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REVIEW

The epidemiology of Dengue fever in Saudi Arabia: A systematic review

Alaa Alhaeli, Salwa Bahkali, Anna Ali, Mowafa S. Househ, Ashraf A. El-Metwally*

College of Public Health and Health Informatics, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

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Summary Dengue fever (DF) is the most serious mosquito-borne viral disease worldwide. DF is an acute febrile illness caused by *Aedes aegypti* and *Aedes albopictus*, which are endemic in certain cities of Saudi Arabia, such as Jeddah and Makkah (Mecca). An online literature search was conducted using relevant keywords to retrieve DF studies conducted in Saudi Arabia. Forty-five articles were identified initially. After screening for exclusion and retrieving full texts, a total of 10 articles were used for this review. Four studies were cross-sectional, and three observed a seroprevalence ranging from 31.7% to 56.9%, either among clinically suspected cases or among patients visiting the hospital for other reasons. Evidence extracted from risk factors and distribution studies indicated that young males are commonly affected. Fever, vomiting, thrombocytopenia and leukopoenia were the common features of the three studies related to clinical presentation of DF. One cross-sectional study concerning an educational program for DF demonstrated that a positive family history of DF, literate mothers, and age over 17 years were the predictors of a high DF knowledge score. However, the paucity of large epidemiological studies limits the generalizability of such evidence. Future studies in Saudi Arabia should focus upon the expansion of DF to other cities in the Kingdom. Larger epidemiological studies are needed for estimating the true burden and incidence of DF in the Saudi population, as they are limited to seroprevalence among clinically suspected cases and hospital-based patients.

* Corresponding author at: Epidemiology and Biostatistics Department, College of Public Health and Health Informatics, King Saud Bin Abdulaziz University for Health Sciences, P.O. Box 22490, Riyadh 11426, Internal Mail Code 2350, Saudi Arabia. Tel.: +966 594800755.
E-mail address: ashraf.elmetwally@gmail.com (A.A. El-Metwally).

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Contents

Introduction

Dengue fever (DF) is a mosquito-borne viral illness with 100 million new cases occurring worldwide. DF is an acute febrile illness caused by *Aedes aegypti* and *Aedes albopictus* [1]. DF occurs primarily in tropical areas around the world affecting both children and adults [1]. The symptoms of DF are associated with hemorrhagic complications (DHF) or shock (DSS), as well as depression and fatigue [2]. There are several risk factors, as well, that can lead to DHF, including age, genetic disposition, and immune status. Transmission of the disease occurs primarily in tropical areas with high humidity and a hot climate. The humidity lengthens the mosquito's lifespan and shortens the time required for viral replication. The mosquito incubation period lasts between 3 and 14 days [2].

DF was first discovered in 1779 in Batavia and, a year later, a pandemic of DF occurred in Philadelphia, USA [3]. In 1998, another pandemic of DF occurred in 56 countries, where 1.2 million people were infected [4]. During the past 50 years, DF incidence has witnessed nearly a 30-fold increase. Today, there are approximately 100 countries in the Americas, South East Asia, the Eastern Mediterranean, the Western Pacific and Africa, where 50 million DF occur annually, out of which 22,000 deaths affect mostly children [5].

