary dengue infections [67]. However, the shortcoming of using blood absorbed in filter paper for a diagnostic test is that a large amount of IgM is lost on absorption, which reduces the diagnostic sensitivity and accuracy for this method. On the other hand, IgG antibodies are not absorbed in filter paper, allowing for their use in epidemiological studies of dengue's prevalence in secondary dengue infections [64].

The control of this disease relies on the reduction of the vector's population and density, as there is no effective treatment or vaccine for dengue [26]. So, control of dengue in many endemic areas focuses on treatment of the water-filled containers where the vector lives and breeds. Although eradication of *Aedes aegypti* is impossible, the incidence can significantly be reduced in a cost-effective manner by targeting only those containers [26, 68]. Surveys of around 3,000 containers in approximately 200 houses in Thailand were conducted through rainy and dry seasons from 2004 to 2005. *Aedes aegypti* laid eggs in all 10 types of containers found; however, large water storage containers produced the majority of the pupae. Since these containers are large, easy to reach, and account for almost 50% of all wet containers, it would be easy to treat them with larvicide or cover them [68].

WHO has a strategic method to vector control called Integrated Vector Management (IVM) [69]. Its five key elements are advocacy, social mobilization and legislation; teamwork within the health sector and with other sectors; an integrated approach to disease control; evidence-based decision making; and capacity building.

Epidemiologic analysis of the occurrence of dengue cases is very helpful for vector control services. Following the incidence of current cases and linking it with the number of

cases by month of the previous 5 years, with confidence intervals set at two standard deviations above and below the average (±2 SD), is called the "endemic channel." If the number of cases documented surpasses two standard deviations above the "endemic channel", in the monthly reporting, an outbreak warning is activated. As a result, this method is epidemiologically better than yearly comparisons of combined numbers of described cases [26].

Travelers from endemic areas play a major role in the transmission of this disease. Viraemic travelers transfer different dengue serotypes and strains into areas with mosquitoes that then spread the infection [26, 70]. Sentinel surveillance can be used as a tool to alert and warn the international community at the start of epidemics in endemic regions where there is no reporting of dengue infections. However, the big disadvantage of sentinel surveillance is the missing denominator, so true risk incidence can't be calculated [26]. Primary health care centers can play an important role in the management of dengue fever by using a stepwise approach.

Management and detection of dengue fever requires several resources. Human resources are the most significant, and this includes skilled staff (doctors and nurses). Special areas are also very important for patients who need urgent care. Consumable resources like intravenous fluids and drugs like antipyretics should be available. Communication between facilities is also significant in the management of dengue fever. Lastly, blood banks are required, especially for the management of severe cases [26]. Continuous monitoring of the delivery of dengue prevention and control packages and the evaluation of the effects of the interventions are vital for effective management [26].

Education about dengue in general and the vector and transmission details of the disease should be integrated into school curricula in countries where dengue fever is endemic [26]. The

mass media can make an important contribution in the fight against this disease. Moreover, nursing and medical students, with the community's participation, can visit homes to give health education in coordination with primary health care centers. These methods have been shown to be effective and inexpensive [26].

The goals of the surveillance system should be well defined, and they should contain the planned usages of the program. The purposes of any public surveillance system, which are more appropriate to dengue, are to:

- notice epidemics rapidly for quick interference;
- measure the burden of disease;
- give data related to the assessment of outcome impact;
- monitor trends;
- assess the efficiency and efficacy of the dengue control and prevention program; and
- help in planning and allocating resources [71, 72].

The surveillance system should encompass population, laboratory, and vector surveillance, and the observation of environmental hazard that lead to dengue epidemics [26]. Dengue cases have to be reported to the WHO under the International Health Regulations (2005) [73].

In planning for any dengue outbreak emergencies, there are three levels of response activity:

- Ongoing prevention: no dengue activity
- Response to sporadic cases: increased number of cases but not at epidemic level

- Outbreak response: evidence of epidemic activity [74]

In endemic countries, the main goal of the emergency response plan is to reduce the risk of dengue epidemics.

Immunity against a specific serotype of dengue fever is usually lifelong; however, prior infection with one serotype is considered a risk factor for a severe form of dengue upon subsequent infection with another serotype [75]. The development of a dengue vaccine has been under research for > 50 years [76]. However, there is a lack of understanding of the protective human immune responses that would provide long-lasting effects.

