Environmental and Population Factors Influencing Dengue Fever Emergence and Spread in Saudi Arabia

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Abstract

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Background: Dengue fever (DF) is the most common mosquito borne viral disease, with an estimated 390 million infections a year, globally. In 1994, Saudi Arabia reported their first confirmed case of DF in the western coastal city of Jeddah. Over the next couple of decades, the disease spread to other parts of the country which led to the Saudi Ministry of Health declaring DF endemic in the western region of Saudi Arabia. Today, Saudi Arabia has one of the largest DF burdens in the Middle East, with the most recently published incidence rate 16 per 100,000 people. While a breadth of scientific literature has demonstrated strong associations between weather and DF, there is very little research into the topic in this region of the world. Saudi Arabia's extreme desert climate, as well as its unique position as host country of the world's

largest annual mass gathering event, the Hajj, presents a unique opportunity to explore the relationships between weather, large population movements between areas with high DF prevalence, and DF in a previously unstudied region. Infectious disease modelling is commonly used to examine and quantify associations between DF and influencing factors, and predict disease incidence, supporting public health systems in DF prevention efforts by providing insight into disease ecology and early warning of increased disease activity.

Methods: We first performed a systematic review of the literature on DF in Saudi Arabia, and the environmental and population factors that may have played a role in DF emergence and subsequent spread and endemicity. Based on the review, we selected a number of weekly weather variables, namely temperature, humidity and rainfall, and population variables that describe the annual Hajj pilgrimage, to statistically explore their association with weekly DF incidence records. We created and tested statistical predictive models using three different approaches; poisson multivariate regression, ARIMA, and random forest regression, and compared their performance using R2 and RMSE as measures of correlation and error, respectively. We also applied these local data points to a previously developed and validated process based dynamic model (DyMSiM). We further built on this model by incorporating processes that describe population movement during the annual Hajj pilgrimage (DyMSiM(P)). The dynamic models were also evaluated using the same measures of correlation and error.

Results: The systematic review identified temperature, humidity, and rainfall as the environmental factors most likely to influence DF incidence, and supported the hypothesis of the Hajj pilgrimage as a potential source of virus importation. A bivariate analysis revealed temperature and relative humidity to have the strongest correlations with DF incidence. Among the three predictive models tested, the random forest model performed the best. The DyMSiM model performance was variable, but incorporation of pilgrimage data points using DyMSiM(P) improved overall performance.

Discussion: The results of the bivariate analyses between DF and weather variables support previous work locally and globally that suggest that temperature and humidity play an important role on disease incidence, likely due to their effect on mosquito population dynamics. The influence of precipitation was less accentuated most probably because the primary breeding habitat for mosquitoes in urban areas such as Jeddah are indoor containers. The association with pilgrimage variables in the bivariate analyses pointed towards the Hajj as an important source of virus importation and introduction of novel DENV serotypes, but quantifying the association is complicated by biases on disease reporting due to stress on public health resources during this period. The short study period compounded by the seasonal variability of the timing of the annual Hajj season further limited our ability to accurately evaluate this association. Among the three predictive models, the random forest model performed the best primarily due to its ability to capture non-linear associations and has the most practical application as it is not dependent on surveillance data. Both process-based models DyMSiM and DyMSiM(P) performed better during years of more moderate temperature and humidity variables which is explained by the effect of extreme temperature and humidity on mosquito populations. This suggests that in geographical areas such as Saudi Arabia where extremes of weather are common, it is very likely that traditional sources of weather data do not reflect weather variables in the urban pockets where mosquitoes flourish. While the addition of pilgrimage data points to the dynamic model improved performance this effect was blunted by the profound influence of high temperature and humidity on the mosquito population.

Conclusion: Temperature and humidity play an important role on DF transmission in Saudi Arabia. Among the predictive models evaluated the model using a random forest approach performed the best at predicting DF in this region. The DyMSiM model applied to this dataset also performed relatively well, particularly when altered to include data points describing the Hajj. These findings suggest that large scale population movement as occurs during the pilgrimage likely leads to virus importation and introduction of new virus strains. There is potential for further refinement of these associations with extension of the study period and with the acquisition of on the ground weather data that more accurately reflects mosquito habitats in large urban areas.

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Introduction

Dengue fever (DF) is the most common mosquito borne viral disease, with an estimated 390 million infections a year, globally (Bhatt et al. 2013). Until recently the virus, which is spread by the aedes genus of mosquitoes, predominantly affected tropical and subtropical regions, commonly referred to as the malaria belt (WHO 2019). However, over the last few decades, increased urbanization, population migration, and a changing climate, have led to expanding geographic range of both the vector and the virus (Phillips 2008), resulting in increased risk of disease in 129 countries (WHO 2019). In 1994 Saudi Arabia reported their first confirmed case of DF in the western coastal city of Jeddah. Over the next 10 years, the city recorded sporadic small-scale outbreaks of the disease (M. Fakeeh and Zaki 2001). Between 2004 and 2015 the virus spread to other cities in the region resulting in annual DF that follows a seasonal distribution. These areas have since been declared endemic for the disease by the Saudi Ministry of Health (Alhaeli et al. 2016). Today, Saudi Arabia has one of the largest DF burdens in the Middle East (Humphrey et al. 2016), with the most recently published incidence rate 16 per 100,000 people (Saudi Ministry of Health 2018).

Research has shown DF is sensitive to weather variables (particularly humidity, temperature, and rainfall) due to associations with aspects of the mosquito life cycle dynamics, such as feeding, breeding, etc. (Morin, Comrie, and Ernst 2013). Further, various environmental and population factors have also been reported in the literature as potential contributors to disease importation and spread, including inconsistent water supplies, crowded living conditions, population movement, and mass gathering events (Phillips 2008; Morin, Comrie, and Ernst 2013). While studies can be found in the literature which describe associations between the DF virus, mosquito vectors, and a variety of climate and environmental factors, there is still uncertainty in the strengths and consistency of the causal links (Morin et al. 2015; Horta et al. 2014; Shang et al. 2010). Quantifying such relationships can play an important role in the design, implementation and assessment of preventive methods through the prediction of DF outbreaks. Due to variability in the effects of temperature, precipitation, humidity, and land cover on both virus and vector, in addition to the effects on the interaction between them (Morin, Comrie, and Ernst 2013), local and regional studies need to be conducted to fully appreciate the nature and magnitude of the associations and to predict future outbreaks.

Recently, the use of predictive modelling, including both statistical and process-based models, has become a popular approach to help determine the effect of weather and climate variables on mosquito-borne diseases, as well as in predicting future disease incidence (Bannister-Tyrrell et al. 2013; Morin et al. 2015). One such model created by Morin et al. incorporates a dynamic mosquito life-cycle model and a SEIR (susceptible-exposed-infectious-recovered) model for dengue virus transmission. The model applied in San Juan, Puerto Rico had high accuracy in predicting Dengue cases in 3 out of the 4 years studied (Morin et al. 2015).

Interest in this project developed as a result of communications with the Department of Environmental Health at the Saudi Ministry of Health, in which they emphasized that DF was currently the most important climate-associated disease in Saudi Arabia, and informed preventive measures were needed. While a few small-scale epidemiologic studies evaluating associations between environmental factors and DF have been conducted in Saudi Arabia (Kholedi et al. 2012; A. T. Aziz et al. 2012a; El-Badry, Al-Ali, and Others 2010; Zaki et al. 2008; Hashem, Abujamel, et al. 2018), there have been none that utilized a predictive modelling approach. Additionally, although some phylogenetic analyses studies have discussed the role that pilgrimage to Makkah may play in virus importation (Zaki et al. 2008; Hashem, Abujamel, et al.

2018; El-Kafrawy et al. 2016; Azhar et al. 2015), there have been no efforts to quantitatively explore this association.

The ultimate goal of this project was to provide further insight into the factors influencing DF incidence in Saudi Arabia, to better inform public health intervention efforts, and to create a predictive model that could serve as an early warning system improving DF preparedness systems. The objectives for this project were, first, to perform a review of the literature on DF in Saudi Arabia, describing the environmental and population factors that may have played into the disease's first emergence and subsequent spread in the region. The second objective was to examine and quantify the relationships between weather and dengue in Saudi Arabia, as well as the relationships with unique regional population factors, such as the Hajj pilgrimage. We could then utilize this information for the third objective, to create a predictive model for DF incidence using statistical modelling methods, e.g., multivariate regression. The fourth objective was to validate the dynamic mosquito simulation model, a process-based model, developed by Morin et al in 2015, by applying it to local data points. Finally, we planned to expand on this model by incorporating processes that reflect unique local population factors.

Chapter 1

Dengue Fever in Saudi Arabia: A Review of Environmental and Population Factors Impacting Emergence and Spread

1. Introduction

Dengue fever (DF) is a potentially life-threatening viral disease transmitted by *Aedes* mosquitoes (Nedjadi et al. 2015). 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 (Bowman, Donegan, and McCall 2016; WHO 2016a). However, the total burden of disease, including asymptomatic carriers, may be up to 4 times greater (Nedjadi et al. 2015; Bhatt et al. 2013; WHO 2016a). Even these figures may be underestimated because of under-reporting, particularly in Africa (Stoler et al. 2014). Most DF research focuses on Latin America and Asia, where burdens are highest (Phillips 2008). 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 (Humphrey et al. 2016). 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 (M. Fakeeh and Zaki 2001). Over the next several years small outbreaks of no more than 15 cases were reported in Jeddah (Mazen Fakeeh and Zaki 2003b). 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 (Alhaeli et al. 2016). In 2015, the incidence rate was 16 per 100,000 person-years (Saudi Ministry of Health 2018) (for comparison, incidence rates range from 15-130 per 100,000 person-years in most Latin American countries (PAHO 2011)).

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 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 (Al-Tawfiq and Memish 2018). 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 (Bowman, Donegan, and McCall 2016). Phylogenetic studies have demonstrated clustering of genotypes geographically as well as associations between genotype and disease severity (Azhar et al. 2015; El-Kafrawy et al. 2016).

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 (Bowman, Donegan, and McCall 2016). 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 (Braks et al. 2003). 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 (Nedjadi et al. 2015). This process takes 1-3 weeks, and is faster at warmer temperatures (Morin, Comrie, and Ernst 2013).[16] Both species are primarily day biters but *Ae. aegypti* can also bite at night if artificial lighting is strong enough (Arya and Agarwal 2014).

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) (Kliks et al. 1989; Katzelnick et al. 2017). Case fatality from DHF can reach 15%, but early detection and treatment can decrease this number to around 1% (Nedjadi et al. 2015). 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 (Nedjadi et al. 2015; Joob and Wiwanikit 2017).

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 (Morin, Comrie, and Ernst 2013; Bhatt et al. 2013). For instance, researchers estimate that only 1 of every 23 cases in Singapore is reported to health authorities (Jamjoom et al. 2016). 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) (Jamjoom et al. 2016; Ahmed M. Ashshi 2015; El-Badry et al. 2014).

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% (WHO 2016b; Flasche et al. 2016). 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 (WHO 2016b; Flasche et al. 2016). 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 (SAGE 2018).

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 (Phillips 2008; Morin, Comrie, and Ernst 2013) . *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 (Kholedi et al. 2012; A. T. Aziz et al. 2012a). 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 (Beebe et al. 2009; Morin et al. 2015). Accordingly, having an interrupted water supply was associated with DF in Cuba, and Brazil and with other mosquito-borne illnesses in India (Kholedi et al. 2012). These water storage behaviors may increase in some regions with increased warming and decreased rainfall as the climate changes further (A. T. Aziz et al. 2012a).

Transmission of mosquito-borne disease, including DF, is highly sensitive to temperature, rainfall and humidity (Alhaeli et al. 2016; Morin, Comrie, and Ernst 2013; A. T. Aziz et al. 2012a; Morin et al. 2015; Horta et al. 2014). Temperature influences the physiology and behavior of mosquito vectors and development of the virus (Morin, Comrie, and Ernst 2013; Mordecai et al. 2017; Sowilem, Kamal, and Khater 2013). 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 (Mordecai et al. 2017)*. 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 (A.

T. Aziz et al. 2012a). 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 (Schmidt et al. 2018). A study conducted in Taiwan, further asserted that favorable weather conditions can help imported cases of DF become local epidemics (Shang et al. 2010).

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 (Morin, Comrie, and Ernst 2013). Microclimates are created by interactions of rainfall, temperature, and humidity with land cover, resulting in heterogeneity across an urban area in locations suitable for *Aedes* mosquitoes (Morin, Comrie, and Ernst 2013).

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 (Sowilem, Kamal, and Khater 2013). The primary control methods are insecticide use via indoor residual spraying and skin repellants (A. Aziz et al. 2014). 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 (Bowman, Donegan, and McCall 2016; WHO 2016b). Increasing vector resistance and environmental contamination further complicate the use of insecticides. A systematic review of vector control and DF prevention concluded that data for intervention program evaluation was sorely lacking globally (Bowman, Donegan, and McCall 2016).

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 (El-Kafrawy et al. 2016). 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 (Figure 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 (Humphrey et al. 2016)) (Figure 2). DENV 1-3 have been reported in the Red Sea countries; DENV-4 has only been reported in Pakistan (Humphrey et al. 2016)) and very recently in Saudi Arabia (Ahmed Mohamed Ashshi 2017).

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 (Humphrey et al. 2016). 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 (Humphrey et al. 2016). 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 (Humphrey et al. 2016).

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 (Weather Online n.d.; CIA n.d.), which generally occurs during the rainy season in March and April (Weather and Climate n.d.). Inland mean temperatures vary from 45°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 (Weather Online n.d.; CIA n.d.). 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 (Weather Online n.d.). When DF began spreading in Saudi Arabia, some researchers argued that the low levels of precipitation would not favor efficient spread (Mazen Fakeeh and Zaki 2003b). 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 (Alswaidi et al. 2013). The country hosts more than 5 million visitors each year for the Hajj and Umrah pilgrimages (Aleeban and Mackey 2016). 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 (CIA n.d.; Elachola and Memish 2016). 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 (Aleeban and Mackey 2016).

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 (Figure 3) (M. Fakeeh and Zaki 2001). By March 1994, the Disease Control Division in Jeddah had initiated a dengue surveillance system that recorded 289 cases that year (Kholedi et al. 2012). Over the following years, sporadic outbreaks occurred, each with no more than 15 cases per year (Mazen Fakeeh and Zaki 2003b). 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 (Alhaeli et al. 2016). In 2015, DF incidence was 13.68 per 100,000 people (Saudi Ministry of Health 2018). The majority of cases are men between the ages of 15 to 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 (Al-Tawfiq and Memish 2018; Alshammari et al. 2018).