The spread of DF in traditionally DF-free countries, such as Pakistan, Saudi Arabia, Yemen, Sudan, and Madagascar, between 2000 and 2007 has been alarming. In Saudi Arabia, the first experience of virus isolation during a DF outbreak was in 1994 in Jeddah, where 289 confirmed cases were recorded [6]. The first documented case was caused by DENV-2. During the outbreak, DENV-2 and DENV-1 were isolated during a peak of cases in the summer and in the rainy season at the end of the year. In 1997, emergence of DF occurred with DENV-3 identified during the rainy season in Jeddah. The virus was not isolated in the next seven years until 2004 when DENV-1, DENV-2 and DENV-3 were isolated in Jeddah. During the same year (2004), the first outbreak in Makkah occurred with the isolated DENV-2 and DENV-3 [7]. The next outbreaks occurred in Jeddah in the winter seasons of 2005 and 2006 [8,9]. After another outbreak of DF occurred in 2006, the Saudi Preventive Department in the Ministry of Health (MOH) launched a comprehensive plan to control the disease [10]. In 2008, the first cases were reported from Al-Madinah with DENV-1 and DENV-2 isolated serotypes [11]. In 2009, the Saudi MOH reported a total of 3350 cases of DF in the Kingdom and estimated the case fatality rate to be 4.6 per thousand [12]. The reemergence of DF in Saudi Arabia can be explained by the growing levels of urbanization, international trade and travel [13].

There are currently no review articles summarizing the evidence of DF as it relates to the burden and knowledge of health determinants in Saudi Arabia. The present article summarizes studies on DF prevalence and risk factors that had been conducted in Saudi Arabia.

Methods

An electronic search was conducted by two independent researchers to identify articles in PubMed that met our inclusion criteria. Local journals were also reviewed, but no relevant articles were found for inclusion in the study. Keywords were used in the PubMed's advanced search, and they covered three categories: Disease of interest (Dengue), Epidemiological terms (Distribution or epidemiology or incidence, or odds, or pattern or prevalence or prognosis or risk or trend, or burden or knowledge)

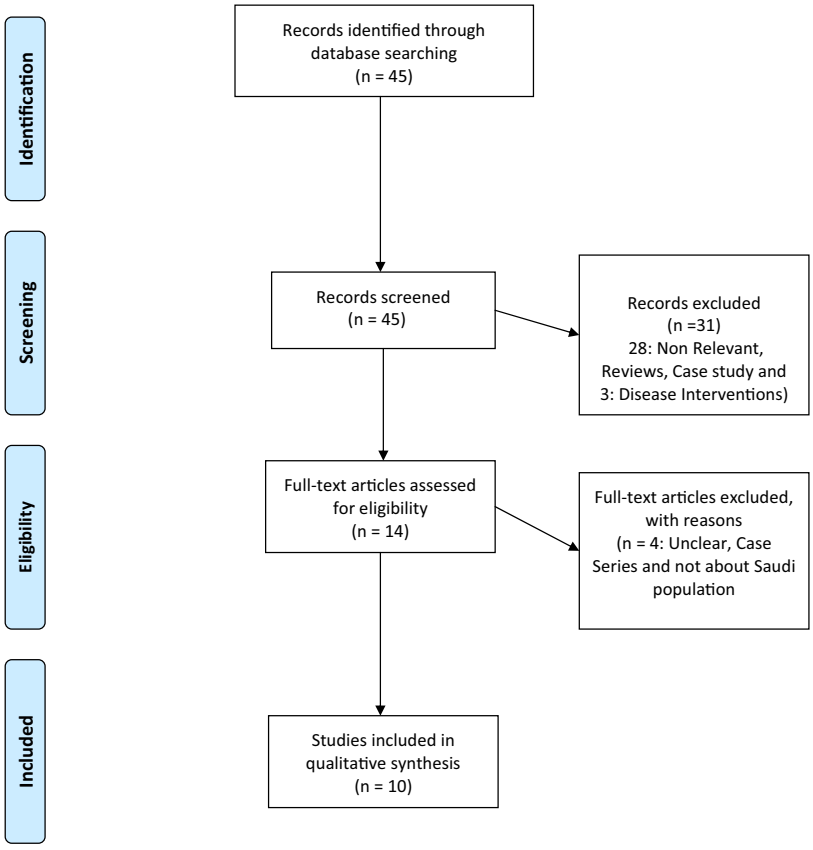

Figure 1 Flow chart of the systematic review.
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and Geographical locations (Saudi, or a list of all major cities and region of the Kingdom). A Boolean phrase was used to link all three categories of keywords. Inclusion criteria were articles in the English language, epidemiological studies, dengue fever articles, and articles conducted in Saudi Arabia from 2006 to March 2014. Case reports, case series, and randomized clinical trials regarding treatment modalities were excluded, as well as articles regarding laboratory diagnosis of dengue fever.