Several studies have been done in KSA on dengue fever. A case-control study done in Jeddah found that face-to-face health education significantly decreased the risk of dengue fever [77]. Moreover, the study showed that the presence of immobile water indoors (OR = 4.9), indoor larvae (OR = 2.2), nearby construction sites (OR = 2.2), and the older age of patients (OR = 1.2) were independent determinants of dengue infection (with $P < 0.01$). The author's recommend using health education for prevention of the infection [77]. Another study done in a large hospital in Jeddah described the characteristics of dengue fever patients who were admitted. In this study, 48.72% of the patients were seen in the summer seasons, with clinical presentations of fever (100%), headache (48.72%), myalgias (66.7%) and vomiting (25.64%). Rashes and positive tourniquet tests were rare. Thrombocytopenia (79.49%) and leucopenia (48.72%) were very common, and sometimes there were elevations of the patients' PTT (25.64%). There were no reported cases of death in this study [78].

Another study done in Jeddah showed that a seasonal pattern of dengue fever occurred during the first 6 months of the year. In addition, men (70.8%) and younger age-groups (67.3%)

were more likely to be affected [79]. A different study was done among females in Jeddah high schools to assess their knowledge, attitudes and practices relating to dengue fever, and it found deficiencies overall. [80]

5. METHODS

Data Source

Dengue fever is a notifiable disease in KSA; weekly and yearly aggregates (2008-2009) of dengue fever cases by gender, nationality, age and work were reported to VBDU department in Makkah. Since 2008, the dengue fever registry has been maintained electronically. Population data (i.e., nationality, age, gender) were obtained from the KSA Ministry of Economy and Planning, Central Department of Statistics and Information, which draws statistical information from censuses, field surveys, and statistical studies, in addition to extracting data from administrative records [81].

Statistical Analyses

We used secondary data and incidence rates calculated per 100,000 persons. Rates were analyzed over a 5-year period (2008 – 2012) using Poisson regression and classified as increasing, decreasing, or stable as determined by positive, negative or non-significant coefficients. Significance was determined at a 5% level using two-sided P values. Rates were compared using rate ration and 95% confidence intervals.

Ethics

This secondary data analysis (without any personal identifiers) did not meet the definition of Human Subjects Research, so it did not require Institutional Review Board approval.

6. RESULTS

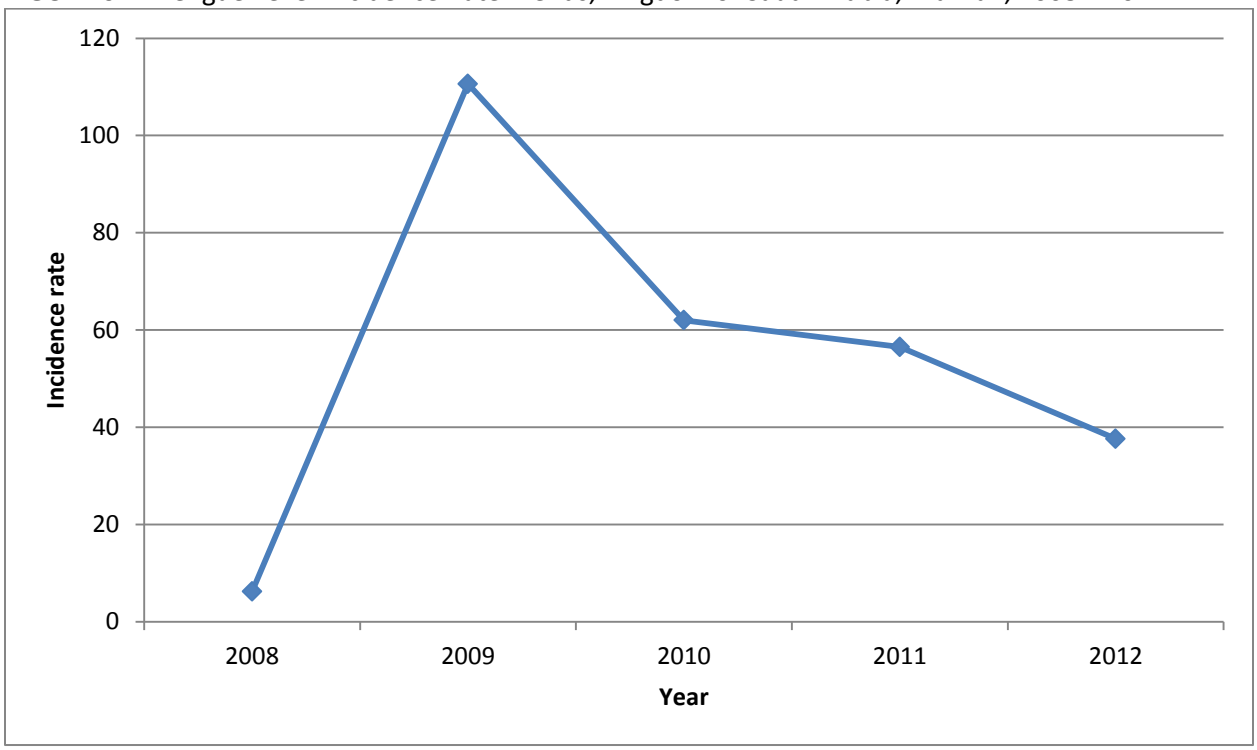
The incidence rate for dengue fever was lower in 2008 than in any of the other years that were studied (Table 6-1). The highest incidence rate occurred in 2009. This indicates that there was an outbreak of dengue fever in 2009. After 2009, the incidence rate started to gradually decrease again, and continued to do so from 2010 to 2012. The dengue fever incidence rate trends from 2008 to 2012 were as follows: it was low in 2008, then it increased significantly in 2009, and after that, it started to decrease gradually from 2010 to 2012 (Figure 6-1).

