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Dengue fever in Saudi Arabia: A review of environmental and population factors impacting emergence and spread

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ABSTRACT

Dengue fever (DF) is the most important mosquito-transmitted viral disease causing a large economic and disease burden in many parts of the world. Most DF research focuses on Latin America and Asia, where burdens are highest. There is a critical need for studies in other regions where DF is an important public health problem but less well-characterized and can differ, such as the Middle East. The first documented case of DF in Saudi Arabia occurred in 1993. After a decade of sporadic outbreaks, the disease was declared endemic in 2004 and this designation persists. Climate, sociodemographic factors, and increasing urbanization impact the spread of DF in Saudi Arabia, as in other areas. However, DF transmission in Saudi Arabia is also affected by several unique factors, including large numbers of migrant workers and religious pilgrims from other dengue endemic areas across the Middle East, North Africa, and Asia. Important knowledge gaps relate to the role of climatic factors as drivers of DF in Saudi Arabia and the role of foreign workers and pilgrims in the original and continuous importation of dengue virus. Filling these gaps would improve health system preparedness.

1. Introduction

Dengue fever (DF) is a potentially life-threatening viral disease transmitted by *Aedes* mosquitoes [1]. The range of mosquito vectors and the virus has expanded geographically in recent decades, resulting in endemic disease in 128 countries. The World Health Organization estimates there are 96 million symptomatic cases each year [2,3]. However, the total burden of disease, including asymptomatic carriers, may be up to 4 times greater [1,3,4]. Even these figures may be underestimates because of under-reporting, particularly in Africa [5]. Most DF research focuses on Latin America and Asia, where burdens are highest [6]. There is a critical need for studies in other regions where DF is an important public health problem but less well-characterized and where DF epidemiology may differ, such as in the Middle East.

Saudi Arabia has one of the largest DF burdens in the Middle East. DF emerged in Saudi Arabia in the 1990s. In November 1993, a male patient visited a health clinic in Jeddah, Saudi Arabia complaining of fever, hemorrhagic signs, and non-specific symptoms. The patient died a few weeks later from hepato-renal failure, initially believed to result from viral hepatitis. Further investigation in collaboration with the Yale arbovirus research unit revealed that the patient had been infected with dengue virus (DENV). This case was the first isolation of DENV in Saudi Arabia. By February 1994 a surveillance system was established; it recorded nearly 300 cases of DF in Jeddah that year [7]. Over the next several years small outbreaks of no more than 15 cases were reported in Jeddah [8]. Between 2004 and 2015 significantly larger outbreaks occurred, primarily during the rainy season, and reached beyond Jeddah into the nearby cities of Makkah, Al-Madinah, Jizan, and Najran, leading the Saudi Ministry of Health to declare the western region of Saudi Arabia endemic for DF [9]. In 2015, the incidence rate was 13.68 per 100,000 person-years [10] (for comparison, incidence rates range from 15 to 130 per 100,000 person-years in most Latin American countries [11]).

In this review we describe the history of DF in Saudi Arabia and explore environmental and population factors that may have contributed to its emergence and continued spread. To provide relevant

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context, we first briefly describe DF biology and review major epidemiological findings globally, and then describe DF in the Middle East and North Africa region. This background is useful for those with less topical knowledge of DF; it also allows us to highlight distinct aspects of DF in Saudi Arabia and to note likely social and ecological determinants of its epidemiology there.

1.1. Dengue fever biology and clinical features

DENV is a group of closely-related RNA viruses in the flavivirus family [12]. There are four globally prevalent serotypes (DENV 1–4), with substantial genotypic variation within each serotype. A fifth serotype was recently identified but little is known about it [2]. Phylogenetic studies have demonstrated clustering of genotypes geographically as well as associations between genotype and disease severity [13,14].

The virus is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. The vectors breed in small bodies of stagnant water, particularly in water storage containers around homes [2]. While both species can share habitats, *Ae. aegypti* are generally more common inside homes (both as adults and larvae) and in highly urban areas, and *Ae. albopictus* are more common outside homes and in suburban or rural areas [15]. Female mosquitoes typically require a bloodmeal to obtain the protein needed to lay their eggs. After a mosquito ingests the virus in a bloodmeal from an infected host, the virus replicates in the mosquito midgut and migrates to the salivary glands where it can be transmitted to a new host during the next bite [1]. This process takes 1–3 weeks, and is faster at warmer temperatures [16]. Both species are primarily day biters but *Ae. aegypti* can also bite at night if artificial lighting is strong enough [17].

The clinical presentation of DENV infection varies widely. Most cases are asymptomatic. Symptomatic cases typically present with mild, non-specific symptoms: fever, nausea, rash, headache, and myalgia. Recovered patients retain antibodies to DENV and are protected from reinfection with the same serotype. However, individuals are not protected from secondary infection with a different serotype; these cases have a higher probability of developing severe disease in the form of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (a process known as antibody-dependent enhancement) [18,19]. Case fatality from DHF can reach 15%, but early detection and treatment can decrease this number to around 1% [1]. There are no specific therapies for dengue infection. The main approach is symptomatic treatment and supportive care for patients with severe symptoms. Early detection and management is key to preventing mortality from DHF and DSS [1,20].