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% (Jamjoom et al. 2016)); on the low end, a 2010 national study of soldiers found a rate of 0.1% (Alhaeli et al. 2016). 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 have also been circulating since 1994 and 1997, respectively (El-Kafrawy et al. 2016). A recent seroprevalence study using samples from Makkah in 2015-16 identified DENV-4 (Ahmed Mohamed Ashshi 2017).

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 (A. T. Aziz et al. 2012a), particularly after the rainy season (Sowilem, Kamal, and Khater 2013). *Ae. aegypti* is considered the primary vector, but *Ae. albopictus* also contributes to the spread of the disease (Bowman, Donegan, and McCall 2016). *Ae. Aegypti* has been increasing its geographical distribution in Saudi Arabia, and can be found in Jeddah, Makkah, Jizan, and Aseer (A. Aziz et al. 2014; Al-Azraqi, El Mekki, and Mahfouz 2013)) (Figure 4). *Ae. aegypti* also recently emerged in Al-Madinah (A. Aziz et al. 2014). It is believed that traffic between Jeddah and Al-Madinah is responsible for importation of the mosquito, possibly through the transportation of tires (El-Badry, Al-Ali, and Others 2010). 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 (Al-Azraqi, El Mekki, and Mahfouz 2013).

Regular application of mosquito adulticides and larvicides are the primary methods of disease prevention. For instance, the city of Makkah used approximately 17,975 liters of adulticide and 3,899 liters of larvicide in 2007 (A. Aziz et al. 2014). 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. Both of these factors could promote vector resistance to insecticides (A. Aziz et al. 2014). 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 (Al-Azraqi, El Mekki, and Mahfouz 2013).

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 (Zaki et al. 2008). 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 (Hashem, Abujamel, et al. 2018). 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 (A. T. Aziz et al. 2012a). In Al-Madinah the number of trapped female Ae. *aegypti* in particular peaked from March to May (El-Badry, Al-Ali, and Others 2010). 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 (Kholedi et al. 2012). 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 (Hashem, Abujamel, et al. 2018). 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 (A. Aziz et al. 2014), availability of electricity in homes (Al-Azraqi, El Mekki, and Mahfouz 2013), rapid growth and development of urban centers (Jamjoom et al. 2016), geographical proximity to DF endemic areas (primarily Yemen) (El-Kafrawy et al. 2016), and developed transportation networks (A. Aziz et al. 2014). 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 (El-Gilany, Eldeib, and Hammad 2010).

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 (Ayyub et al. 2006). A similar study in Jizan and Aseer reported that of the observed cases, a statistically significant proportion had animal water basins outside their homes (Al-Azraqi, El Mekki, and Mahfouz 2013). A 1995 study found an association between DF and living near a construction site, which was regarded as a source of open water tanks (Jamjoom et al. 2016).

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 (A. T. Aziz et al. 2012a). 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 (Kholedi et al. 2012). In addition, poor plumbing and presence of cracks in homes, resulting in water leaks were reported more commonly among DF cases compared to controls (Kholedi et al. 2012).

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 (El-Badry, Al-Ali, and Others 2010). 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 (Alhaeli et al. 2016). 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 (Al-Azraqi, El Mekki, and Mahfouz 2013).

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 (Zaki et al. 2008).

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 (Alswaidi et al. 2013), 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 (Azhar et al. 2015). 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 (Jamjoom et al. 2016). Many pilgrims remain after their legal status expires and settle in slum areas with overcrowding and poor housing infrastructure (Kholedi et al. 2012; A. T. Aziz et al. 2012a). 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 (Al-Azraqi, El Mekki, and Mahfouz 2013; Khan et al. 2008).

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” (Alhaeli et al. 2016; El-Kafrawy et al. 2016; Ahmed M. Ashshi 2015; El-Badry et al. 2014; El-Badry, Al-Ali, and Others 2010; Azhar et al. 2015). 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 (Elachola and Memish 2016). Pilgrimage slots are based on a pilgrimage visa allocation specified by the Ministry of Hajj of 1 per 1000 people for every Muslim country (Aleeban and Mackey 2016). The majority of visitors are from the Indian sub-continent, southeast Asian, and eastern African nations (El-Kafrawy et al. 2016; El-Gilany, Eldeib, and Hammad 2010). Many of these countries are also endemic for a variety of vector-borne diseases including DF (El-Kafrawy et al. 2016; Sowilem, Kamal, and Khater 2013; Khan et al. 2008). 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 (A. T. Aziz et al. 2012a; Azhar et al. 2015).

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 (El-Kafrawy et al. 2016; Hashem, Sohrab, et al. 2018). This is also supported by the fact that the first outbreak in 1994 coincided with the Hajj period (Zaki et al. 2008). Additionally, DF cases cluster in cities visited by pilgrims, most notably Jeddah, where the closest international airport in the region is located (Azhar et al. 2015), further strengthening this argument (El-Kafrawy et al. 2016). 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 (Azhar et al. 2015). 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 (El-Kafrawy et al. 2016). 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 (Hashem, Sohrab, et al. 2018). 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 (El-Kafrawy et al. 2016).

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 (Humphrey et al. 2016). 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 (A. T. Aziz et al. 2012a). 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 (Met Office (UK) 2011a, [b] 2011), 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 (Khormi and Kumar 2012; Khormi, Kumar, and Elzahrany 2011). Dynamic modeling techniques use simulations to quantify the complex relationships among multiple factors affecting DF prevalence (Morin et al. 2015; Bannister-Tyrrell et al. 2013; Gharbi et al. 2011; Descloux et al. 2012). 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 2006-2011, the Hajj coincided with the smaller peak of DF cases that occurs as the temperature decreases in November and December (Alhaeli et al. 2016). 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 (A. T. Aziz et al. 2012a; Aleeban and Mackey 2016). 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 (El-Kafrawy et al. 2016). 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 (Hashem, Sohrab, et al. 2018).

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.

6. Tables and Figures

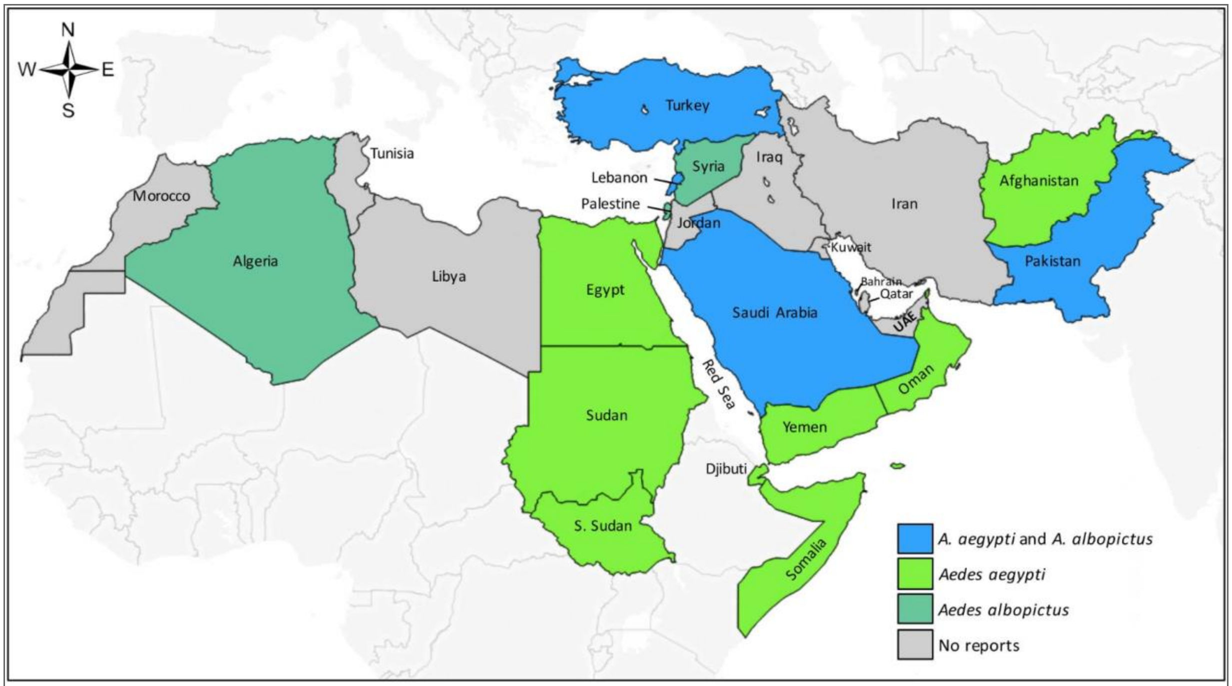


Figure 1: Distribution of *Ae. aegypti* and *Ae. albopictus* mosquitoes in the MENA region (Humphrey et al. 2016).(Source: Reprinted from Humphrey et al. 2016 under the terms for the Creative Commons Attribution License.)

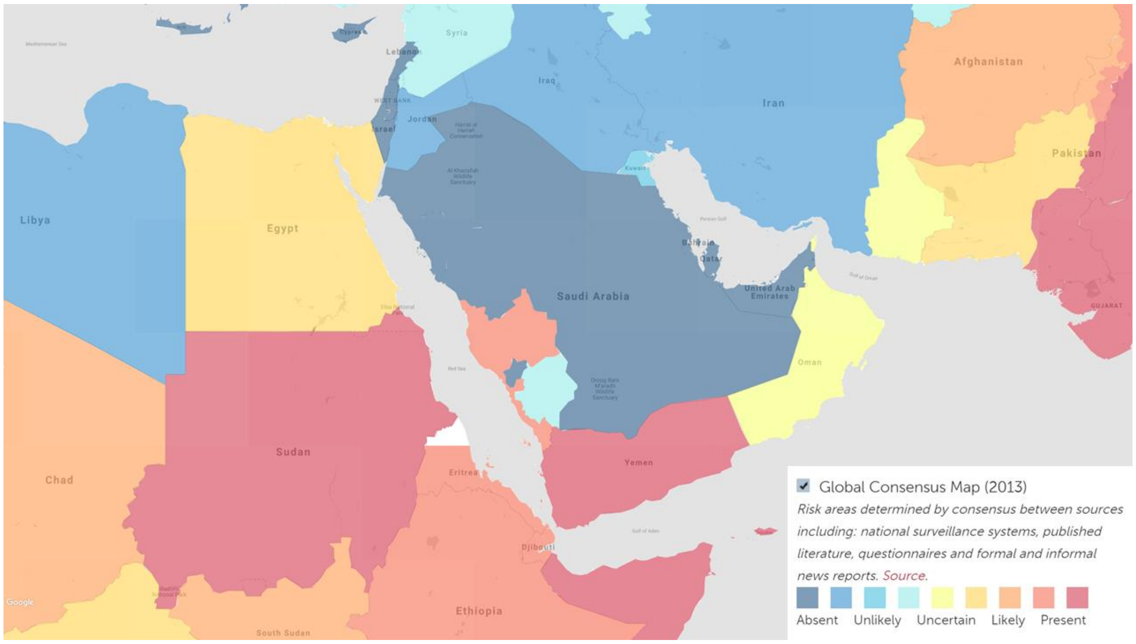


Figure 2: Dengue fever prevalence in the MENA region from the CDC Dengue Map (Source: http://www.healthmap.org/dengue/en/ (Centers for Disease Control (CDC) n.d.).

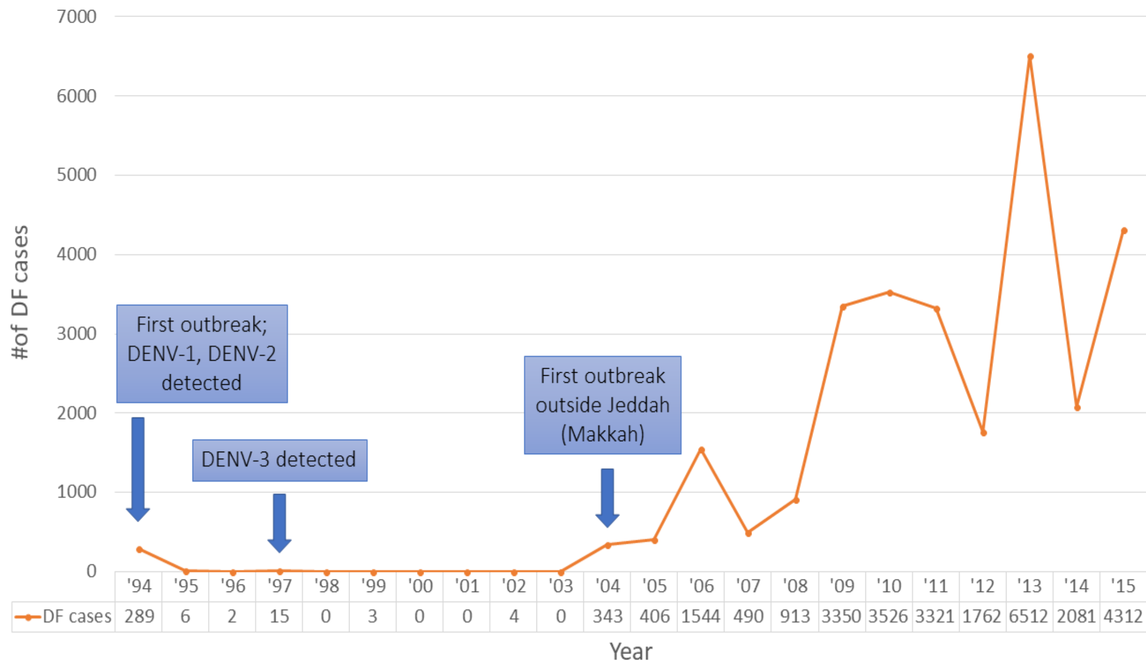


Figure 3: Time series of DF incidence in Saudi Arabia (1994 - 2015) and dates of strain introductions.
*The presence of DENV-4 was reported in Saudi Arabia in 2017 (not shown) (Ahmed Mohamed Ashshi 2017).

Figure 4: DF distribution in Saudi Arabia. (Source: Data from the Ministry of Health) (Alrajhi 2016)

Study	Year	Location	Study sample	IgG prevalence
Memish et al. [47]	2010	National*	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%

Table 1: Estimates of dengue fever seroprevalence in Saudi Arabia based on national or sub-national studies.
*Note that the Memish et al. study reports data from a survey of military recruits from throughout the Kingdom of Saudi Arabia.