TABLE 6.1: Dengue Fever Incidence Rate per 100,000 Population and Number of Cases, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

Year	Rate (n)	95% CI
2008	**6.2 (95)**	5-7.5
2009	**110.6 (1697)**	105.4-115.9
2010	**62(951)**	58.1-66
2011	**56.5 (867)**	52.8-60.3
2012	**37.6(577)**	34.6-40.8

CI = confidence interval

FIGURE 6.1: Dengue Fever Incidence Rate Trends, Kingdom of Saudi Arabia, Makkah, 2008 – 2012



The number of dengue fever cases started to rise in January, peaking between April and May (Figure 6.2). There were more cases during spring, while the number of cases during summer and early winter (from January to December) was low.

Breaking down dengue fever rates by gender, males had an almost two-fold greater incidence rate in the KSA from 2008 to 2012 (Table 6.2 and Figure 6.3), assuming the population under surveillance included equal numbers of males and females. So, males were at significant risk of acquiring the dengue fever infection compared to females.

More cases of dengue fever occurred among Saudis than non-Saudis in the KSA from 2008 to 2012. More than 70% of all cases were among Saudis, and this is a significant percentage (Table 6.3) (Figure 6.4).

Regarding the affected age groups, there was an increase in the number of cases among those between the ages of 25 and 44 compared to other age group; that group had almost 50% of all cases. On the other hand, there were very few cases among those who were less than one year old. The number of cases started to decrease in those older than 45 years (Figure 6.5).

Aedes aegypti has a population density that varies throughout the year and from one year to another (Figure 6.6). In 2008, its population density peaked in January. In 2009, its density peaked in June. In 2010, it peaked in March. In 2011, it peaked in October, and in 2012, April.

FIGURE 6.2: Dengue Fever Reported Cases by Month, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