The symptoms of DF are similar to those of a variety of viral hemorrhaging fevers and other diseases, including Chikungunya, Zika virus disease, West Nile virus disease, and yellow fever. Consequently, there is a high rate of misdiagnosis with over- and under-reporting, depending on awareness of health care professionals and other factors. Additionally, changes in case definitions, health care availability, diagnostic capabilities, and subclinical cases influence the number of cases reported [16,21]. For instance, researchers estimate that only 1 of every 23 cases in Singapore is reported to health authorities [22]. ELISA testing is the most common method to detect current (IgM antibodies) and previous (IgG antibodies) infection. Although the test is relatively inexpensive and simple, it often produces false-positive results due to cross-reactivity from infection with other flaviviruses (e.g., West Nile virus and yellow fever) [22–24].

There is currently one dengue vaccine on the market (Dengvaxia, live attenuated) and several others in Phase II and III clinical trials. The current vaccine targets all four circulating serotypes, with an efficacy around 60% [25,26]. The World Health Organization recommends only countries with more than 70% seroprevalence implement the vaccine in adults and children > 9 years of age, because it can cause antibody-dependent enhancement and higher rates of severe DF [25,26]. A recent review by the Strategic Advisory Group of Experts on Immunization published in April 2018 has further suggested a "pre-vaccination screening strategy" be implemented in which only individuals that were found to be sero-positive anti-DENV IgG be vaccinated [27].

1.2. Global DF transmission

The dramatic increase in DF worldwide over the past 50 years has been attributed to many factors. These include increased urbanization, local and foreign population migration, erratic water supplies, and geographically expanding vector populations associated with a changing climate [6,16]. *Ae. aegypti* primarily breeds in artificial containers and thrives in highly urban environments. The presence of stagnant water in indoor and outdoor water basins, and areas where rainwater may have collected, such as old tires and construction sites, play a primary role in the spread of mosquito-borne illness as these sites provide an optimal environment for mosquito oviposition [28,29]. Human behavioral responses to water shortages also influence vector breeding habitat. In areas without reliable water supplies, and during periods of drought people tend to store water in or around homes [30,31]. Accordingly, having an interrupted water supply was associated with DF in Cuba, and Brazil and with other mosquito-borne illnesses in India [28]. These water storage behaviors may increase in some regions with increased warming and decreased rainfall as the climate changes further [29].

Transmission of mosquito-borne disease, including DF, is highly sensitive to temperature, rainfall and humidity [9,16,29,31,32]. Temperature influences the physiology and behavior of mosquito vectors and development of the virus [16,33,34]. Mechanistic models based on these traits predict that transmission should peak at 29 °C for dengue in *Ae. aegypti* and 26 °C for dengue in *Ae. albopictus* [33]. On the other hand, statistical models found a wide range of results quantifying this relationship. In Thailand, observations showed DF transmission peaked at temperatures ≥ 30 °C, while research in Taiwan demonstrated that months with an average temperature > 18 °C had higher rates of DF. Vezzani et al., 2004 contend that average temperatures higher than 20.8 °C are most suitable for *Ae. aegypti* population growth [29]. Seasonality of DF is thought to stem in part from seasonal precipitation as rainfall provides pockets of stagnant water around human dwellings. Although humid weather conditions generally coincide with rainfall, often ambient humidity itself is enough to prevent desiccation of the mosquito ova. Hales et al. found that average annual vapor pressure was the strongest predictor of DF distribution [35]. A study conducted in Taiwan, further asserted that favorable weather conditions can help imported cases of DF become local epidemics [36].

In many locations, DF incidence is associated with vegetation indices, tree cover, and land cover, as these habitat characteristics impact the size of vector populations. Adult *Ae. aegypti* are more likely to be present in areas with built structures and medium-height trees [16]. Microclimates are created by interactions of rainfall, temperature, and humidity with land cover, result in heterogeneity across an urban area in locations suitable for *Aedes* mosquitoes [16].

Because there is no effective treatment for DF and the vaccine cannot be used in many locations, DF prevention strategies have centered around vector control. Of note, *Ae. aegypti* eggs are resistant to desiccation and can survive long periods of drought, making control of this species difficult [34]. The primary control methods are insecticide use via indoor residual spraying and skin repellants [37]. However, these methods are often ineffective or unsustainable in many settings. Additionally, although these methods can reduce mosquito indicators, there is little evidence they affect disease incidence [2,25]. Increasing vector resistance and environmental contamination further complicate the use of insecticides [37]. A systematic review of vector control and DF prevention concluded that data for intervention program evaluation was sorely lacking globally [2].