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%

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

Chapter 2

Statistical Modeling of Dengue Fever in Saudi Arabia using Meteorological and Pilgrimage Variables

1. Introduction

Dengue fever (DF) is an important potentially life-threatening viral disease transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. With half of the world's population at risk, it causes a large economic and disease burden estimated at 390 million infections a year (Bhatt et al. 2013; WHO 2019). The mosquito vectors breed in small bodies of stagnant water, particularly in water storage containers around homes. More recently the range of the vectors and the virus has expanded geographically (Bowman, Donegan, and McCall 2016), resulting in increased risk of disease in 129 countries. Early detection and management is key to preventing mortality from severe dengue (WHO 2019).

Saudi Arabia has one of the largest DF burdens in the Middle East. DF emerged in Saudi Arabia three decades ago with the first documented case appearing in Jeddah in late 1993 (M. Fakeeh and Zaki 2001). By March 1994, the Disease Control Division in Jeddah had initiated a dengue surveillance system that recorded 289 cases that year (Kholedi et al. 2012). Over the following several years, sporadic outbreaks occurred, each with no more than 15 cases per year (Mazen Fakeeh and Zaki 2003a). However, between 2004 and 2015, significantly larger outbreaks occurred, primarily during the rainy season, which reached beyond Jeddah and into the nearby cities of Makkah, Al-Madinah, Jizan, and Najran, and led the Saudi Ministry of Health to declare DF endemic in the western region of Saudi Arabia (Alhaeli et al. 2016). In 2015, DF incidence was 16 per 100,000 people per year in Saudi Arabia (Saudi Ministry of Health 2018). DENV-2 is the predominant serotype in Saudi Arabia, however, DENV-1 and 3 have also been circulating since 1994 and 1997, respectively (El-Kafrawy et al. 2016) and a recent study also identified the presence of DENV-4 (Ahmed Mohamed Ashshi 2017).

The dramatic increase in DF globally over the past 50 years has been attributed to many factors including increased urbanization, local and foreign population migration, erratic water supplies, and geographically expanding vector populations associated with a changing climate (Phillips 2008; Morin, Comrie, and Ernst 2013). Transmission of mosquito-borne diseases, including DF, generally follows a seasonal distribution and is highly sensitive to weather variables, particularly temperature, rainfall, and humidity (Horta et al. 2014; Morin, Comrie, and Ernst 2013; A. T. Aziz et al. 2012b; Morin et al. 2015; Alhaeli et al. 2016). Temperature influences both the physiology and behavior of the mosquito vectors, as well as the replication rate of the virus (Mordecai et al. 2017; Morin, Comrie, and Ernst 2013; Sowilem, Kamal, and Khater 2013). Statistical models have found a wide range of results quantifying this relationship (Fan et al. 2014; Xiang et al. 2017; Morin, Comrie, and Ernst 2013; Kamiya et al. 2019; Taghikhani and Gumel 2018). Additionally, DF may be governed by seasonal precipitation as rainfall provides pockets of stagnant water around human dwellings. Because *Ae. aegypti* primarily breeds in artificial containers, 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) plays a primary role in the spread of DF, as these sites provide an optimal environment for mosquito oviposition (A. T. Aziz et al. 2012b). Although humid weather conditions generally coincide with rainfall, often ambient humidity itself is enough to prevent desiccation of the mosquito ova. Hales et al. (2002) found that average annual vapor pressure was the strongest predictor of DF distribution (Schmidt et al. 2018). Favorable weather conditions can also help imported cases of DF become local epidemics (Shang et al. 2010).

At the onset of DF emergence in Saudi Arabia, researchers hypothesized that the desert climate would not favor efficient spread of the virus (Mazen Fakeeh and Zaki 2003a). However, some areas of Saudi Arabia have conditions that allowed the virus to become endemic, and several studies have demonstrated that DF incidence in Saudi Arabia follows a seasonal pattern. Cases peak primarily in the spring (March-May), and then again to a lesser extent in November and December (Zaki et al. 2008). This pattern has been reported 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 (Hashem, Abujamel, et al. 2018). A 2007 study in Jeddah reported that 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 (Kholedi et al. 2012). Further, *Aedes* larvae sampled from water containers in Makkah peaked between January and March during the "wet season" and then gradually decreased from April to September (A. T. Aziz et al. 2012b). The increase in disease incidence at the beginning of winter might be attributed to the lower temperatures which are optimal for DF transmission (Hashem, Abujamel, et al. 2018). Infection rates are then catalyzed in the spring with the start of the rainy season which provides an abundance of *Aedes* breeding habitat.

Population factors may also affect Saudi Arabia's DF epidemiology. Saudi Arabia's population is approximately 30 million people, a third of which are foreign workers, including skilled workers and laborers (Alswaidi et al. 2013). The country hosts over 8 million visiting Muslim pilgrims every year in the city of Makkah, arriving primarily through Jeddah international airport (Saudi General Authority for Statistics n.d.). The city of Jeddah, with its moderate temperatures, high humidity, and role as the gateway for religious pilgrims, was particularly favorable for DENV introduction and emergence and remains a location where DF persistence is high (Altassan et al. 2019). Inter-regional population movement, particularly during the annual religious pilgrimages of Hajj and Umrah, increase the risk of disease importation (Humphrey et al. 2016). Based on Islamic doctrine Muslims are obligated to participate in the Hajj once during their lifetime resulting in one of the largest mass gatherings in the world. Between 1.5 to 2.5 million pilgrims from over 180 different countries participate in the week-long event (Aleeban and Mackey 2016), with the majority from countries in Eastern Asia and Africa, which are endemic for DF (El-Kafrawy et al. 2016; Almutairi et al. 2018). Millions of pilgrims also travel to Makkah to perform the Umrah pilgrimage with the month of Ramadan being the most popular time to visit for domestic pilgrims. These mass gathering events further drive DENV serotype mixing and transmission (Humphrey et al. 2016) as evidenced by phylogenetic analysis of circulating DENV serotypes (El-Kafrawy et al. 2016; Zaki et al. 2008). Furthermore, as the Hajj falls on the 12th month of the Islamic lunar calendar this leads to seasonal variability of the event, resulting in varying public health challenges every year (Aleeban and Mackey 2016).

Despite rich evidence on the effects of weather and climate on DF globally, the role of these variables on DF incidence in Saudi Arabia remains largely unexplored. A better understanding of meteorological 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 on dengue incidence (A. T. Aziz et al. 2012b). Additionally, understanding the role of pilgrims in the original and continuous importation of dengue virus would improve health system preparedness (Altassan et al. 2019).

DF prevention and control is a global public health challenge that requires targeted cost-effective strategies. Traditional preventive measures, in the form of insecticide use and similar vector control modalities, have thus far been shown to be ineffective in curbing disease incidence and spread. The World Health Organization (WHO) has emphasized the importance of identifying the factors, particularly weather variables, that may act as early warning signals for DF outbreaks. Attempts to utilize various statistical methods in the development and implementation of predictive models highlights the significance of determining these sensitive indicators, and the potential effect it may have on the overall effort to minimize the burden of DF (Vásquez et al. 2019).

The objectives of this study are 1) to examine and quantify the relationships between weather, pilgrimage events, and dengue fever in Saudi Arabia, 2) to determine the best statistical modelling approach for DF prediction in this locale, and 3) to utilize this information to create a predictive model for DF incidence.

Research efforts investigating the factors responsible for DF emergence and spread within Saudi Arabia are limited, possibly due to lack of consistent publicly available datasets. We were able to obtain electronic DF data from three cities in Saudi Arabia for a period of 10 years. To our knowledge, this is the first research effort utilizing this rich resource. This study is also the first attempt to predict DF incidence in the Arabian Peninsula using an empirical model. Studying DF in this region presents a unique context as the area is non-tropical and known for its arid climate. It further poses a novel question pertaining to the effect of hosting the Hajj and Umrah pilgrimages on DF epidemiology.

This study evaluates the dependent weather variables that can be used to predict DF in Saudi Arabia based on current and lagged observations. We also compare between 3 different predictive modeling approaches previously utilized in other geographic regions.

2. Methods

2.1 Data Collection

DF data: We obtained electronic weekly DF records for the geographical areas Jeddah, Makkah, and Jizan, from their respective public health centers. The cases were reported as required by the national mandatory reporting of hemorrhagic disease policy. All suspected DF cases were included from 2009 to 2018 for Jeddah and from 2012 to 2018 for Makkah and Jizan. Cases were dated based on the date of reporting.

Weather data: We used the *GLDAS Noah Land Surface Model L4 3 Hourly 0.25 x 0.25 degree* data subsets provided by Goddard Earth Sciences Data and Information Services Center. Weekly measurements of temperature, rainfall, and relative humidity were produced by aggregating the GLDAS 3-hourly measurements of temperature, rainfall, surface pressure, and specific humidity. The geographical coordinates selected were 21.375°, 39.375° for Jeddah, 21.375°, 39.875° for Makkah, and 17.375°, 42.625° for Jizan. We based our coordinates selection on the coordinates of the city of Jeddah, the city of Makkah and the province of Jizan as per Google search results. The aggregated temperature variables included *mean*, *mean minimum*, *mean maximum*, *minimum minimum* (the lowest temperature measured in a week), and *maximum maximum* (the highest temperature measured in a week) in degrees Celsius (°C). The aggregated relative humidity variables included *mean*, *mean minimum*, *mean maximum*, *minimum minimum* (the lowest measurement of relative humidity in a week), and *maximum maximum* (the highest measurement of relative humidity in a week) as a percentage. The aggregated precipitation variables included *total rainfall* and *average rainfall* in mm/day, and *number of rainy days*.

Pilgrimage data: The number of pilgrims per year was obtained from the Saudi General Authority for Statistics' publicly available online data. Annual timing of the Hajj was defined as the Gregorian dates coinciding with the 6^{th} of Thul Hijjah to the 13^{th}. The timing of the month of Ramadan, which is the 9th month of the lunar calendar, was calculated as the 11th - 14th weeks preceding the week of the Hajj. Pilgrimage variables included *number of pilgrims* and *proportion of foreign pilgrims* of the previous year, as well as *week of Hajj* and *month of Ramadan* as binary variables.

2.2 Analysis and Model Selection

Our analysis was conducted on the geographical areas individually. We used RStudio Data Analytics Software version (1.2.1335). The variables selected to be included in the models were based on a bivariate analysis performed on the complete dataset which investigated the relationship between each variable of interest and the number of DF cases per week, and an assessment of the resulting Pearson correlation coefficient (r) and p-value. Similar to the approach taken in other studies, (Vásquez et al. 2019) each weather variable was tested at lags between 0 and 12 weeks resulting in a total 169 weather variables tested. The four pilgrimage variables were also analyzed with the variables *Hajj week* and *month of Ramadan* tested at lags between 0 and 12 weeks. This lag period was selected to match the one selected for the weather variables, as well as account for the time necessary for imported dengue viruses to circulate in the environment resulting in increased disease transmission and new outbreaks. Twenty pilgrimage variables were assessed in total, with only one selected for inclusion from each of the two binary variables, respectively; the variables *number of pilgrims* and *proportion of foreign pilgrims* for the previous year were included only if they were found significant (p -value ≤ 0.05). Additionally, *year* and *number of cases the previous week* were also assessed for inclusion in the model based on a significant Pearson correlation analysis result. Different covariate groups were created to reflect real-world scenarios and limitations. In total four groupings of covariates were created for inclusion in the models:

Group 1: One variable from each category of weather variables and from each of the four pilgrimage variables was selected to include in the model based on their *r* measurement and a p-value $\leq$ 0.05. Both *year* and *number of cases the previous week* were included in this group.

Group 2: This group only considered variables taken with at least 1 week lag but still selected the variables based on significance (p-value $\leq$ 0.05) and having the highest *r* measurement in its variable category. *Year* and *number of cases the previous week* were also included in this group.

Group 3: Includes all the variables from group 1 except *number of cases the previous week*.

Group 4: Includes all the variables from group 2 except *number of cases the previous week*.

Three regression modeling methods were employed:

A. Poisson multivariate regression**:** a generalized linear regression model based on a Poisson distribution of count data. The default parameters selected for the *glm* model are *family = Poisson*. Analysis was done in a backward stepwise approach where initially all covariates are included, and subsequently taken out of the model at each step. The best fit model was determined by the Akaike Information Criterion (AIC).

B. Auto Regressive Integrated Moving Average (ARIMA) regression: a type of linear regression model that combines autoregression with calculations of differences between consecutive observations. This method exclusively uses time series data. In this analysis we used the function *auto.arima* from the forecasting library in r and added external regressors from the covariate groups. Originally, we specified the use of a seasonal model with the function seasonal = TRUE but a non-seasonal ARIMA was determined to be the best fitting model by the program. We also specified no use of a stepwise approach or approximation for model selection, which was also based on a lower AIC.

C. Random Forest regression: a tree-based machine learning method that functions by generating many tree sub-models at random from a dataset; trees are then aggregated based on the mean to create a final tree model. This method allows the addition of one covariate at a time wherein the newly added covariate improves on the already trained ensemble further improving the model's accuracy. In our analysis we specified the use of 750 trees (*ntree = 750*).

2.3 Model Validation and Assessment

We utilized an iterative holdout method by dividing the dataset into training and testing subsets. We withheld one year of data from the dataset to train the model and then tested the model on the year withheld. This led to ten iterations of model training and validation in which each time one of the years was excluded and used for the model validation. To evaluate the performance of the models both the R^2, and the mean square root error (RMSE) were calculated based on the predicted and observed number of cases. A higher R^2 and lower RMSE indicates a better performing model. The model residuals were also visually inspected for patterns.

3. Results

3.1 Descriptive and trend analyses

DF incidence for the entire sample showed a seasonal pattern with a large peak in the late spring (weeks 22 to 30) and another smaller peak in the early winter (weeks 49 to 53; Figure 1). The three cities' average temperatures, precipitation, and humidity patterns are shown in Figure 2(a - c). Annual DF incidence has shown an overall upward trend since electronic reporting began in 2009 with small dips in the curve every couple of years (Figure 3).

In the remainder of this section we will present the results of the statistical analyses for the city of Jeddah. We chose Jeddah as it is the largest of the 3 cities and home to the main airport through which pilgrims travel. It is also where the first outbreaks of DF began and still has a disproportionately higher number of cases than the other areas. Figures describing the preliminary analyses for Makkah and Jizan can be found in Appendix B.

3.2 Bivariate analyses between DF and independent variables

3.2.1 Correlations between DF case counts and weather variables

Temperature: Positive correlation decreases with lag time up to 5-6 weeks where it drops to nearly 0. It then increases negatively with lag time up to 12 weeks. Twelve week lag was the longest lag measured but this trend could continue with longer lag times. The strongest correlation overall was found between average maximum weekly temperature and weekly number of cases at 12 week lag. It is a moderately strong significant negative association (R = -0.42). The strongest positive correlation was found between average minimum temperature at no lag. It is a moderately strong significant positive association (R = 0.38) (Figure 4(a)).