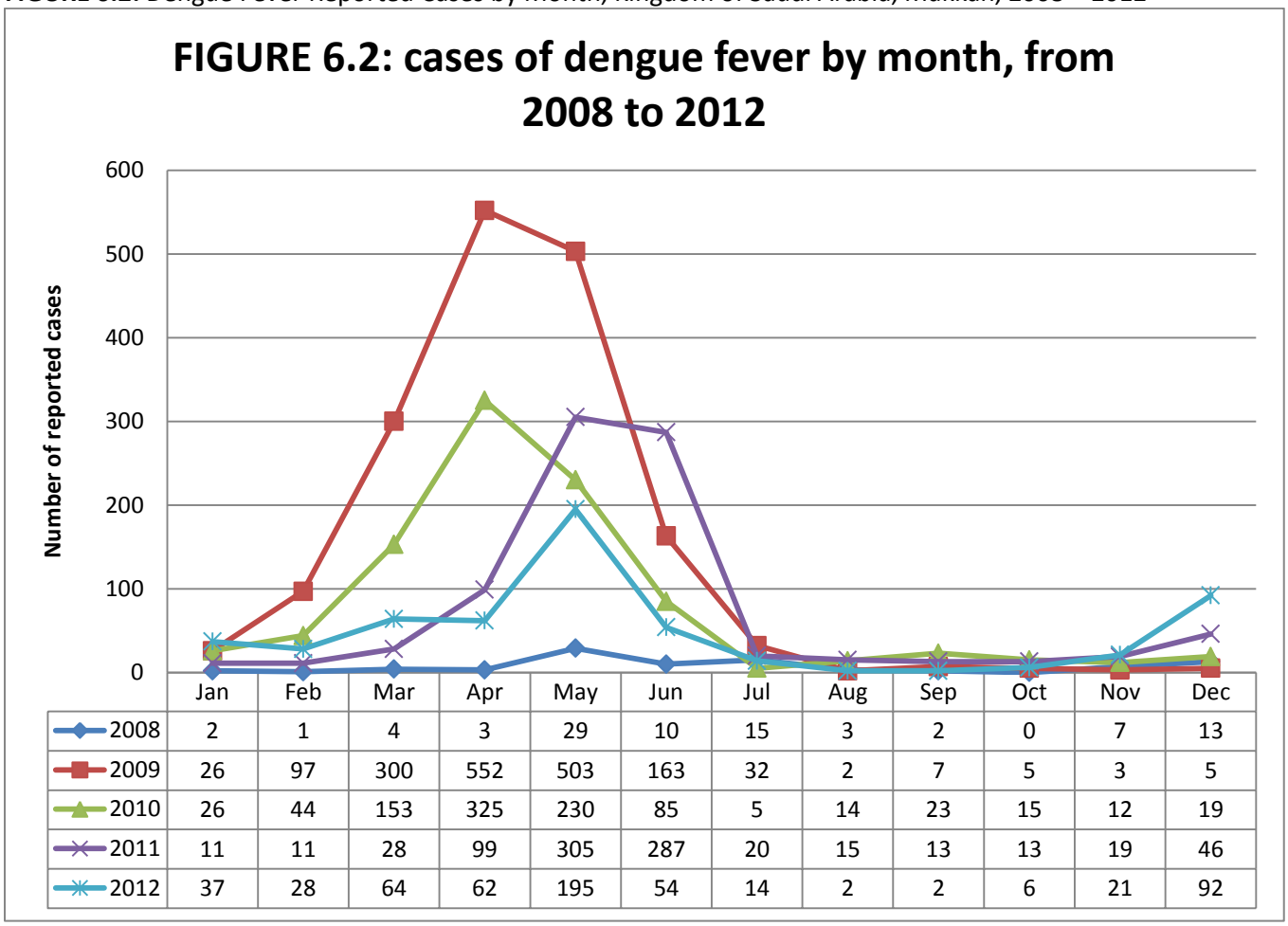


TABLE 6.2: Dengue Fever Incidence Rate per 100,000 Population and Number of Cases among Gender, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

Year	Male		Female	
	Rate (n)	95% CI	Rate (n)	95% CI
2008	*7.9(68)*	6.1-9.9	4(27)	2.7-5.8
2009	*148.3(1278)*	140.3-156.7	62.3(419)	56.5-68.4
2010	*79.9(663)*	71.2-83	42.8(288)	38.1-48
2011	*69.2(596)*	63.8-74.9	40.3(271)	35.7-45.3
2012	*50.2(433)*	45.7-55.1	21.4(144)	18.1-25.1

CI = confidence interval.