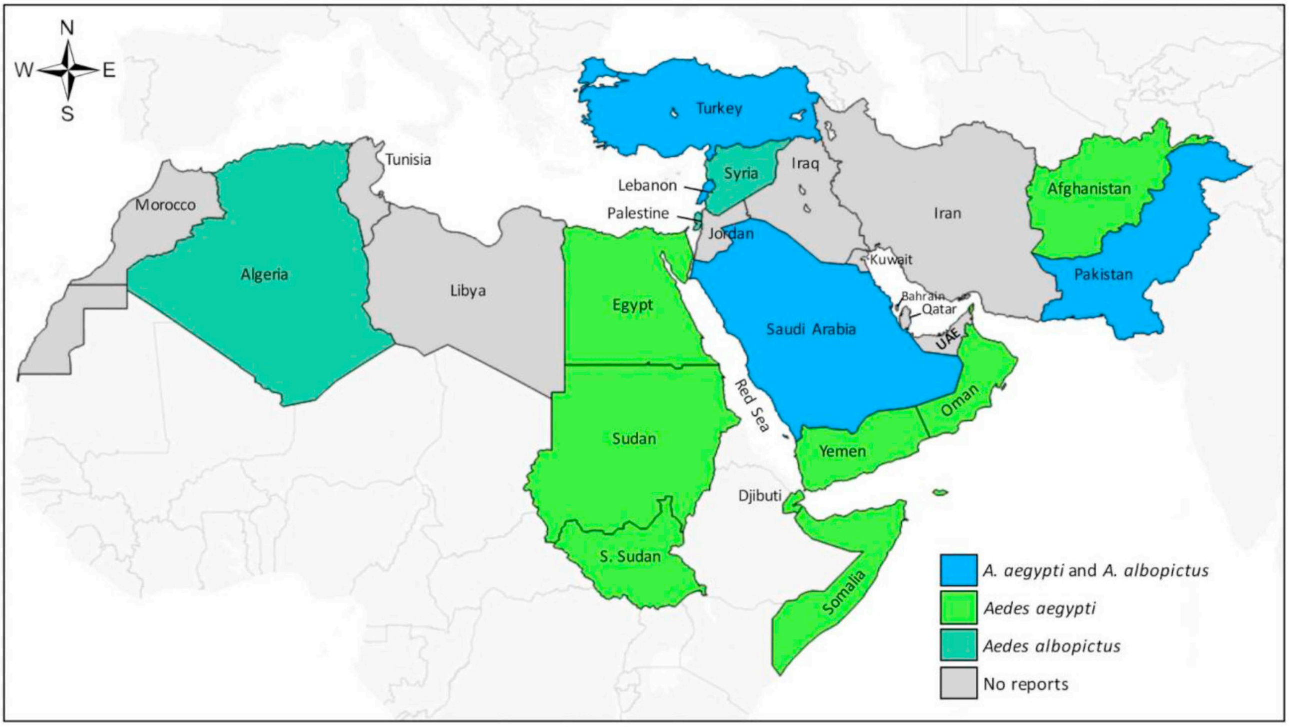

Fig. 1. Distribution of *Ae. aegypti* and *Ae. albopictus* mosquitoes in the MENA region [38]. (Source: Reprinted from Humphrey et al., 2016 under the terms for the Creative Commons Attribution License.).

2. DF in the Middle East and North Africa region

There are historical references of dengue-like illness in the Arabian Peninsula dating back to the 19th and early 20th centuries [14]. After decades without reports of DF, the disease recently reappeared in the Middle East and North Africa (MENA) region, including the emergence of DF in Saudi Arabia in the early 1990s and a large outbreak in Egypt in 2015. However, regional DF epidemiology remains poorly characterized. Inadequate medical and vector surveillance and poor diagnostic capacity limit DENV detection in many MENA countries, resulting in delayed outbreak recognition and sparse data for estimating disease burden and infection rates.

Ae. aegypti and *Ae. albopictus* are reported in eleven and seven of the twenty-four nations in the MENA region, respectively (Fig. 1). Only seven MENA countries have no reports of either species (and consequently no reported cases of DF): Bahrain, Iran, Iraq, Jordan, Kuwait, Qatar, and United Arab Emirates. It is worth noting that these countries border or are in close proximity to Saudi Arabia, and therefore may be vulnerable to invasion by the mosquito vectors and the subsequent introduction of the disease. Currently, countries in the Red Sea region (Djibouti, Egypt, Sudan, Saudi Arabia, Yemen, and Somalia) and Pakistan have the highest seroprevalence of DF within the MENA region [38] (Fig. 2). DENV 1–3 have been reported in the Red Sea countries; DENV-4 has only been reported in Pakistan [38] and very recently in Saudi Arabia [39].