Humidity: Negative correlation decreases with lag time up to 8-11 weeks and then increases positively with lag time up to 12 weeks. Again, this trend could continue with longer lag times. The strongest overall correlation was found between average relative humidity and weekly number of cases with no lag time. It is a moderately strong significant negative association (R = -0.53). The strongest positive correlation was found with average minimum weekly relative humidity at 12 week lag. It is a weak significant positive association (R = 0.17) (Figure 4(b)).

Precipitation: There is a negative barely significant correlation between precipitation variables and weekly DF cases that decreases with lag time. The strongest significant negative association was with both maximum weekly precipitation and total weekly rainfall with no lag time (R = -0.09). The only significant positive correlation was found with the number of rainy days at 7 week lag time (R = 0.09) (Figure 4(c)).

3.2.2 Correlation between DF case counts and pilgrimage variables

a) Timing of mass gathering events:

Hajj week: There is a significant weak negative correlation between Hajj week and number of weekly dengue cases at no lag and at 1-, 2-, 4-, 5-, and 6-week lags. The strongest significant correlation is at no lag (R = -0.11) (Figure 4(d)).

Ramadan: There is a significant positive correlation between Ramadan and number of weekly dengue cases at no lag and 1 week lag. The strongest significant positive correlation is at no lag (R = 0.2). There is also a significant negative correlation between Ramadan and number of weekly dengue cases from 6 to 12 week lag time. The strongest significant negative correlation is at 12 week lag (R = -0.2) (Figure 4d).

b) Number of Hajj pilgrims the previous year: There is a weak significant negative correlation between the number of DF cases and the proportion of foreign pilgrims during the Hajj pilgrimage the previous year (R = -0.11)

c) Proportion of foreign pilgrims the previous year: No significant correlation.

The remainder of the analyses was only performed for the Jeddah dataset.

3.3 Predictive models

Based on the Pearson correlation coefficient of the bivariate analyses we ran as well as a significance level of $p \leq 0.05$, we determined the most appropriate variables to include in the model (Table 1). In our first covariate group, we included average minimum temperature with no lag, minimum minimum temperature at 12 weeks lag, average relative humidity with no lag, average minimum humidity at 12 weeks lag, total precipitation at 1 week lag, Hajj week with no lag, Ramadan period at 12 week lag, and proportion of foreign pilgrims the previous year. We also included the variables *year* and *number of DF cases the previous week* which also demonstrated significant positive associations with DF case counts. In the second covariate group, average minimum temperature with no lag, average relative humidity with no lag, and Hajj week with no lag were excluded and replaced with average minimum temperature and average relative humidity at 1 week lag, and Hajj week at 4 week lag. Results of the bivariate for selected covariates is summarized in Table 1.

All 3 regression methods performed well with models containing group 1 and 2 covariates which included *number of cases the previous week*. The ARIMA and Random Forest models performed the best with an average $R^2 = 0.78$ and 0.77 respectively, and an average RMSE = 20.7, and 24.5 respectively. They are followed by the poisson regression models with an average $R^2 = 0.74$ and an average RMSE = 28.2. For the majority of years all 3 approaches had high correlation measures (R^2 = 0.76 - 0.89). The predictive ability decreased for years 2017 and 2018 (R^2 = 0.53 - 0.75). The models demonstrated the lowest predictive ability for 2012 with average R^2 = 0.34 with the poisson regression, average R^2 = 0.48 with ARIMA, and average R2 = 0.34 with random forest.

For the models containing group 3 and 4 covariates in which *number of cases the previous week* was excluded, all three regression approaches decreased in performance. Here the best performing regression approach was random forest with an average R^2 = 0.62, followed by poisson regression (average R^2 = 0.56), and finally ARIMA (average R^2 = 0.17). The most significant decrease in performance between the models was between ARIMA regression with covariate groups 1 and 2 (R^2 = 0.78 for each) and ARIMA regression with covariate group 3 (R^2 = 0.04). The R^2 and RMSE for all models are summarized in Table 2 and Table 3 (appendix).

4. Discussion

DF ecology in the Arabian Peninsula has not been well described, and has two unusual elements: the region's aridity, which some thought would preclude the disease becoming endemic (M. Fakeeh and Zaki 2001), and the unique large annual religious pilgrimages that bring in people from other endemic regions around the world. To assess environmental and social factors affecting the disease's ecology in the region, we performed a descriptive analysis of a time series of DF cases in Saudi Arabia, conducted a series of bivariate analyses between environmental and pilgrimage factors, and then analyzed the data using a multivariate poisson regression model, an ARIMA model, and a random forest machine learning model. The ultimate goal of this work is to develop a predictive model that could facilitate early warning and intervention to reduce future infections. This is, to our knowledge, the first time an empirical model describing DF epidemiology in Saudi Arabia has been developed. While overall random forest modeling performed best, both the ARIMA and poisson regression models lend insights into the environmental and social factors affecting the epidemic and allows us to examine biologic plausibility and other factors that the black box random forest model can obscure.

The seasonal distribution of DF in our dataset has previously been described locally (A. T. Aziz et al. 2012b; Hashem, Abujamel, et al. 2018; Kholedi et al. 2012), and globally (Horta et al. 2014; Morin, Comrie, and Ernst 2013; Carvajal et al. 2018), and as previously mentioned, largely linked to the effect of weather on vector life cycle dynamics. The overall annual increase in DF case counts with slight dips in the trend at 2-3 years (Figure 3), has previously been discussed in the literature. Jayaraj et al. (2019) explained this phenomenon of ebb and flow in DF epidemiology by replacement of the dominant circulating viral serotype with another serotype resulting in a process of virus extinction and reinvasion termed "clade replacement" (Jayaraj et al. 2019).

To investigate the role of environmental factors on DF epidemiology the literature has suggested looking at the dependent variables with lag periods of at least 1 - 2 weeks to account for the timing of the extrinsic and intrinsic incubation periods (X. Wu et al. 2018) and possibly longer lag periods to account for the effect on the vector life cycle dynamics (Fan et al. 2014). The most commonly used lag periods are between 4 and 8 weeks, with some studies using lags of up to 8 months ((Fan et al. 2014; Xiang et al. 2017; Akter et al. 2020; X. Wu et al. 2018)). For this study we opted to use lag periods between 1 to 12 weeks as we felt confident that this period would safely cover the timeframe at which the covariates would have the most impact on DF outcomes.

The bivariate analysis looking at the association between the number of DF cases and weather variables found a moderately strong association with temperature variables, particularly the average weekly minimum temperature with no lag, and the average weekly maximum temperature at 12 week lag. The strength and direction of the relationship changed as the lag period increased. The negative association at 12 week lag was stronger than the positive association at 12 week lag. There is support in the literature for the associations we observed. Temperature has been found to act on multiple components of the ecologic pathway including viral replication, mosquito oviposition, and larval development and density, with higher temperatures favoring these processes (WHO 2019; Morin, Comrie, and Ernst 2013; P.-C. Wu et al. 2007). Wu et al. (2009) contend that minimum temperature was the most critical for mosquito survival and development (P.-C. Wu et al. 2009). The literature also suggests that average temperatures between 20 and 30°C are most suitable for *Ae. aegypti* population growth (A. T. Aziz et al. 2012b; Kholedi et al. 2012; WHO 2019; Morin, Comrie, and Ernst 2013). Morin et al (2013) emphasize that this association needs to be considered in the context of the local climate. For at least a third of the year, average temperatures in this region are over 30°C, and can reach up to 40°C.("Jeddah Climate: Average Temperature, Weather by Month, Jeddah Water Temperature - Climate-Data.org" n.d.) This might explain the shift we see in the direction of the relationship between temperature and dengue incidence with increasing lag. At lower temperatures the relationship between temperature and DF cases is positive; however, as temperatures continue to rise past ~32°C conditions become detrimental to the mosquito(29) (Fan et al. 2014; Xiang et al. 2017) (34) (Morin, Comrie, and Ernst 2013) (35)(Kamiya et al. 2019) (28) (Taghikhani and Gumel 2018) and so the relationship inflects.

Similarly, the relationship with humidity variables was also strong and followed a similar pattern of increasingly weaker association with increased lag followed by associations that became stronger but changed direction. In the case of relative humidity, the negative association with no lag period was nearly 3 times stronger than the positive association with a 12 week lag. While, it is likely that, as relative humidity is in part derived from temperature, there is an element of collinearity between the two weather variables that resulted in the association we see between humidity and dengue incidence, independently humidity also plays a role in mosquito vector ecology. High humidity is associated with increased mosquito feeding, survival, and egg development (Morin, Comrie, and Ernst 2013). Lab studies have shown that although higher humidity generally favors the mosquito life cycle, higher temperatures and moderate humidity levels (28°C and 50 to 55% relative humidity) are better suited to the vector compared to environments of very high relative humidity and slightly lower temperature (25°C and 85 to 90%) (X. Wu et al. 2018). In studies investigating DF in Guangzhou, China, both Wu et al (2018), and Xiang et al (2017) found that similar to temperature very high relative humidity has a negative relationship with DF incidence (X. Wu et al. 2018; Xiang et al. 2017). Discrepancies in the relationship between humidity and DF among studies has been explained in part by differences in climate between the various geographic locations where DF has been studied. For example studies looking at tropical regions where average humidity is very high year round (70 - 80%) such as Indonesia, found no significant association between humidity and DF cases, whereas subtropical areas with more moderate levels of humidity reported significant positive associations (Xiang et al. 2017).

Although some studies have reported an association between precipitation and DF (Jayaraj et al. 2019) it is still debatable whether this factor is considered significant in large urban areas where the primary vector breeding habitats may be in indoor containers (Carvajal et al. 2018). In this study the weaker association we found with rainfall is likely attributed to the fact that rain is quite rare in this region. Similarly, water storage behaviors in response to water shortages are more likely to be the source of the mosquito breeding habitats, rather than rainfall accumulation (Altassan et al. 2019; Kholedi et al. 2012). Unfortunately, we do not have access to any data on behaviors related to indoor water storage in the region.

The positive correlation between Ramadan and DF is likely due to crowding and increased movement in the Jeddah/Makkah region with the exponential increase in the number of domestic pilgrims during the month. While this pilgrimage can be performed at any time throughout the year, most domestic pilgrims prefer visiting during the holy month of Ramadan. In 2016, the number of domestic Umrah pilgrims throughout the year was 16.5 million, nearly half of which visited during the month of Ramadan (Saudi General Authority for Statistics n.d.). Curiously, a similar association was not found with the timing of the Hajj. This may be a result of several factors. First there may be a reporting bias during the Hajj period as many local health resources are focused on coping with the large influx of visitors in a very small time frame. As most DF infections present as mild non-specific symptoms, this may lead to less patient visits to health centers and less reporting by medical professionals during this busy time. Secondly, the majority of Hajj pilgrims are foreign, and although they come from many dengue endemic countries, they must undergo numerous health screenings before and upon entering the country. In addition heat sensitive cameras monitor passengers arriving at Jeddah international airport and the local public health authorities isolate those suspected of being infectious (Mina 2014). Further, as the hajj pilgrimage is a physically demanding event it is unlikely that a person recently ill would attempt the trip. This leads to the possibility that although these foreign pilgrims may be the source of dengue virus introduction, they are not contributing significantly to the magnitude of the epidemic as the majority are not infectious upon arrival. This idea combined with the virus extinction reinvasion concept described earlier, also explains the negative correlation between DF cases and number of pilgrims the previous year. Finally, it is our hypothesis that the negative association with the timing of pilgrimage events is most likely an artifact of the seasonality of these events. The timing of the Hajj in the last 10 years has not coincided with the peak season of DF incidence. In fact, it has occurred in early fall, a time when DF incidence is historically low. The month of Ramadan has also failed to coincide with peak DF season in the last 10 years. Islamic events are based on a lunar calendar, therefore the corresponding dates on a solar calendar move back 11 days every year. By 2025 the Ramadan and Hajj events will take place between March and June. Notably, DF first emerged in 1993 when these two holy events also took place during the spring. Additional data, including viral serotyping, and further analyses, such as hindcasting to the period of DF emergence in the region, are required to make any causal mechanism of the impacts of the pilgrimages on DF incidence over the past 25 years.

For several years poisson multivariate regression has been the standard method for studying the impact of weather on DF. Several studies have successfully identified associations between temperature, humidity and rainfall with DF (Morin, Comrie, and Ernst 2013). In this study although the poisson model performed well overall, it was not able to capture the magnitude of the disease during the peaks.

ARIMA models have also become a commonly used approach for investigating the role of environmental factors on infectious disease outcomes (Carvajal et al. 2018; Racloz et al. 2012). While this modelling technique is ideal for tackling large datasets, it is also known for its sensitivity to outlier data points and its poor handling of missing values and multicollinearity

(Carvajal et al. 2018). In the present study the ARIMA model performed very well with group 1 and 2 covariates but its performance decreases significantly when the variable *number of cases the previous week* is removed from the model in groups 3 and 4. This makes sense as the ARIMA approach in predicting relies heavily on historical data. This presents an issue when attempting to forecast infectious disease incidence in places where there is no surveillance data or DF incidence is poorly captured.

The random forest model showed superior predictive ability compared to the linear regression models. This is likely because a random forest approach, unlike conventional statistical models, is more equipped to handle outlier data (Carvajal et al. 2018) and can better capture non-linear relationships that exist between the dependent variables and DF incidence (Scavuzzo et al. 2018). A number of studies attempted to develop a robust predictive model for DF using various modelling approaches (Carvajal et al. 2018; Guo et al. 2017; Rajathi et al. 2018; Vásquez et al. 2019). Althouse et al. (2011) looked at a number of regression models for DF prediction in Singapore, and found a linear model using a step-wise approach was superior. A similar Singapore study found the least absolute shrinkage and selection operator (LASSO) model performed best (Guo et al. 2017). Machine learning methods such as random forest have also recently become popular for the prediction of DF. It is important to note that the climate in Singapore, and many other locations where DF studies have been performed, is much different than that of Saudi Arabia. In assessing DF prediction methods, researchers have emphasized the superiority of tree based and support vector machine learning models compared to those utilizing linear regression (Guo et al. 2017; Carvajal et al. 2018). In China, Guo et al. compared the predictive ability of several predictive methods including support vector regression (SVR), a support vector model, and found SVR to be the most accurate (Guo et al. 2017). Additionally, Carvajal et al. demonstrated the advantage of a random forest approach compared to a variety of other models (Carvajal et al. 2018). Tree based methods have also been utilized to project the geospatial expansion of the disease vector while subject to varying climate change scenarios. Machine learning methods are particularly suited to investigate questions where in spite of accumulating large amounts of data many theoretical knowledge gaps persist (Scavuzzo et al. 2018). Although the random forest approach has been shown to be promising in DF prediction, the complex role that several environmental and population factors play on disease incidence leads to differing findings in the relationship between climate and DF in various locations (Vásquez et al. 2019).