FIGURE 6.3: Dengue Fever Incidence Rate per 100,000 Population and Number of Cases among Gender, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

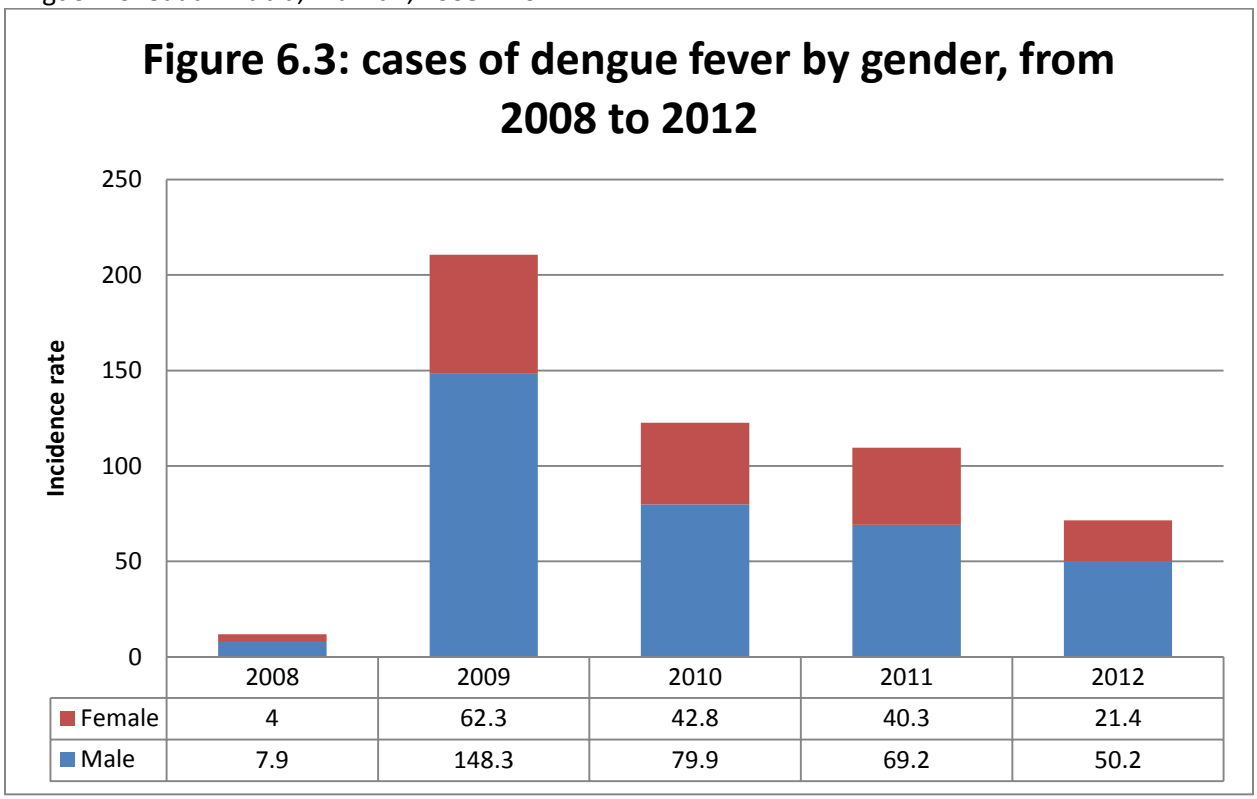


TABLE 6.3: Dengue Fever Incidence Rate per 100,000 Population and Number of Cases among Nationality, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

Year	Saudi		Non-Saudi	
	Rate (n)	95% CI	Rate (n)	95% CI
2008	*8.9(73)*	7-11.1	3.1(22)	2-4.6
2009	*146.8(1205)*	138.7-155.3	68.9(492)	63-75.2
2010	*87.6(719)*	81.4-94.2	32.5(232)	28.5-36.9
2011	*64.9(533)*	59.6-70.6	46.8(334)	42-52
2012	*43.4(356)*	39.1-48.1	31(221)	27.1-35.2

CI = confidence interval

FIGURE 6.4: Dengue Fever Incidence Rate per 100,000 Population and Number of Cases among Nationality, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