A total of 45 articles met the inclusion criteria. Titles were reviewed to scan for the exclusion criteria, as described above. Twenty-eight articles were either not relevant, review articles or case reports and were therefore excluded. Three more articles concerned disease intervention and were also excluded. A total of 14 articles remained, and their abstracts were later retrieved for careful evaluation. Four more articles were excluded for the following reasons: one due to unclear purpose and three because they were either case series or were not focused on the Saudi population. As a result, ten articles were finally included in the review. Based on their information, the studies were divided into prevalence studies, risk factors studies, laboratory and clinical findings or educational studies to cover all aspects related to DF. This review also enabled us to highlight the future research needs related to DF in Saudi Arabia. A flow chart of our research strategy can be seen in Fig. 1.

Results

Prevalence studies

Four cross-sectional questionnaire-based studies conducted in different regions gave the prevalence of DF in the Saudi population. A study conducted in 2011 that enrolled 1026 soldiers in 5 administrative units in Jazan found a low seroprevalence of DF of only 0.1% [14]. Another study was conducted in 2013 in 30 hospitals and 387 primary health care centers in Jizan and Aseer, two cities in southern Saudi Arabia. This study detected 31.7% positive cases of dengue virus IGg among 965 random patients attending the outpatient clinics for any reason [15].

Risk factors from studies of infections

A study by Khormi et al. in 2012 used a combination of environmental and socioeconomic variables to model areas at risk for DF. These variables included clinically confirmed DF cases, mosquito counts, population density in inhabited areas, total population per district, water access, neighborhood quality, and the spatio-temporal risk of DF based on the average weekly frequency of DF incidence. Increased mean population density was a significant factor in determining the risk for DF [16].

A case—control study conducted in 2012 reported the following significant risk factors for DF: presence of stagnant water in indoor drainage holes, indoor larvae, nearby construction sites, and old age [18].

Another study conducted in 2013 documented an increased incidence of DF in the first half of that year. The significant risk factor was being a male between 15 and 29 years of age [19]. The same two factors were also reported by two other studies, one conducted in 2006 and another in 2008 [7,20]. The south and central-north regions were the most infected areas [19]. Lack of electricity and having water basins in the house were identified as significant risk factors for DF in the 2006 study [20].

Laboratory confirmed cases and clinical profile studies

Three studies conducted between 2006 and 2010 reported clinical profiles for DF. Common symptoms in all these studies were fever, headache, myalgia and vomiting [7,20,21]. A study completed in 2006 documented the demographic, clinical and laboratory profile of all patients diagnosed with DF admitted to King Abdul Aziz Hospital & Oncology Center in Jeddah, Saudi Arabia, from May 2004 to April 2005. Among the 80 patients suspected of DF and Dengue Hemorrhagic Fever, 48.75% had the disease [20]. Khan et al., in 2008, described the clinical profile of patients with DF hospitalized at a single center during the first outbreak in Makkah, Saudi Arabia, from April to July 2004. The study reported a seroprevalence of 56.25% among the 160 patients suspected of DF [7]. Khan et al. reported malaise, musculoskeletal pain and abdominal pain as common factors for DF [7]. Rash, hemorrhagic manifestations and a positive tourniquet test were relatively uncommon in the study conducted between 2006 and 2010 [7,20,21]. The main hematological abnormalities were thrombocytopenia and leukopenia in all three studies [7,20,21]. However, Khan et al. documented that serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated in most patients [7].