Xiang et al (2017) described the relationship between weather variables and DF as being linear up to a specific threshold after which the association is less straightforward and more nuanced.(Xiang et al. 2017; X. Wu et al. 2018) This might explain why the linear regression models are able to predict DF epidemiology with relative accuracy outside of the seasonal peak but fail to capture the magnitude of the epidemic during the peak. Another possible explanation is that the vector population which is very sensitive to climate conditions, is responding to both the macroclimate variables captured in our models, and the urban microclimate conditions we were unable to measure (Scavuzzo et al. 2018). There may also be other overlooked contributing factors at work not included in our model whose effect is more profound during the peak of the epidemic. This is supported by the fact that even the random forest model which is non-linear struggles to accurately represent the magnitude of the contagion during the seasonal peak.

Our study has several limitations. The first is missing DF count data. We found 19 days of missing data in the Jeddah dataset from May 2nd to May 19th, 2018 (Figure 1). This likely influenced the magnitude of the correlation between the observed number of DF cases and the number of cases as predicted by either model but had no bearing on the comparison between the two models. Similarly to many countries (Horta et al. 2014), we also suspect significant under-reporting due to asymptomatic cases, misdiagnosis of mild cases of DF, or a change in the reporting standards or recognition of DF and rates of DF testing over the course of the study period. Another limitation specific to models using covariate groups 1, and 3 is the consideration of causal temporality when looking at the association between independent variables and DF cases with no lag time. As these variables are based on a weekly aggregate, the number of cases at the beginning of the week cannot be influenced by variable measurements occurring after the cases are reported. Yet, weather variables in this study are considered as weekly summary parameters. This can pose an issue as it contradicts the temporality of the causal hypothesis we are investigating. In contrast, investigating models that exclusively include lagged covariates allows us to subvert this issue. Moreover, in the context of early prediction, models that incorporate variables with no lag times have potentially less accurate predictive application as the weather covariates would need to be modeled or estimated. In an effort to correct for this, we opted to create a group of covariates that only included lagged variables. Additionally, as noted, we have no data on other factors known to affect dengue ecology, such as water storage, household density, and protective factors such as window screens and air conditioning prevalence, that might affect the extent of suitable habitat or transmission dynamics. Lastly, our findings also suffer from a lack of generalizability as statistical models are usually very location specific and yield varying results when applied to areas with differing geography, climate, and urban and population structures (Racloz et al. 2012).

5. Conclusion

DF, which has become endemic in the Arabian peninsula, has complex ecology that is strongly affected by local environmental and social factors (Altassan et al. 2019). Local virus serotypes, immunity patterns, population demographics and movement, and intervention programs, all of which vary across geographic locations, affect the relationship between DF and environmental and weather variables (Vásquez et al. 2019). DF ecology in Saudi Arabia had not been well characterized prior to our study. We found that temperature, humidity, and, to a far lesser extent, rainfall, all play a role on DF incidence in the Arabian Peninsula. Additionally, the two main pilgrimage events occurring in the city of Makkah might also play some role in the incidence of DF, but it is still unclear how and to what extent.

This study found that a nonlinear machine learning approach had better accuracy in predicting DF in Saudi Arabia, particularly in the absence of accurate surveillance data. These models could have varying applications depending on the timing of the application. For example, the ability to predict disease incidence 2 or 3 months in advance potentially allows for primary prevention interventions, such as vector control, including eliminating mosquito breeding habitats in the form of household water containers. Whereas, predicting the disease a week or 2 in advance gives medical personnel time to prepare for the influx of patients.

Further investigation is needed to better understand the role various environmental and population factors play on DF incidence in this sparsely studied geographic area, and to better prepare the region’s healthcare system to anticipate and intervene to reduce the spread of this disease.

6. Tables and Figures

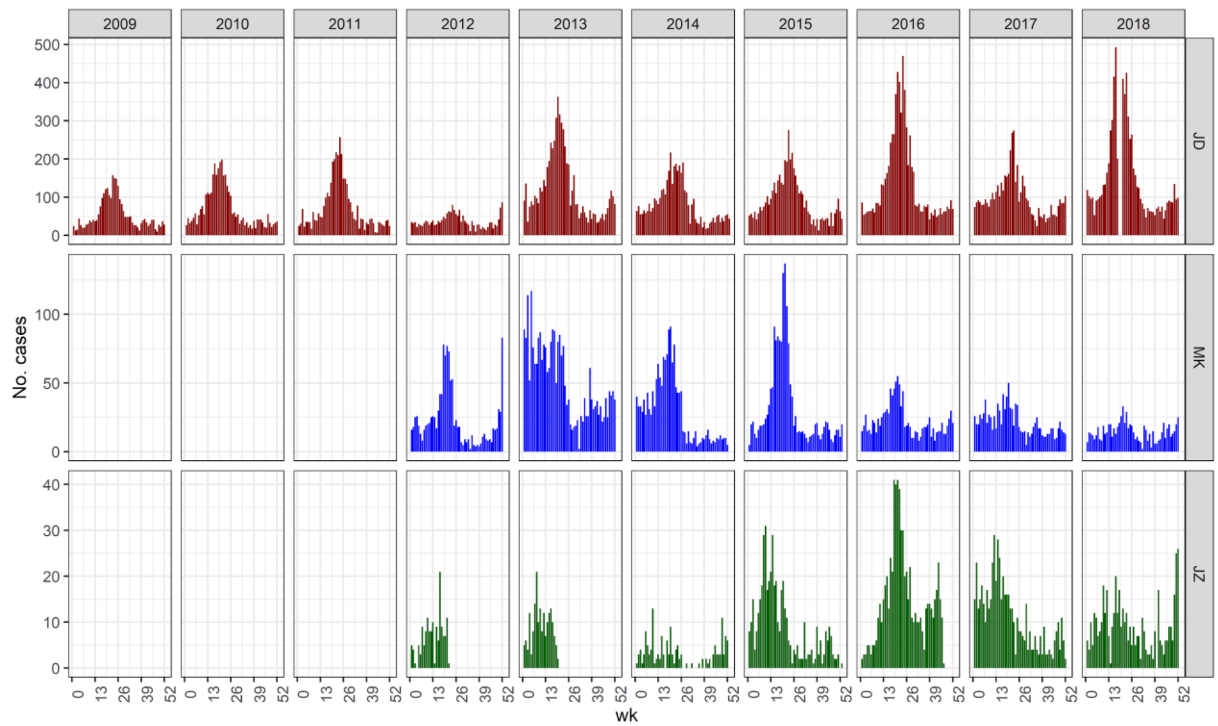


Figure 1. Seasonal distribution of DF cases in Jeddah, Makkah, and Jizan from 2009 to 2018.

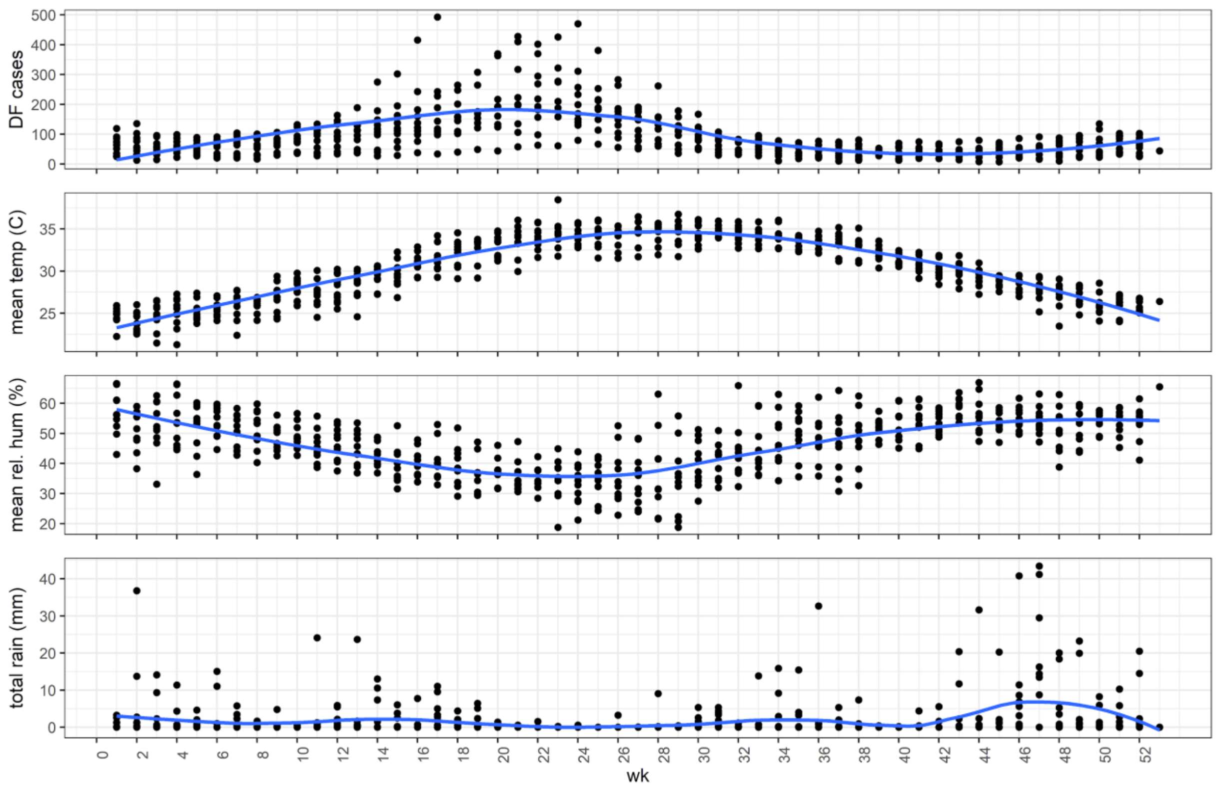


Figure 2(a). Distribution of DF cases, average temperature, relative humidity and total rainfall throughout the year in Jeddah based on measurements for 2009 to 2018.

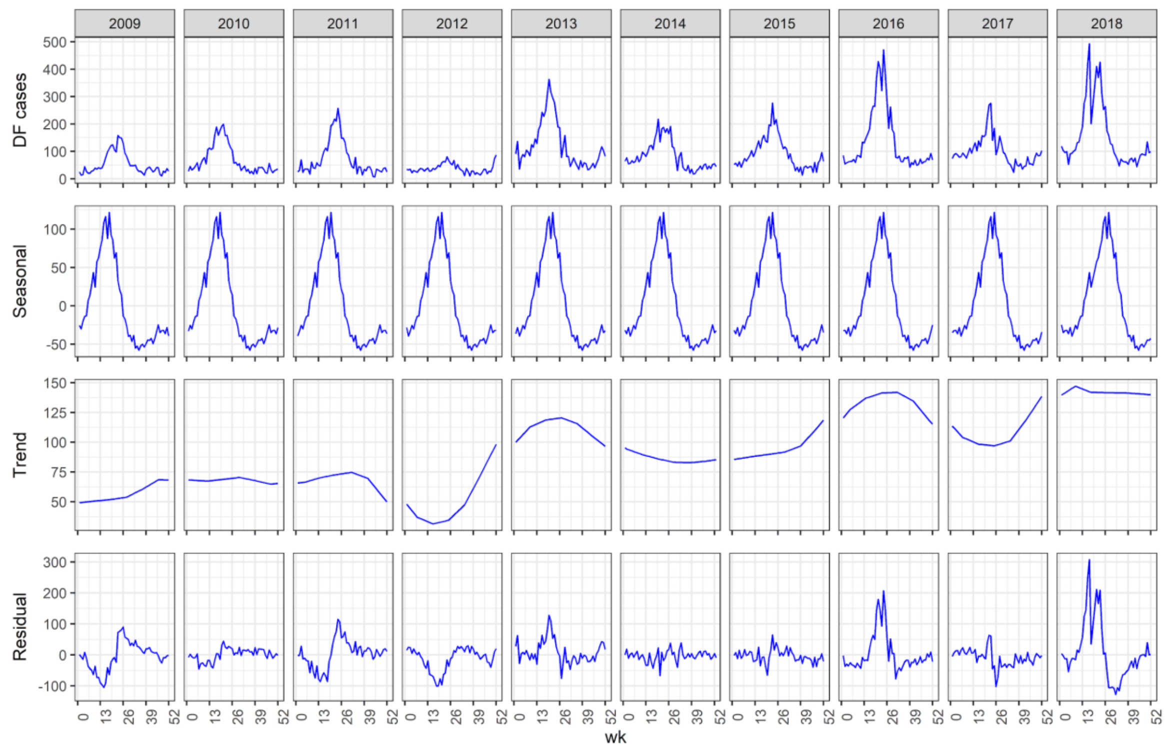


Figure 3. Distribution of DF cases in Jeddah decomposed of seasonal pattern from 2009 to 2018.