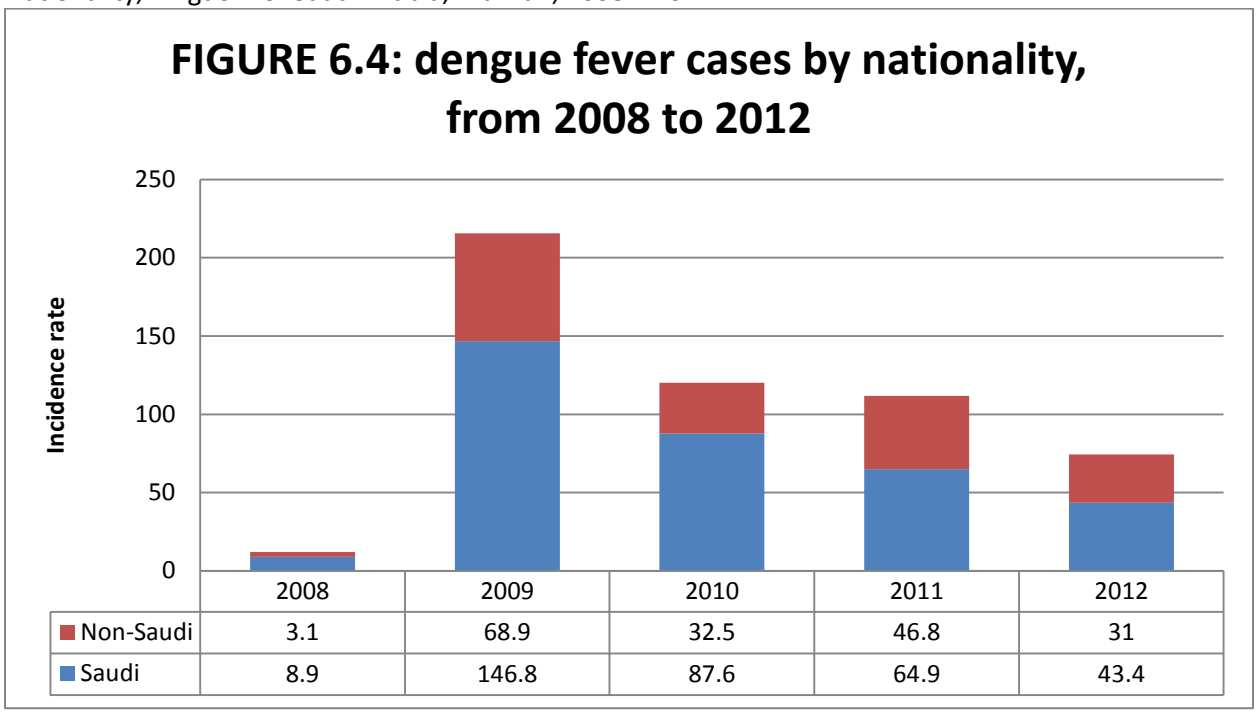


FIGURE 6.5: Number of Reported Cases of Dengue Fever by Age Group, Kingdom of Saudi Arabia, Makkah, 2008 – 2012