Many ecological and social factors are associated with the spread of mosquito-borne diseases in the region. Heavy rainfall was linked to DF outbreaks in Sudan, Djibouti, and Yemen [38]. Increasing urbanization provides ideal habitat for *Ae. aegypti* populations. Additionally, armed conflict and economic turmoil in countries such as Iraq, Syria, and Yemen render these areas vulnerable to vector-borne diseases while further diminishing the capacity for surveillance and response [38]. Inter-regional population movement increases the risk of disease importations, particularly during the annual religious pilgrimages of Hajj and Umrah. Lastly, heavy intra-regional commerce in the Red Sea region further drives DENV serotype mixing and transmission, as evidenced by multiple DENV outbreaks occurring in port cities in Djibouti, Saudi Arabia, Sudan, and Yemen [38].

3. DF in Saudi Arabia

3.1. Overview of Saudi Arabia; climate, geography, and population

Saudi Arabia consists primarily of a harsh desert landscape, with sand dunes, gravel plains, and salt flats interspersed with few lakes or streams. The climate is extremely arid: rainfall is infrequent in most of the country, with average precipitation around 100 mm a year [40,41], which generally occurs during the rainy season in March and April [42]. Inland mean temperatures vary from45 °C in the summer to just above 0 °C in the winter; during the short, more mild spring and autumn seasons, mean temperatures are around 29 °C. The coastal areas maintain a more consistent climate, with high humidity and a constant mean temperature of 30–40 °C throughout the year [40,41]. Humidity also varies with the majority of the country experiencing a dry climate with nearly 0% humidity and up to 100% humidity in the coastal regions [40]. When DF began spreading in Saudi Arabia, some researchers argued that the low levels of precipitation would not favor efficient spread [8]. Yet, the country now struggles to control the increasing number of DF cases reported each year.

Saudi Arabia's population is approximately 30 million people. A third of these are foreign workers, including skilled workers and laborers [43]. The country hosts more than 5 million visitors each year for the Hajj and Umrah pilgrimages [44]. Eighty-five percent of Saudi Arabia's economy is dependent on the production and export of oil. This dependence on oil can cause financial instability, especially in recent years when extreme fluctuations in global oil prices have occurred [41,45]. Healthcare is available to all citizens, residents, and pilgrims, either by coverage in government hospitals and clinics or in private facilities covered by mandatory private health insurance [44].

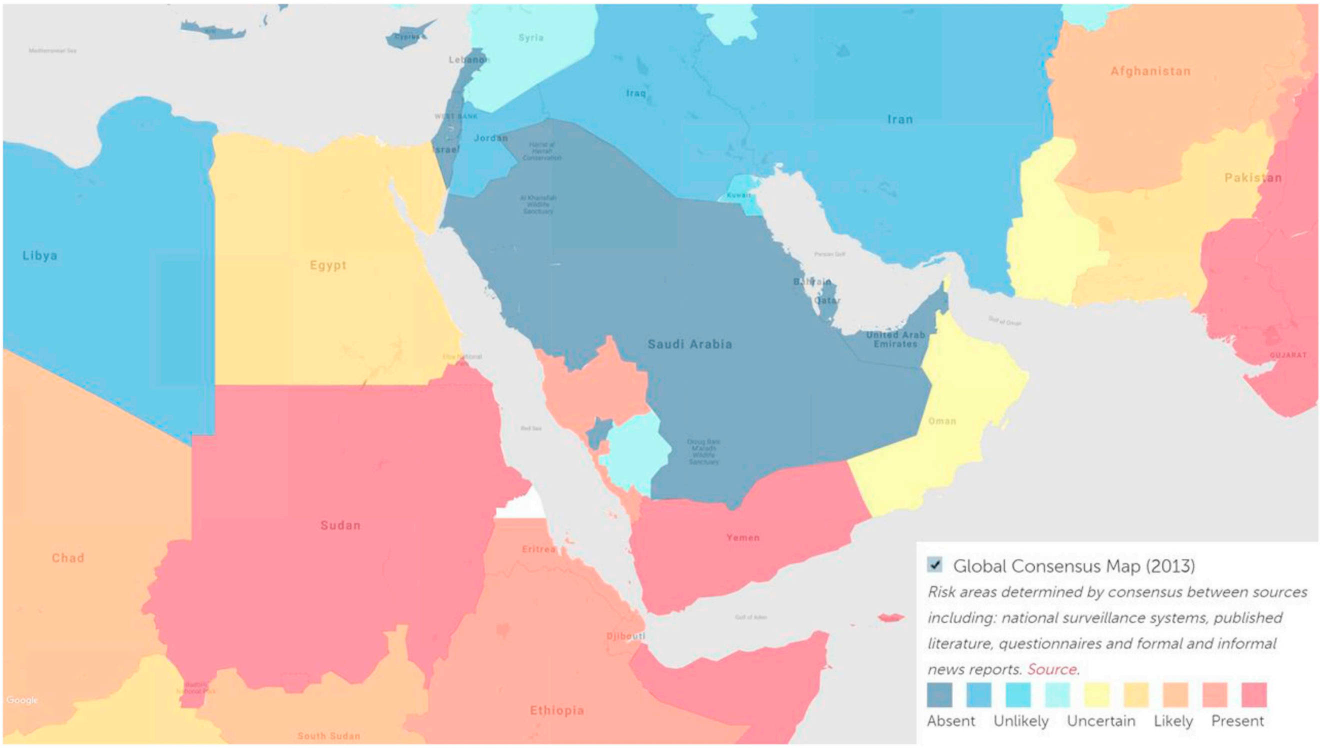

Fig. 2. Dengue fever prevalence in the MENA region from the CDC Dengue Map [66].