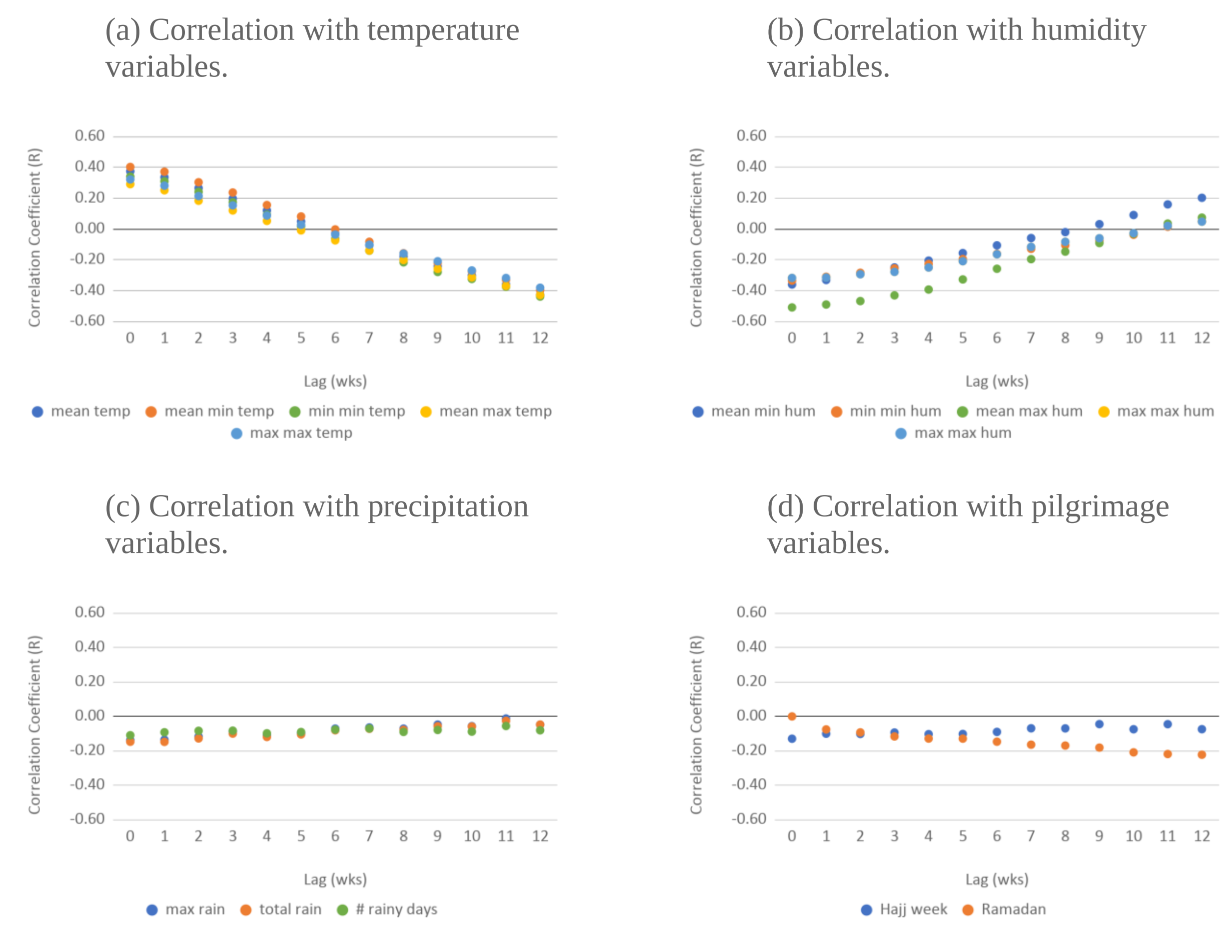


Figure 4(a-d). Results of the univariate analysis between DF cases and weather and population variables in the city of Jeddah between 2009 to 2018.

Covariate group 1				
Variable type	**Variable name**	**Lag period (weeks)**	**Pearson Correlation Coefficient (R)**	**p-value**
Weather	*Mean maximum temperature*	12	− 0.42	$< 2.2e^{-16}$
	Mean minimum temperature	none	0.38	$< 2.2e^{-16}$
	Mean relative humidity	None	− 0.53	$< 2.2e^{-16}$
	Mean minimum relative humidity	12	0.17	$1.22e^{-4}$
	Number of rainy days	7	− 0.09	0.032
Pilgrimage	*Hajj week*	none	− 0.11	0.011
	Ramadan	none	0.2	$6.66e^{-6}$
	Ramadan	12	− 0.2	$5.39e^{-6}$
	Number of pilgrims the previous year	N/A	− 0.11	0.014
Other	*Number of cases the previous week*	N/A	0.91	$< 2.2e^{-16}$
	Year	N/A	0.33	$2.83e^{-15}$
Covariate group 2				
Variable type	**Variable name**	**Lag period (weeks)**	**Pearson Correlation Coefficient (R)**	**p-value**
Weather	*Mean maximum temperature*	12	− 0.42	$< 2.2e^{-16}$
	Mean minimum temperature	1	0.35	$< 2.2e^{-16}$

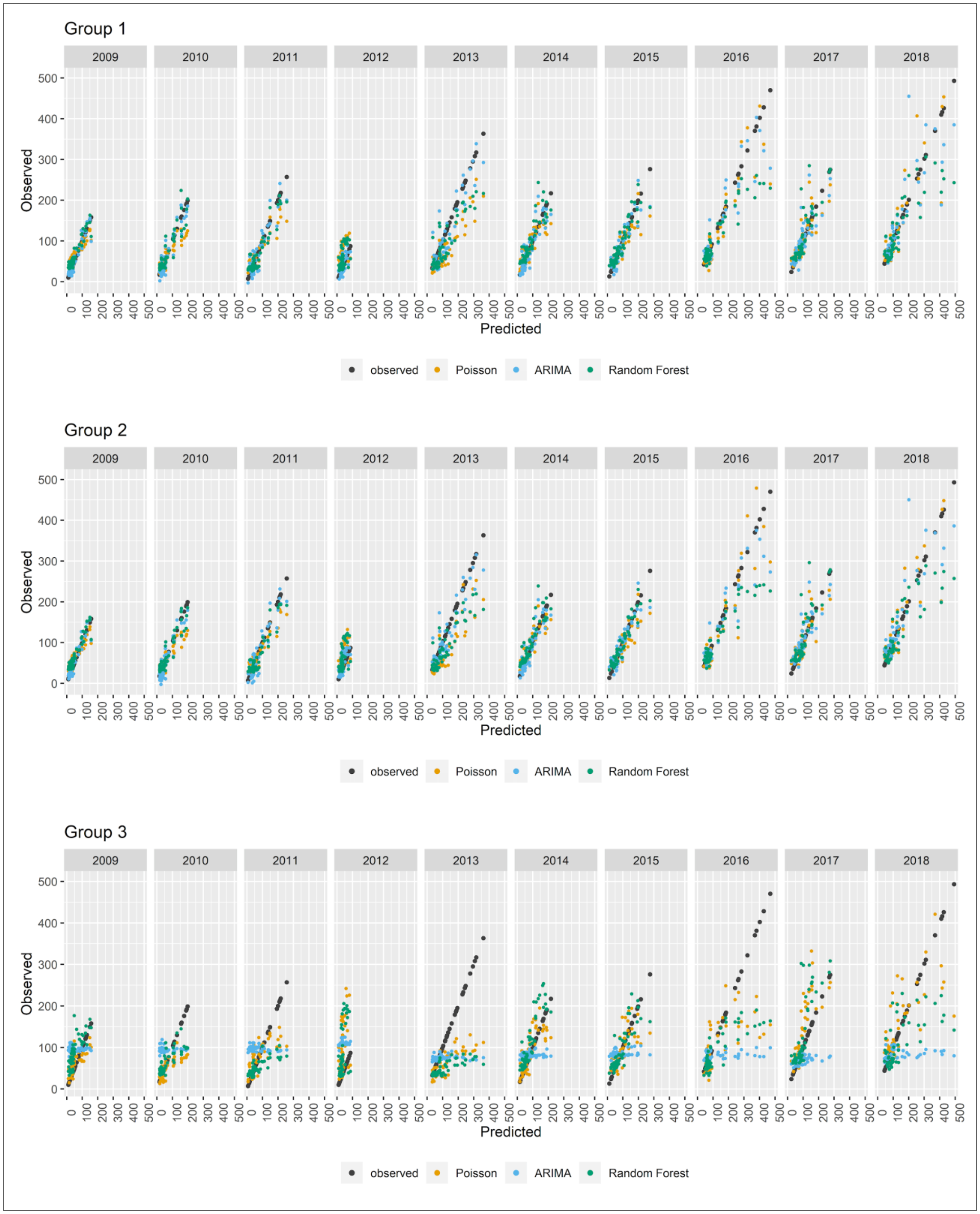
	Mean relative humidity	1	− 0.51	< $2.2e^{-16}$
	Mean minimum relative humidity	12	0.17	$1.22e^{-4}$
	Number of rainy days	7	− 0.09	0.032
Pilgrimage	*Hajj week*	5	− 0.10	0.029
	Ramadan	12	− 0.2	$5.39e^{-6}$
	Number of pilgrims the previous year	N/A	− 0.11	0.014
Other	*Number of cases the previous week*	N/A	0.91	< $2.2e^{-16}$
	Year	N/A	0.33	$2.83e^{-15}$

*N/A not applicable

Table 1. Strength of the association between variables in covariate groups 1 and 2 with DF cases based on a bivariate regression analysis.

Covariate Group	Regression model	R^2	RMSE
1	Poisson	0.73	28.8
	ARIMA	0.78	20.6
	Random Forest	0.76	24.3
2	Poisson	0.75	27.6
	ARIMA	0.78	20.8
	Random Forest	0.78	25.1
3	Poisson	0.55	40.7
	ARIMA	0.04	57.8
	Random Forest	0.60	42.6
4	Poisson	0.56	40.7
	ARIMA	0.30	54.1
	Random Forest	0.65	41.3

Table 2. Correlation measure (R^2) and error (RMSE) for each regression model with each of the 4 covariate groupings averaged for all years 2009 - 2018.


Group 1
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Observed
Predicted
observed
Poisson
ARIMA
Random Forest
Group 2
Group 3

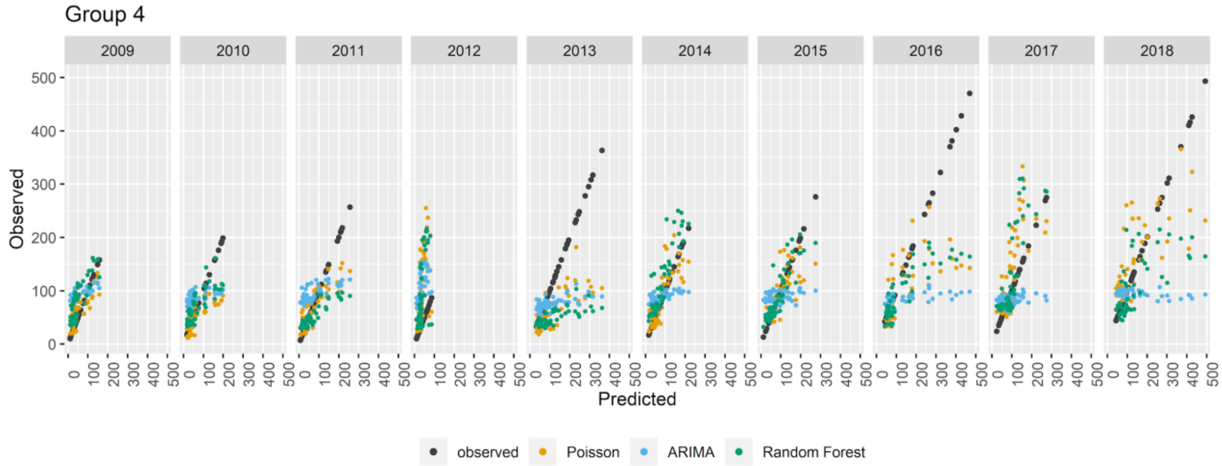
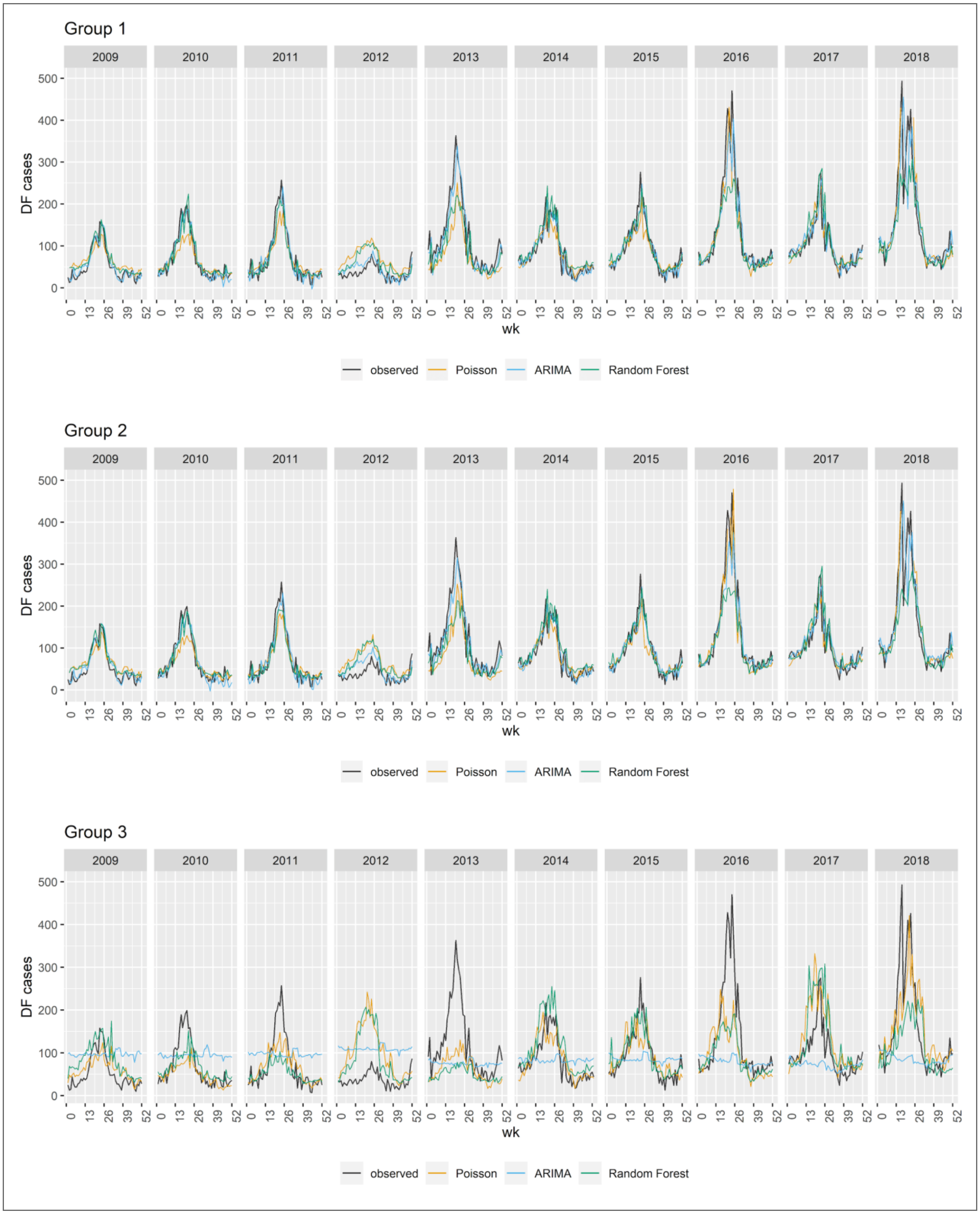


Figure 5. Correlation between observed and model predicted DF cases in Jeddah as predicted by poisson, ARIMA, and Random Forest regression models. Group number refers to the group of covariates used in the models. Note: For the purpose of visual clarity the number of cases was capped at 500.