Educational study

In 2009, a study was conducted on female high school students to assess their knowledge of DF. The study showed that the most common sources of DF information were street advertisements and the media (including newspapers and television) while primary healthcare centers were the least common source of information. Inadequate DF knowledge was observed among the majority of the sampled population. A high DF knowledge score was predicted by positive family history of DF, high level of maternal education and increased student age. The knowledge of the students was improved with education [22].

Discussion

Through this review, we highlighted that prevalence studies were severely lacking in Saudi Arabia in comparison with other countries. This study does not reflect DF prevalences at the population level, as DF is usually a self-limited flu-like illness and asymptomatic in 80% of infants and children. Three studies found prevalence ranging from 31.7% to 56.9% among clinically suspected patients [7,15,20], and one study determined an unexpected prevalence of 0.1% [14]. This result may be observed because the researcher examined soldiers from different provinces in the Kingdom, while DF is endemic only in certain cities in Saudi Arabia (Jeddah, Makkah, Madinah and Jizan). Another issue is that although DF prevalence has been investigated in four cities (Jeddah, Makkah, Jizan and Aseer), such results cannot be extrapolated to other cities due to socioeconomic differences in the population, which could be a risk factor. For example, several outbreaks of DF have been reported from Jeddah and Makkah. These cities are the sites of both the annual pilgrimage (Hajj) and the minor pilgrimage (Umrah), which are performed by nearly three million Muslims from all over the world. Second, even more visitors come to Jeddah during the summer time. Third, these pilgrimages occur during the rainy season. Fourth, more humidity and high temperatures may help exacerbate the situation [16,17], making Makkah and Jeddah more susceptible to infectious diseases [7]. Some sporadic cases in Jizan have been described as due to the nature of the city; Jizan is relatively flat and located at sea level; hence, the likelihood of

Table 1 Studies conducted in different region of Saudi Arab related to DF.

Author, year, reference	Regions/cities	Sample size	Study design	Main findings
Prevalence studies and risk factors studies				
Memish et al. (2011) [14]	Jazan	Serological evaluation of 1,026 soldiers	Cross-sectional	Low sero-prevalence of DF[1] (0.1%).
Al-Azraqi et al. (2013) [15]	Jizan and Aseer cities	965 random sample of patients attending the outpatients' clinics of for any reasons	Cross-sectional	31.7% positive cases. Risk factors were male gender and younger age (15—29 years), lack of electricity and having water basins in the house.
Khormi and Kumar (2012) [16]	Jeddah	Annual population data for 111 district was obtained from the Central Department of Statistics and Information	Cross-sectional	Factors model of DF[a] risk (clinically confirmed DF cases, mosquito counts, population density in inhabited areas, total population per district, water access, neighborhood quality and the spatio-temporal risk of DF) 15% = high risk, 22% = medium risk, 16% = low risk and 46% = very low risk.
Khormi and Kumar (2012) [17]	Jeddah	111 districts	Cross-sectional	Knowledge of appropriate temporal and spatial scales can provide an opportunity to specify the health burden of DF[a].
Kholedi et al. (2012) [18]	Jeddah	129 lab confirmed cases and 240 controls	Case—control study	Risk factors were: stagnant water in indoor drainage holes, indoor larvae, construction sites and older age ($p < 0.01$). Face to face health education significantly decreased the risk of dengue fever.
Alzahrani et al. (2013) [19]	Jeddah	2288 dengue cases	Cross-sectional	Risk factors were male gender and younger age 15—29 years.
Laboratory confirmed cases and clinical findings				
Ayyub et al. (2006) [20]	Jeddah	80 patients with a suspected diagnosis of DF and Dengue Hemorrhagic Fever	Cross-sectional	Male to female ratio 3.3:1 Mean age at infection = 27years. summer months symptoms = fever, headache, myalgia and vomiting. Main hematological abnormalities = thrombocytopenia and leucopenia.
Khan et al. (2008) [7]	Makkah	160 clinically suspected patients	Cross-sectional	91 = laboratory confirmed dengue. Young adults, median age = 26 years, male:female ratio = 1.5:1. Symptoms = fever, malaise, musculoskeletal pain, headache, nausea, vomiting and abdominal pain. Laboratory investigations = leucopenia and thrombocytopenia, raised serum ALT[b] and AST[c].