3.2. History and epidemiology of DF in Saudi Arabia

As noted, the first documented case of DF in Saudi Arabia occurred in Jeddah in late 1993 (Fig. 3) [7]. By March 1994, the Disease Control Division in Jeddah had initiated a dengue surveillance system that recorded 289 cases that year [28]. Over the following years, sporadic outbreaks occurred, each with no more than 15 cases per year [8]. Between 2004 and 2015, the disease spread to other cities in the region, leading the Saudi Ministry of Health to declare the region endemic for DF [9]. In 2015, DF incidence was 13.68 per 100,000 people [10]. The majority of cases are men between the ages of 15–30, which is believed to be a result of this group being more likely to work outdoors in occupations such as farming and shepherding. Additionally, due to cultural norms, women are often covered, reducing their exposure to mosquito bites [12,46].

Seroprevalence estimates vary widely (Table 1). At the high end, a 2016 study using randomly selected clinic visitors in Jeddah reported a seroprevalence rate of 47.8% [22]; on the low end, a 2010 national study of soldiers found a rate of 0.1% [9]. This large range may be due to variable risk for different demographic groups and geographic locations, as well as changes over time. Other research efforts quantifying the burden of disease in the country are limited, possibly due to lack of a consistent publicly available dataset.

DENV-2 is the predominant serotype in Saudi Arabia. DENV-1 and 3

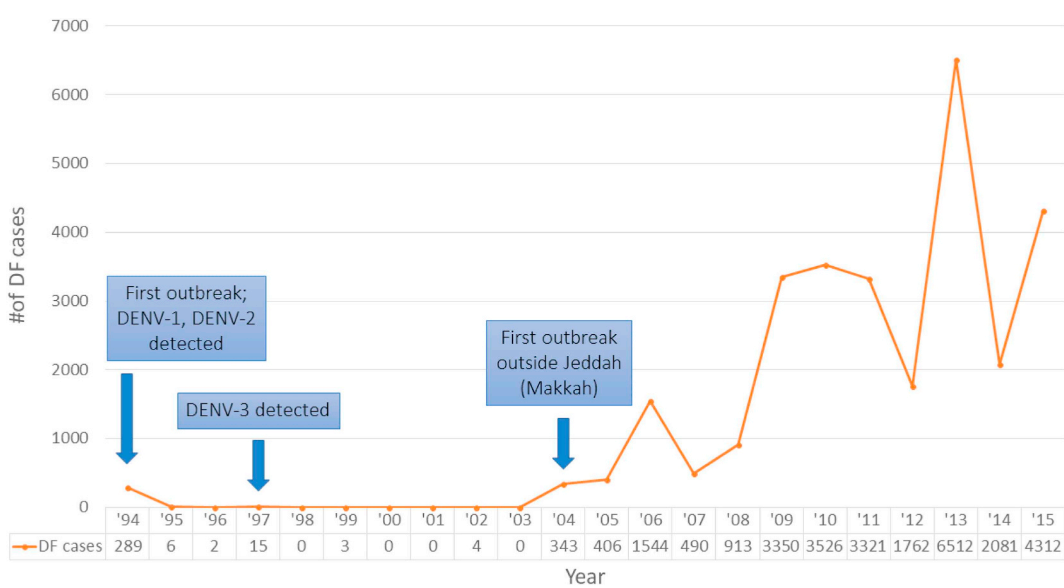

Fig. 3. Time series of DF incidence in Saudi Arabia (1994–2015) and dates of strain introductions.
*The presence of DENV-4 was reported in Saudi Arabia in 2017 (not shown) [39].

Table 1
Estimates of dengue fever seroprevalence in Saudi Arabia based on national or sub-national studies.

Study	Year	Location	Study sample	IgG prevalence
Memish et al. [47]	2010	National[a]	Military recruits (n = 1024)	0.1%
Al-Azraqi et al. [48]	2013	Jizan	Clinic visitors (n = 268)	26.5%
		Aseer	Clinic visitors (n = 697)	33.7%
Ashshi et al. [23]	2014	Makkah	Blood donors (n = 100)	7%
Jamjoom et al. [22]	2016	Jeddah	Clinic visitors (n = 1939)	47.8%
			Blood donors (n = 184)	37%
Ashshi et al. [49]	2017	Makkah	Blood donors (n = 910)	39%

[a] Note that the Memish et al. study reports data from a survey of military recruits from throughout the Kingdom of Saudi Arabia.

have also been circulating since 1994 and 1997, respectively [14]. A recent seroprevalence study using samples from Makkah in 2015–16 identified DENV-4 [39].