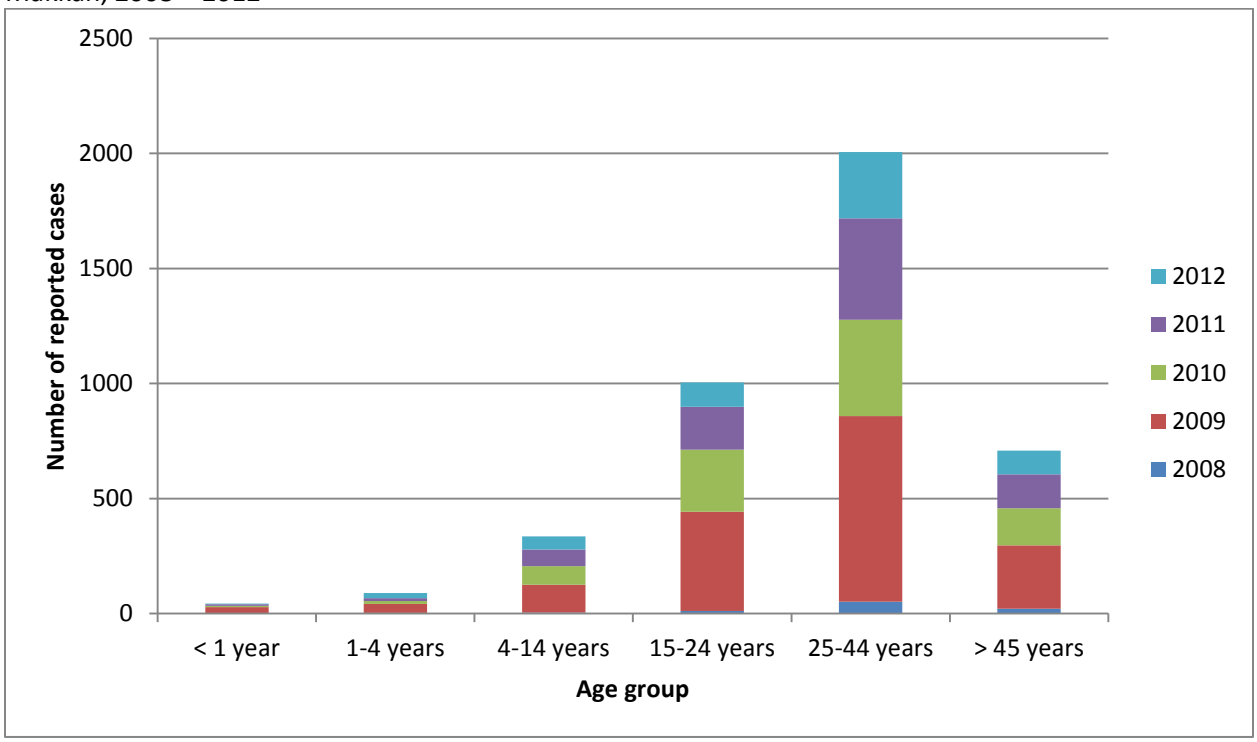
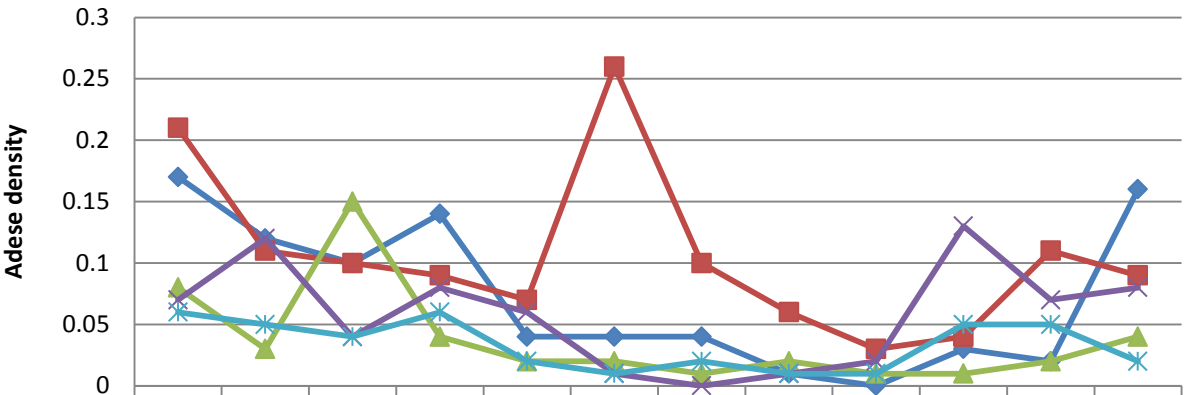


FIGURE 6.6: Aedes Density Each Month, Kingdom of Saudi Arabia, Makkah, 2008 – 2012



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2008	0.17	0.12	0.1	0.14	0.04	0.04	0.04	0.01	0	0.03	0.02	0.16
2009	0.21	0.11	0.1	0.09	0.07	0.26	0.1	0.06	0.03	0.04	0.11	0.09
2010	0.08	0.03	0.15	0.04	0.02	0.02	0.01	0.02	0.01	0.01	0.02	0.04
2011	0.07	0.12	0.04	0.08	0.06	0.01	0	0.01	0.02	0.13	0.07	0.08
2012	0.06	0.05	0.04	0.06	0.02	0.01	0.02	0.01	0.01	0.05	0.05	0.02

7. DISCUSSION

The incidence rate of dengue fever in Makkah is high. Although it started to decrease after 2009, it is still high. That makes Makkah an endemic city for dengue fever. The incidence rate in 2008 was 6.2 (CI 95% 5-7.5), considered high, though it was the lowest rate found from 2008 to 2012. An outbreak occurred in 2009 and the incidence spiked at 110.6 per 100,000 persons (95%CI=105.4-115.9); this was mainly due to an increase in *Aedes aegypti* activity during that year.