Table 1 (*Continued*)

Author, year, reference	Regions/cities	Sample size	Study design	Main findings
Ahmed MM (2010) [21]	Jeddah	147 patients infected with dengue	Cross-sectional	Clinical presentations = fever, vomiting and abdominal pain. Hematological abnormalities = thrombocytopenia, leucopoenia and a WBC of <4.0 × 109/L.
Educational study				
Ibrahim et al. (2009) [22]	Jeddah	Twenty female high schools	Cross-sectional	Common source knowledge = street advertisements and media (including newspapers and television). Inadequate DF knowledge = majority of the sampled population.

[a] DF: Dengue fever.
[b] ALT: serum alanine aminotransferase.
[c] AST: aspartate aminotransferase.

the formation of small stagnant water collections is high following the rainfall [15]. A systematic review about the association between climatic conditions and dengue transmission, which included 16 studies published between January 1991 and October 2012, describes similar results. Most studies in the review found that dengue transmission is highly sensitive to climatic conditions, especially temperature, rainfalls and relative humidity [23]. Another study in Brazil also confirmed that the risk of dengue transmission increased with high temperatures [24].

Four studies have shown that male gender and young age are significant risk factors for DF [7,15,19,20]. These findings are inconsistent with three studies performed in Australia, France and Mexico, which documented that DF was more common among the female population. However, they did not find statistically significant relationships [23,25,26].

Two clinical studies found that fever, nausea, vomiting, headache, musculo-skeletal pain, and abdominal pain were common clinical symptoms [17,18]. A similar study in Pakistan found that abdominal pain, nausea, epistaxis and rash were the most frequent clinical symptoms ($p < 0.05$) [27]. Such results are in line with a study in Bangladesh where headache and arthralgia were the most common symptoms [28]. Thrombocytopenia, leukopoenia, high ALT and AST levels and a WBC of less than 4.0 × 109/L were the common findings of laboratory investigations of DF (Table 1). A study conducted in 2014 found the common lab presentations of DF were thrombocytopenia (96%), abdominal pain (71%), and vomiting (59%), with rash ($p < 0.01$) and anemia ($p < 0.01$) being statistically significant findings [28]. Furthermore, another study conducted during the clinical course of DF in Czech workers returning from a job in the Maldives, found fever, headache, muscle and joint pain, and rash as common symptoms. Typical laboratory findings in the study were leukocytopenia, thrombocytopenia and elevated aminotransferase activity [29].

An interventional study showed significant improvement in knowledge, attitudes and practices related to DF after implementing an educational program (Table 1). These results concur with those of a study conducted in Peru where a mobile phone educational program on dengue prevention was implemented. This study found that repeated exposure to health information helped control the household risk factors for DF. The study also reported marginally significant effects of the program on self-reported dengue symptoms [30].

There are several limitations to this review. First, the articles were limited to English. However, most, if not all, studies conducted by research institutes and universities in the Arab world are in English. Second, although PubMed and local journals were also searched, there is still the possibility that some articles may have been missed. Efforts were made to reduce the chance of overlooking an article by having two researchers search both PubMed and local journals.

Conclusions

Through this review, we conclude that DF is prevalent in Saudi Arabia. Thus, strong and effective

health education programs regarding DF risk factors are recommended to help prevent DF. However, the paucity of large epidemiological studies limits generalizability of such evidence. Future studies in Saudi Arabia should focus on the expansion of DF to other cities in the Kingdom. Larger epidemiological studies are needed for estimating the true burden and incidence of DF in the Saudi population. Currently, there are few epidemiological studies about DF, and these studies are limited to seroprevalence among clinically suspected cases and among hospital-based patients.

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Competing interests

None declared.

Ethical approval

Not required.

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