3.3. DF vectors and vector control in Saudi Arabia

Both vector species are present in Saudi Arabia and their proliferation is associated with DF transmission [29], particularly after the rainy season [34]. *Ae. aegypti* is considered the primary vector, but *Ae. albopictus* also contributes to the spread of the disease [2]. *Ae. Aegypti* has been increasing its geographical distribution in Saudi Arabia, and can be found in Jeddah, Makkah, Jizan, and Aseer [37,48] (Fig. 4). *Ae. aegypti* also recently emerged in Al-Madinah [37]. It is believed that traffic between Jeddah and Al-Madinah is responsible for importation of the mosquito, possibly through the transportation of tires [50]. In Jizan and Aseer, two diseases spread by other mosquitoes, malaria (spread by *Anopheles* species) and Rift Valley Fever (spread by a variety of *Culex* and *Aedes* species, are also endemic [48].

Regular application of mosquito adulticides and larvicides are the primary methods of disease prevention. For instance, the city of Makkah used approximately 17,975 L of adulticide and 3,899 L of larvicide in 2007 [37]. The application of these chemicals is generally delegated to private companies with little quality control or oversight to assure efficient application. There are reports that some companies use adulterated chemicals [37]. Both of these factors could promote vector resistance to insecticides [37]. Alternative vector control methods are being explored. In Aseer, *Gambusia affinis*, a fish that feeds on mosquito larvae, was introduced in ponds as an alternative method to control mosquito populations [48].

Fig. 4. Aedes *aegypti* distribution in Saudi Arabia. (Source: Data from the Ministry of Health) [67].

3.4. Weather factors influencing DF in Saudi Arabia

As elsewhere, DF in Saudi Arabia is seasonal. DF infection rates in Saudi Arabia peak primarily in the spring (March–May), and then again to a lesser extent in November and December [51]. This pattern was seen in all cities where DF outbreaks occurred, and is likely related to the seasonal abundance of the mosquito vectors in response to appropriate conditions of temperature, precipitation, and humidity [52]. In Makkah, *Aedes* larvae sampled from water containers reached a peak between January and March during the “wet season” then gradually decreased from April to September [29]. In Al-Madinah the number of trapped female Ae. *aegypti* in particular peaked from March to May [50]. Similarly, a 2007 study in Jeddah reported the percentage of positive Ae. *aegypti* traps peaked in the spring and to a lesser extent at the beginning of winter, which correlated with the number of DF cases [28]. The increase in disease incidence at the beginning of winter could be attributed to the decreased temperatures which are optimal for DF transmission. A recent Jeddah study found that the number of cases peaked at temperatures between 31° and 33 °C [52]. Infection rates may be further catalyzed in the spring with the start of the rainy season which provides an abundance of *Aedes* breeding habitat. Differences in the exact timing of the peaks between cities may be due to annual and geographic variations in seasonal weather patterns.

3.5. Socio-environmental factors influencing DF in Saudi Arabia

Many socio-environmental factors are noted to contribute to the presence and spread of DF in Saudi Arabia. These factors include water availability and water storage behaviors [53], availability of electricity in homes [48], rapid growth and development of urban centers [22], geographical proximity to DF endemic areas (primarily Yemen) [14], and developed transportation networks [53]. Across the entire country, demographic and social changes such as crowding, substandard housing, inadequate water, and sewer and waste management systems have created “ideal conditions” for increased transmission of mosquito and other vector borne diseases [54].

Water availability and storage behavior are particularly important factors contributing to DF risk throughout Saudi Arabia. A 2006 study of DF patients reported the presence of water basins in the home as a risk factor for DF [55]. A similar study in Jizan and Aseer reported that of the observed cases, a statistically significant proportion had animal water basins outside their homes [48]. A 1995 study found an association between DF and living near a construction site, which was regarded as a source of open water tanks [22].

Additionally, because many areas of the country are arid and some towns and villages outside the main metropolitan areas do not have electricity or running water, communities in these locales are more likely to engage in water storage in indoor and outdoor basins [29]. A case-control study found that homes without a reliable water supply had more cases compared to controls. Increased water storage utilizing multiple containers was reported in Jeddah in 2007 because of increased interruptions of the water supply [28]. In addition, poor plumbing and presence of cracks in homes, resulting in water leaks were reported more commonly among DF cases compared to controls [28].

Some areas within Saudi Arabia also have specific factors that are important for local DF risk. For instance, in Al-Madinah widespread use of air conditioners and evaporative coolers provide pooling water that could be utilized as mosquito breeding sites. Further, agriculture in this area requires frequent watering, which can create sustained mosquito breeding sites [50]. In Jizan, topography plays an important role in DF outbreaks; because the city is relatively flat and located at sea level, large amounts of stagnant water collection occurs following rainfall [9]. Additionally, in the rural villages of Aseer, most residents work as farmers and shepherds and often sleep outdoors to avoid high indoor temperatures, increasing their exposure to mosquitoes [48].