Group 1
Group 2
Group 3
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
DF cases
0
100
200
300
400
500
wk
0
13
26
39
52
observed
Poisson
ARIMA
Random Forest

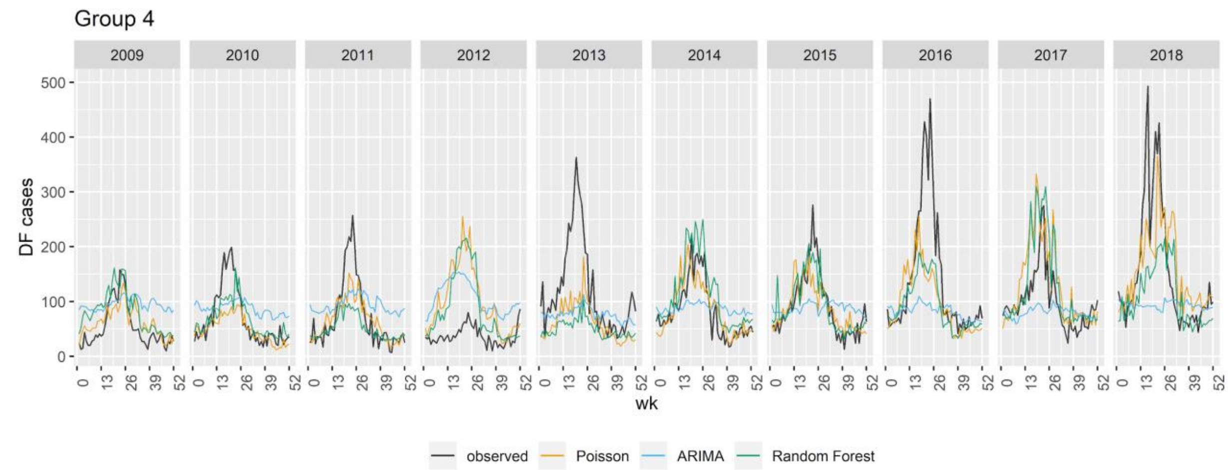


Figure 6. Line graph of observed vs. model predicted DF cases in Jeddah as predicted by poisson, ARIMA, and Random Forest regression models. Group number refers to the group of covariates used in the models' covariates used in the models. Note: For the purpose of visual clarity the number of cases was capped at 500.

Appendix A. Additional tables and figures describing the performance of all three DF predictive models in the city of Jeddah.

Year validated	Covariate group	Regression model	R^2	RMSE
2009	1	Poisson	0.86	19.1
		ARIMA	0.88	10.35
		Random Forest	0.89	15
	2	Poisson	0.85	18.5
		ARIMA	0.87	11.3
		Random Forest	0.89	15.7
	3	Poisson	0.6	23
		ARIMA	0	54.3
		Random Forest	0.65	32
	4	Poisson	0.64	22.4
		ARIMA	0.38	49.5
		Random Forest	0.76	29.3
2010	1	Poisson	0.84	19.3
		ARIMA	0.87	15.6
		Random Forest	0.82	15.8
	2	Poisson	0.85	18.6
		ARIMA	0.87	16.6
		Random Forest	0.87	14.1

	3	Poisson	0.63	28
		ARIMA	0	53.8
		Random Forest	0.6	24.8
	4	Poisson	0.65	27.7
		ARIMA	0.36	45.4
		Random Forest	0.69	23.2
2011	1	Poisson	0.87	20.7
		ARIMA	0.85	19
		Random Forest	0.88	16.3
	2	Poisson	0.89	19.2
		ARIMA	0.85	19.7
		Random Forest	0.89	16.8
	3	Poisson	0.61	27.2
		ARIMA	0.09	61.3
		Random Forest	0.7	31.1
	4	Poisson	0.7	26.3
		ARIMA	0.53	50.3
		Random Forest	0.76	30.6
2012	1	Poisson	0.31	33.6
		ARIMA	0.47	13.4
		Random Forest	0.31	24.3
	2	Poisson	0.36	32.6
		ARIMA	0.49	16.3
		Random Forest	0.37	28.6
	3	Poisson	0.28	66.8
		ARIMA	0.07	72.1

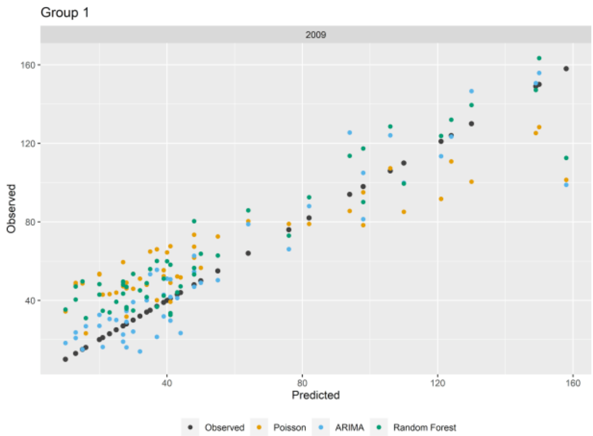
		Random Forest	0.29	55.1
	4	Poisson	0.32	66.7
		ARIMA	0.22	70
		Random Forest	0.34	56.8
2013	1	Poisson	0.85	47.2
		ARIMA	0.85	25.8
		Random Forest	0.81	38.3
	2	Poisson	0.82	46
		ARIMA	0.85	25.4
		Random Forest	0.81	39.2
	3	Poisson	0.61	63
		ARIMA	0	63.3
		Random Forest	0.55	73
	4	Poisson	0.55	62.1
		ARIMA	0.37	60.3
		Random Forest	0.55	72.5
2014	1	Poisson	0.77	18
		ARIMA	0.79	18.5
		Random Forest	0.76	20
	2	Poisson	0.81	17.2
		ARIMA	0.81	17.8
		Random Forest	0.8	19.2
	3	Poisson	0.64	23.5
		ARIMA	0	42.2
		Random Forest	0.79	31.9
	4	Poisson	0.65	22.4

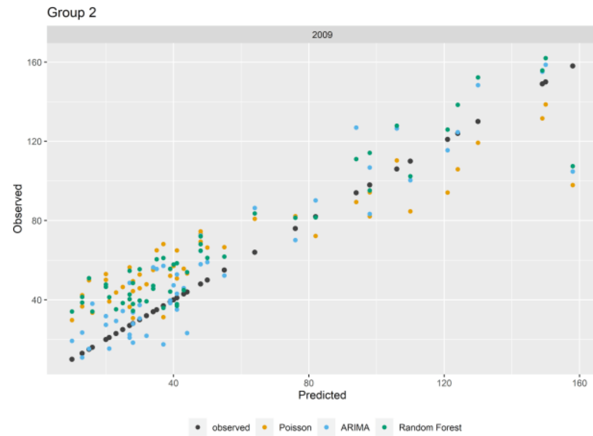
		ARIMA	0.47	38.2
		Random Forest	0.82	30.2
2015	1	Poisson	0.77	19.9
		ARIMA	0.81	18.6
		Random Forest	0.83	17.1
	2	Poisson	0.79	20.3
		ARIMA	0.82	17.7
		Random Forest	0.88	14.8
	3	Poisson	0.54	26.9
		ARIMA	0.05	44.4
		Random Forest	0.72	21.6
	4	Poisson	0.58	25.6
		ARIMA	0.08	43.5
		Random Forest	0.78	18.8
2016	1	Poisson	0.79	31.1
		ARIMA	0.85	27.7
		Random Forest	0.86	36
	2	Poisson	0.85	27.9
		ARIMA	0.86	26.5
		Random Forest	0.86	37.4
	3	Poisson	0.45	56.5
		ARIMA	0.09	74.8
		Random Forest	0.7	53.1
	4	Poisson	0.45	56.8
		ARIMA	0.32	70.3
		Random Forest	0.72	52.8

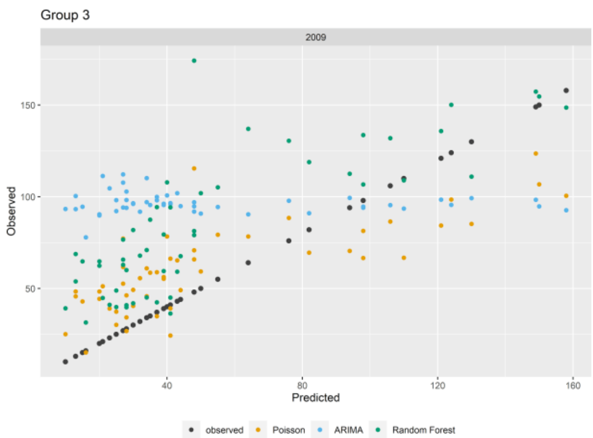
2017	1	Poisson	0.68	22.1
		ARIMA	0.67	21.2
		Random Forest	0.69	20.4
	2	Poisson	0.7	22.4
		ARIMA	0.7	21.5
		Random Forest	0.7	21.5
	3	Poisson	0.6	41.2
		ARIMA	0.11	37.8
		Random Forest	0.6	40.9
	4	Poisson	0.54	44.1
		ARIMA	0.12	37.4
		Random Forest	0.65	38.1
2018	1	Poisson	0.53	57.2
		ARIMA	0.71	35.8
		Random Forest	0.75	39.7
	2	Poisson	0.55	53.3
		ARIMA	0.72	35.2
		Random Forest	0.75	39.2
	3	Poisson	0.52	50.4
		ARIMA	0.01	73.8
		Random Forest	0.42	62.2
	4	Poisson	0.51	53.2
		ARIMA	0.1	75.9
		Random Forest	0.42	62.9

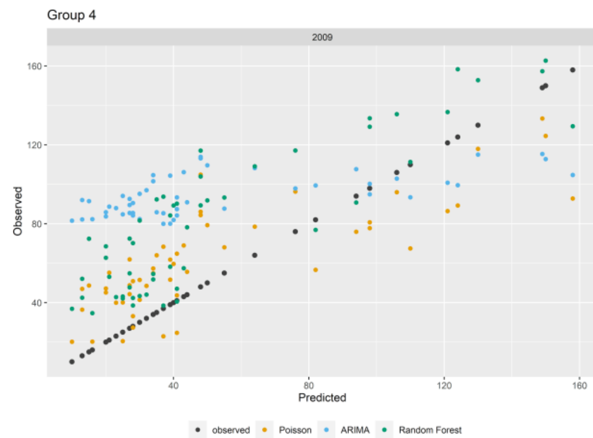
Table 3. Correlation measure (R^2) and error (RMSE) for each regression model in the 4 covariate groupings for each year.