Increased mosquito activity was associated with huge construction projects that took place in Makkah when the government started to expand the city by adding large buildings. The open water containers at these construction sites provide a good environment for *Aedes aegypti* growth. As a result, the MOH increased its support of the VBDU by funding the recruitment of more health educators to provide door-to-door education. Moreover, communication between different government branches started to become more frequent. As a consequence, the incidence of dengue fever decreased gradually in the subsequent years. In 2010, it dropped to 62 (95%CI=58.1-66), in 2011, it was 56.5 (95%CI=52.8-60.3), and by 2012, it had fallen to 37.6 (95%CI=34.6-40.8). However, the incidence was still high, and more work needed to be done to reduce the incidence further. Also of note was that the incidence of dengue increased during late spring and early winter, even though evidence shows that high temperatures increase *Aedes aegypti* activity [27]. So, this area needs more research.

The incidence rate of dengue fever is almost twofold among men compared to women (Table 6-2) (assuming the population under the surveillance included approximately equal numbers of males and females). This is due to fact that men are mainly the ones who work

outdoors, and women, in addition to spending more time indoors, wear clothes that cover them for religious reasons.

We also found also that Saudis experienced almost twice the risk of getting dengue fever than non-Saudis (Table 6.3). This is due to the availability of treatment for Saudis as compared to non-Saudis. Health care in Saudi Arabia is free for Saudis. As a result, Saudis seek medical advice more often than non-Saudis, who must pay. In addition, the nature of the disease is self-limited, and most non-Saudis choose to wait it out rather than paying for a minor illness.

The number of dengue fever cases is high among the 24-44 age group; this case number started to decrease after the age of 44 years. The higher number of cases among those between 24-44 years old is to be expected because of their being outdoors more often than other age groups. Few cases occur among those < 1 year old.

There are limitations to our study. First, data entry for dengue fever cases at the VBDU doesn't follow a classification system. According to their protocol, they followed the old WHO classification scheme (1997)[53], but they do not use it in practice. So, they will label any case with a lab confirmation as dengue fever regardless of its severity. As a result, in the analysis, we didn't know the number of cases classified as DH or DSS.

Moreover, the surveillance data did not include the follow-up result for the patient. We need to know how many patients recovered without complications, how many patients recovered with complications, and how many patients died from this disease.

Another limitation was that our incidence rate was based on a KSA census that was taken in 2010, which is not as accurate as the yearly census. In addition, the national census doesn't provide the number of people by age group in Makkah city.

8. RECOMMENDATIONS

Dengue fever is endemic in Makkah city, with many outbreaks that can be missed easily, and it continues to be a significant health problem. As a result, I recommend the following to control the spread of the infection:

- Using the newer WHO dengue case classifications, revised in 2009 [60]
- Identifying the type of dengue infection (DF, DH, and DSS) instead of reporting cases only as dengue fever from lab confirmations
- Following cases of dengue infection after they have been reported to discover the outcomes (full recovery, recovery with complication, death)
- Differentiating those with primary infections from those with secondary infections
- Providing feedback to the management team in the hospitals immediately after the lab confirmation. Many doctors in the hospitals don't know the results of the lab.
- Engaging in more frequent door-to-door health education with the involvement of the community (who could teach one another at mosques and public gatherings)
- Monitoring all construction sites in Makkah and administering penalties to those who don't cover the water containers properly
- Including health education material about vector control in the school curriculum
- Involving the media, especially TV, to present health education material regarding dengue fever
- Initiating a consultation with the WHO regarding dengue activity needs under the International Health Regulations [73]

- Using statistical analysis for monitoring dengue infections to establish a more useful baseline measurement than the current one, which uses only the number of cases
- Initiating the monitoring and evaluation of the surveillance program soon as possible, and documenting the results
- Disseminating the results of the dengue infection surveillance data to the public to increase the awareness of the magnitude of the problem and encourage changes in their behavior towards vector control
- Ensuring that the VBDU follow the strategic approach to vector control promoted by the WHO, called Integrated Vector Management (IVM) [69]

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