3.6. Population factors influencing DF in Saudi Arabia

Population movement is another important factor affecting DF transmission via importation of new strains of DENV. The major sources are foreign labor and religious pilgrims. A phylogenetic analysis concluded that the virus was likely imported by migrant workers, visiting religious pilgrims, or Saudis traveling abroad [51].

3.6.1. Potential role of expatriate workforce

Saudi Arabia relies heavily on a large expatriate workforce, particularly from the Indian subcontinent and Southeast Asia (Table 2). These migrant workers currently make up around 30% of the population [43]. Since many of these workers come from dengue endemic areas, they may have been the original source of DENV importation as well as a potential source of continuous strain importation as many come from dengue endemic areas. Additionally, Saudis traveling to DF endemic regions for business and leisure present another possible source of DENV importation [56]. Jeddah, the site of the first outbreaks, is home to a large and diverse population from all over the world due to its proximity to the holy city of Makkah. Historically, visitors came to Jeddah as pilgrims and eventually settled in the region [22]. Many pilgrims remain after their legal status expires and settle in slum areas with overcrowding and poor housing infrastructure [28,29]. Furthermore, Jeddah is a major port and one of the country's largest commercial and trade centers, and thus may be a disease transmission hub, particularly to closer cities such as Makkah, Al-Madinah, Jizan, and Najran [48,57].

Table 2
Estimates of expatriate resident population in Saudi Arabia by country based on medical testing from 1997 to 2010 [43]. (Source: Data adapted from Alswaidi et al., 2013).

Country	Male Workers		Female Workers		Total Workers	
	no.	%	no.	%	no.	%
Indonesia	1,390,615	95.24%	69,496	4.76%	1,460,111	34.17%
Philippines	577,263	94.21%	35,470	5.79%	612,733	14.34%
India	533,584	91.12%	52,009	8.88%	585,593	13.71%
Bangladesh	359,337	96.84%	11,707	3.16%	371,044	8.68%
Pakistan	314,611	97.34%	8,598	2.66%	323,209	0.75%
Egypt	227,371	97.31%	6,290	2.69%	233,661	5.47%
Sri Lanka	143,938	81.46%	32,769	18.54%	176,707	4.14%
Sudan	73,633	95.00%	3,878	5.00%	77,511	1.81%
Nepal	33,541	86.21%	5,367	13.79%	38,908	0.91%
Ethiopia	17,912	85.77%	2,972	14.23%	20,884	0.49%
Yemen	16,630	89.79%	1,890	10.21%	18,520	0.43%
Syrian Arab Republic	14,677	84.51%	2,690	15.49%	17,367	0.41%
Turkey	6,685	78.96%	1,781	21.04%	8,466	0.20%
Somalia	2,178	64.17%	1,216	35.83%	3,394	0.08%
Others	258,900	79.82%	65,472	20.18%	324,372	7.59%
Total	3,970,875	92.94%	301,605	7.06%	4,272,480	100%

3.6.2. Potential role of religious pilgrimage

Muslim pilgrims are another potential source of dengue importation unique to Saudi Arabia. The western cities of Makkah and Al-Madinah are home to the holy mosques that are visited by millions of Muslims every year for the performance of the pilgrimages of "Hajj" and "Umrah" [9,14,23,24,50,56]. The Hajj is held annually during a 5-day period and hosts nearly 2 million Muslim visitors from 180 countries, making it the largest mass gathering in the world. The Umrah can be performed at any time and attracts an additional 5 to 6 million Muslims throughout the year [45]. Pilgrimage slots are based on a pilgrimage visa allocation specified by the Ministry of Hajj of 1 per 1000 people for every Muslim country [44]. The majority of visitors are from the Indian sub-continent, southeast Asian, and eastern African nations [14,54]. Many of these countries are also endemic for a variety of vector-borne diseases including DF [14,34,57]. The high population density during the pilgrimages creates an ideal environment for the transmission of infectious pathogens and subsequent exportation and spread to the rest of the world [29,56].

Phylogenetic analysis of DENV isolates circulating in Saudi Arabia closely match endemic strains from countries with high numbers of pilgrimage visitors, such as Indonesia, Pakistan, and India, suggesting pilgrims as a possible source of DENV importation [14,58]. This is also supported by the fact that the first outbreak in 1994 coincided with the Hajj period [51]. Additionally, DF cases cluster in cities visited by pilgrims, most notably Jeddah, where the closest international airport in the region is located [56], further strengthening this argument [14]. Pilgrims from eastern Africa were a probable source for introduction of the Asian genotype of DENV-1 circulating in Saudi Arabia between 2004 and 2011 based on similarity between local isolates and isolates from Somalia [56]. However, there have likely been multiple introductions of the same strain, based on the similarity between an isolate of a locally circulating DENV-2 and a DENV-2 isolate from Pakistan [14]. Similarly a 2018 study suggested 4 introductions of various strains of DENV-3 from several different countries in 1997, 2004, and 2014, with a possible fifth introduction in 2005. Several research efforts have demonstrated the possible back and forth exchange of DENV strains across countries [58]. The congregation of multiple DENV strains from different endemic regions through large-scale gatherings creates opportunities for recombinant events, allowing for spread of new strains of the virus [14].

4. Future directions

DF epidemiology in Saudi Arabia is, in many ways, similar to that in other regions, but specifics related to Saudi Arabia's climate, its large expatriate workforce, and its annual pilgrimages shape DF epidemiology in relatively unique ways that are important to DF prevention and control. Several of these factors are inadequately understood, highlighting a number of research priorities.

First, there is a critical need to strengthen programs for surveillance, reporting, and control of DF and *Aedes* vectors in the country. Data on human infection prevalence and incidence, vector occurrence, and vector infection rates, including both permanent residents and those traveling and working in the country, are lacking in broad areas of the region and the available studies contain methodological limitations. These data are necessary for understanding transmission cycles and conducting epidemiological modeling to inform vector control strategies and predict future transmission and disease risk [38]. Such efforts are particularly important given that high DENV seroprevalence among some populations in the Red Sea region, and recent outbreaks in these sub-regions suggest increases in DF incidence.

The role of weather and climate in dengue ecology in Saudi Arabia and the MENA region is another important potential line of inquiry. Better understanding of climate and weather drivers of DF in the region, and of these drivers' interactions with social and population factors, is needed to anticipate the possible impacts of a changing climate. Despite rich evidence on the effects of weather and climate on DF globally, the role of these variables on the population dynamics of dengue vectors and on DF incidence in Saudi Arabia remains largely unexplored [29]. Climate models project that the Arabian Peninsula will experience large increases in average temperatures, with an estimated 4 °C rise over the next 60 years. The models also project that average rainfall will decrease in most of the country, but increase in the south/south western region of the country [59,60] where DF is currently endemic. These climate predictions have not been rigorously translated into predicted impacts on DF transmission.

Implementing analytical methods used to study DF in other locations could greatly increase our understanding of DF in Saudi Arabia and the MENA region. For instance, geographic information systems (GIS) can map the spatial distribution of DF cases or vector populations [61,62]. Dynamic modeling techniques use simulations to quantify the complex relationships among multiple factors affecting DF prevalence [31,63–65]. These techniques can provide insights into disease dynamics that improve disease control and management but have not been widely applied in the MENA region. Until recently, the lack of publicly accessible data for environmental and social variables has been a primary limitation in conducting quantitative DF research in the region. With further investment in the country's infrastructure and the push for accessible electronic data, there will be new opportunities for this type of research in the next few years.

The role of the Hajj pilgrimage and interaction with other ecological drivers is another key research priority. The annual Hajj follows the Islamic Lunar calendar. Therefore, its date in the Gregorian calendar shifts earlier by 11 days each year. From 2006 to 2011, the Hajj coincided with the smaller peak of DF cases that occurs as the temperature decreases in November and December [9]. In recent years, the Hajj has occurred during a period of relatively low DF transmission. However, in 2030 the Hajj will coincide with the main peak in DF cases that occurs during spring, as it did when the disease first emerged in 1993. In accordance with the Saudi government's “Vision 2030” goals, it is estimated that 5 million pilgrims will perform the Hajj in 2030 [29,44]. Thus, if dengue transmission in Saudi Arabia and/or the rest of the Muslim world is still relatively uncontrolled by that date, the Hajj could have an even larger impact on increasing DF transmission than it does currently. Further population-based studies and molecular analysis of circulating DENV strains in Saudi Arabia are needed to investigate the potential impact of this phenomenon on DF ecology [14]. Additionally the circulation of all four globally prevalent DENV serotypes in Saudi Arabia, and evidence of multiple instances of strain importations emphasizes the need for establishing continuous molecular surveillance of the virus to monitor for further importation and to better understand subsequent viral evolution and recombination [58].

5. Conclusions

Over the past several decades, DF has emerged as a truly global disease. There is a critical need for research in geographical areas where DF is a significant public health problem but its epidemiology is not well-characterized. In this review, we have highlighted factors associated with DF emergence and persistence in Saudi Arabia, including factors that are distinct from those affecting DF transmission in other parts of the world. In particular, large numbers of migrant workers and religious pilgrims from other dengue endemic areas across the MENA and Asia complicate the story of DF in Saudi Arabia. The city of Jeddah, specifically, with its moderate average temperatures, high humidity, and role as the gateway for religious pilgrims and foreign visitors, was particularly favorable for DENV introduction and emergence, and remains a location where DF persistence is high. Understanding the range of drivers of DF in Saudi Arabia can help guide further research, guide prevention efforts, and improve health system preparedness.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authorship statement

Altassan, Morin and Hess worked on concept development. Altassan wrote the first draft of the manuscript and created all tables and created or adapted most figures. Altassan, Morin, Shocket, Ebi, and Hess revised and edited the manuscript. All authors approved the final manuscript.

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