2009

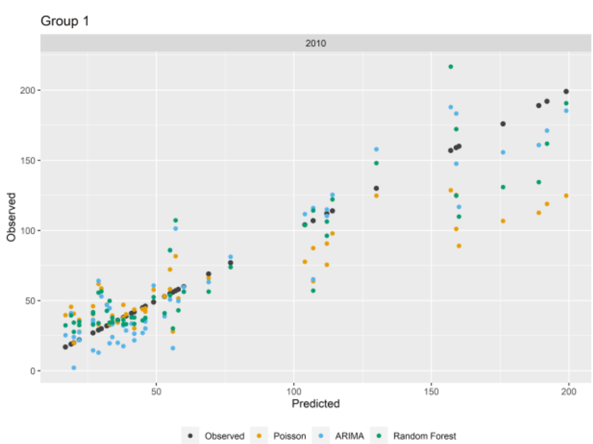

Group 1
2009
Observed
Predicted
Observed Poisson ARIMA Random Forest

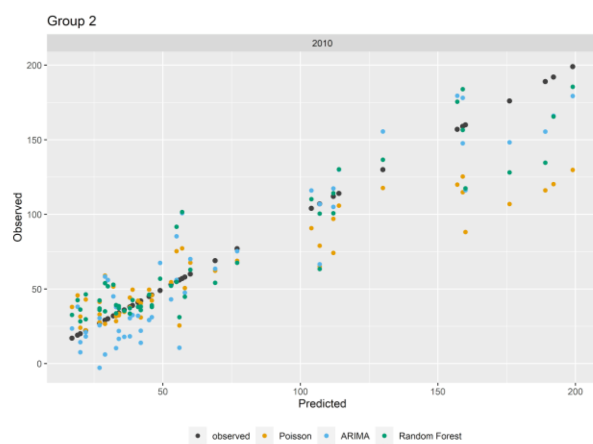

Group 2
2009
Observed
Predicted
observed Poisson ARIMA Random Forest

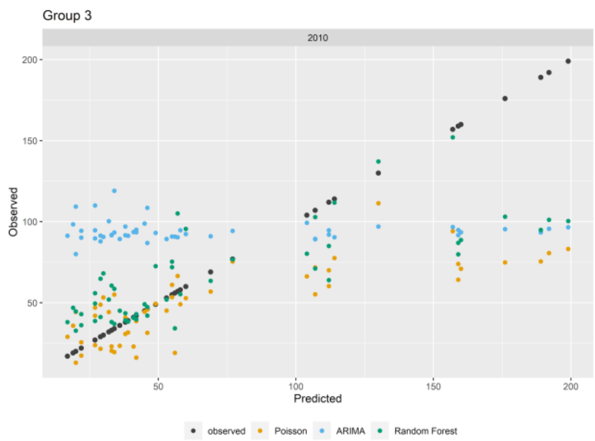

Group 3
2009
Observed
Predicted
observed Poisson ARIMA Random Forest

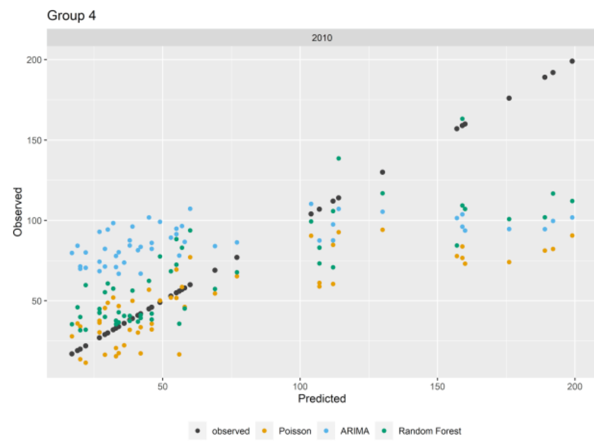

Group 4
2009
Observed
Predicted
observed Poisson ARIMA Random Forest

2010

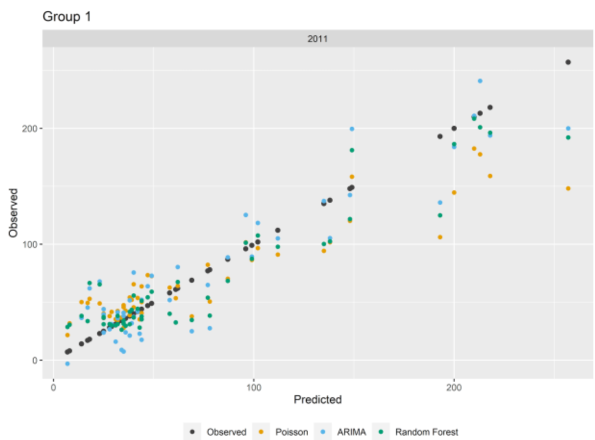

Group 1
2010
Observed
Predicted
Observed Poisson ARIMA Random Forest

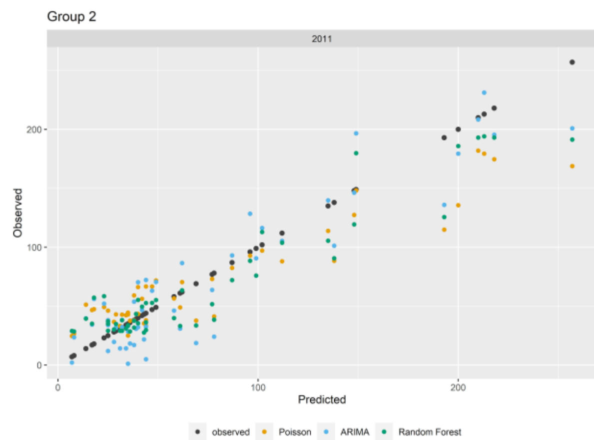

Group 2
2010
Observed
Predicted
observed Poisson ARIMA Random Forest

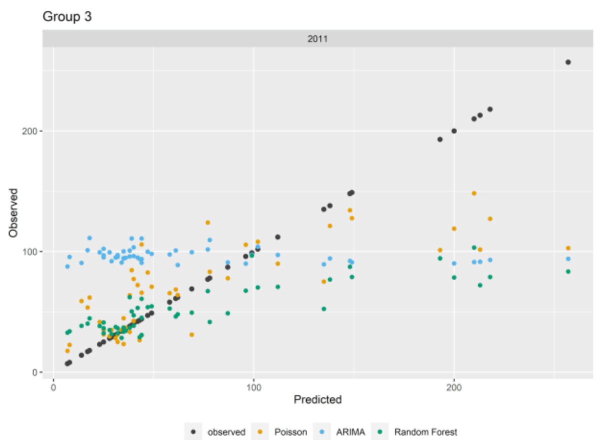

Group 3
2010
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

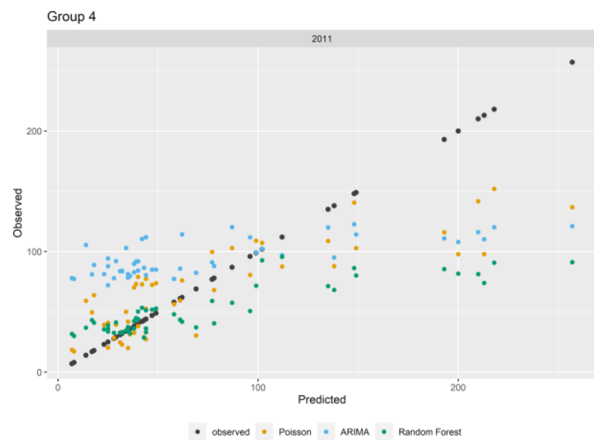

Group 4
2010
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

2011

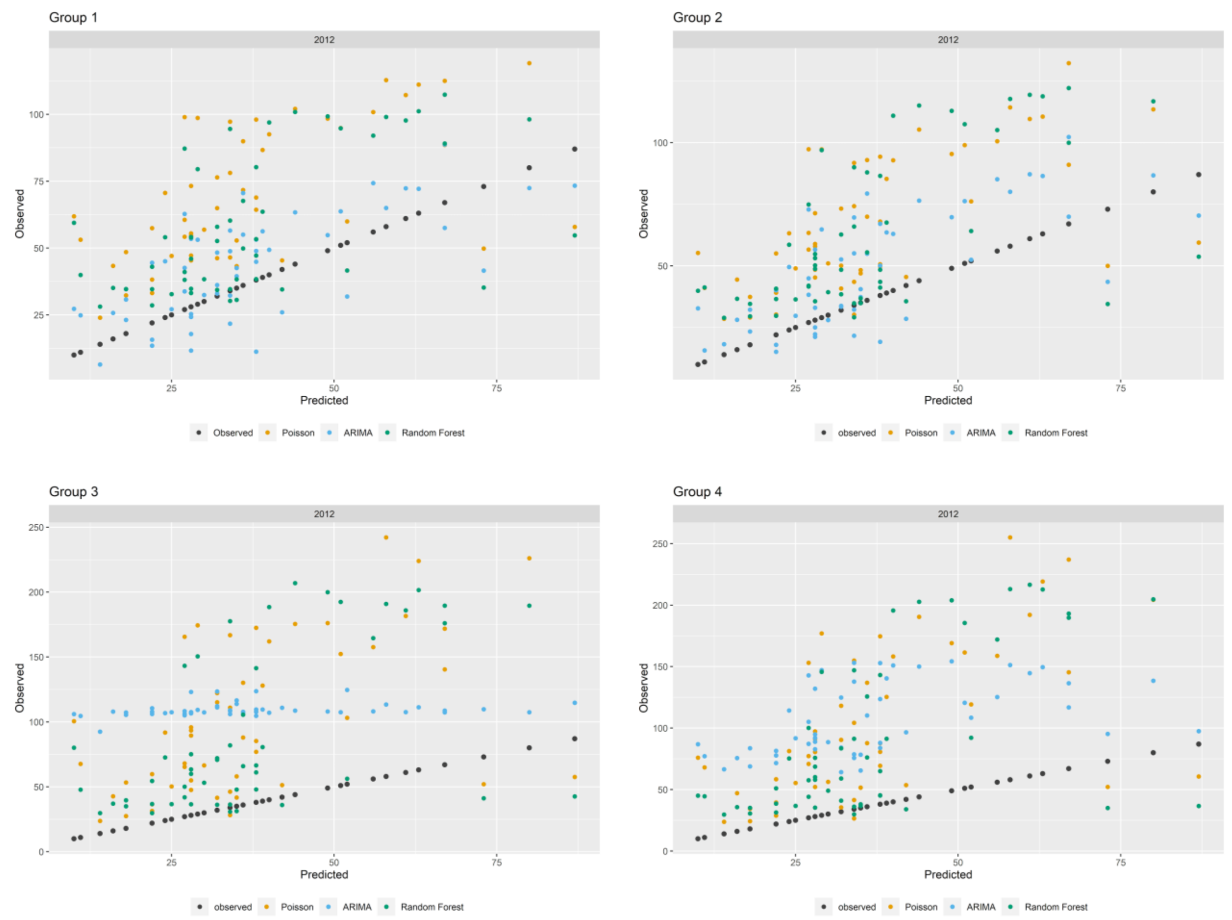

Group 1
2011
Observed
Predicted
Observed
Poisson
ARIMA
Random Forest


Group 2
2011
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

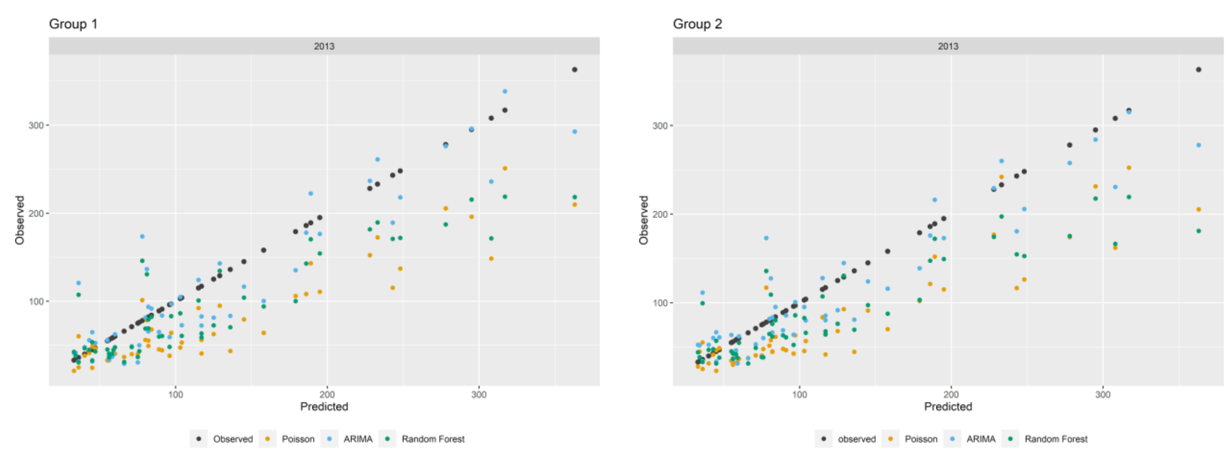

Group 3
2011
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

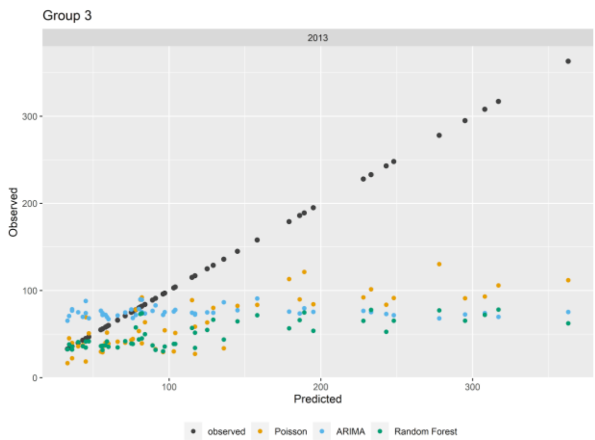

Group 4
2011
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

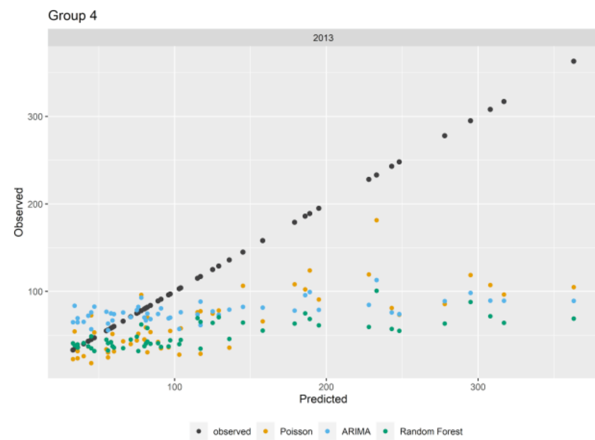
2012


Group 1
2012
Observed
Predicted
Observed
Poisson
ARIMA
Random Forest
Group 2
2012
Observed
Predicted
observed
Poisson
ARIMA
Random Forest
Group 3
2012
Observed
Predicted
observed
Poisson
ARIMA
Random Forest
Group 4
2012
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

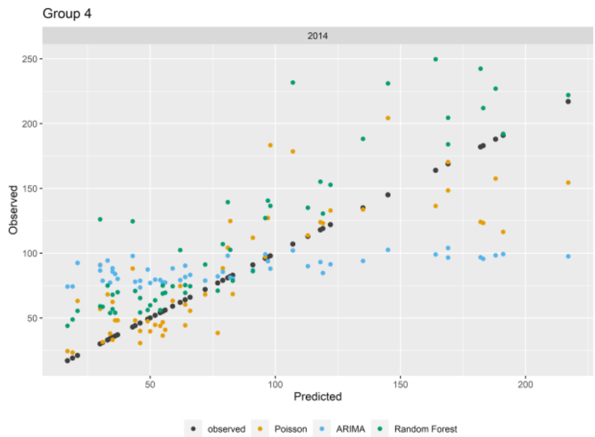
2013

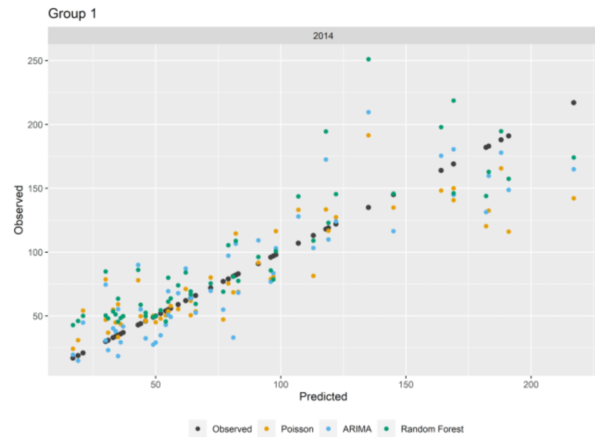

Group 1
2013
Observed
Predicted
Observed
Poisson
ARIMA
Random Forest
Group 2
2013
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

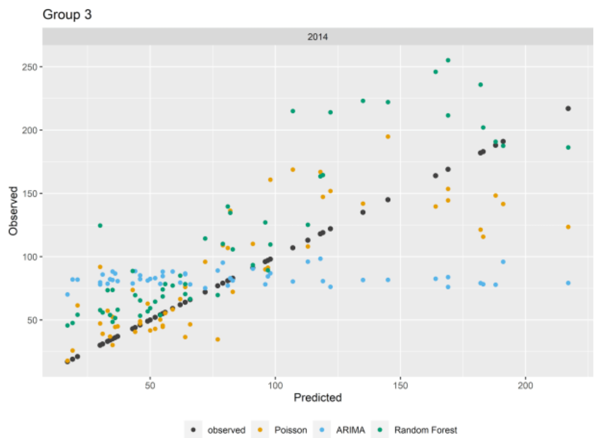

Group 3
2013
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

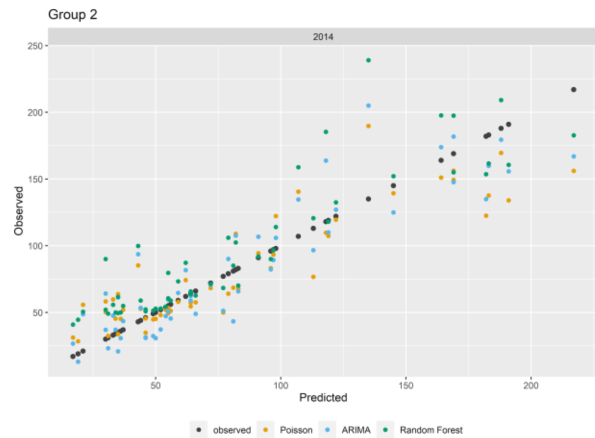

Group 4
2013
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

2014

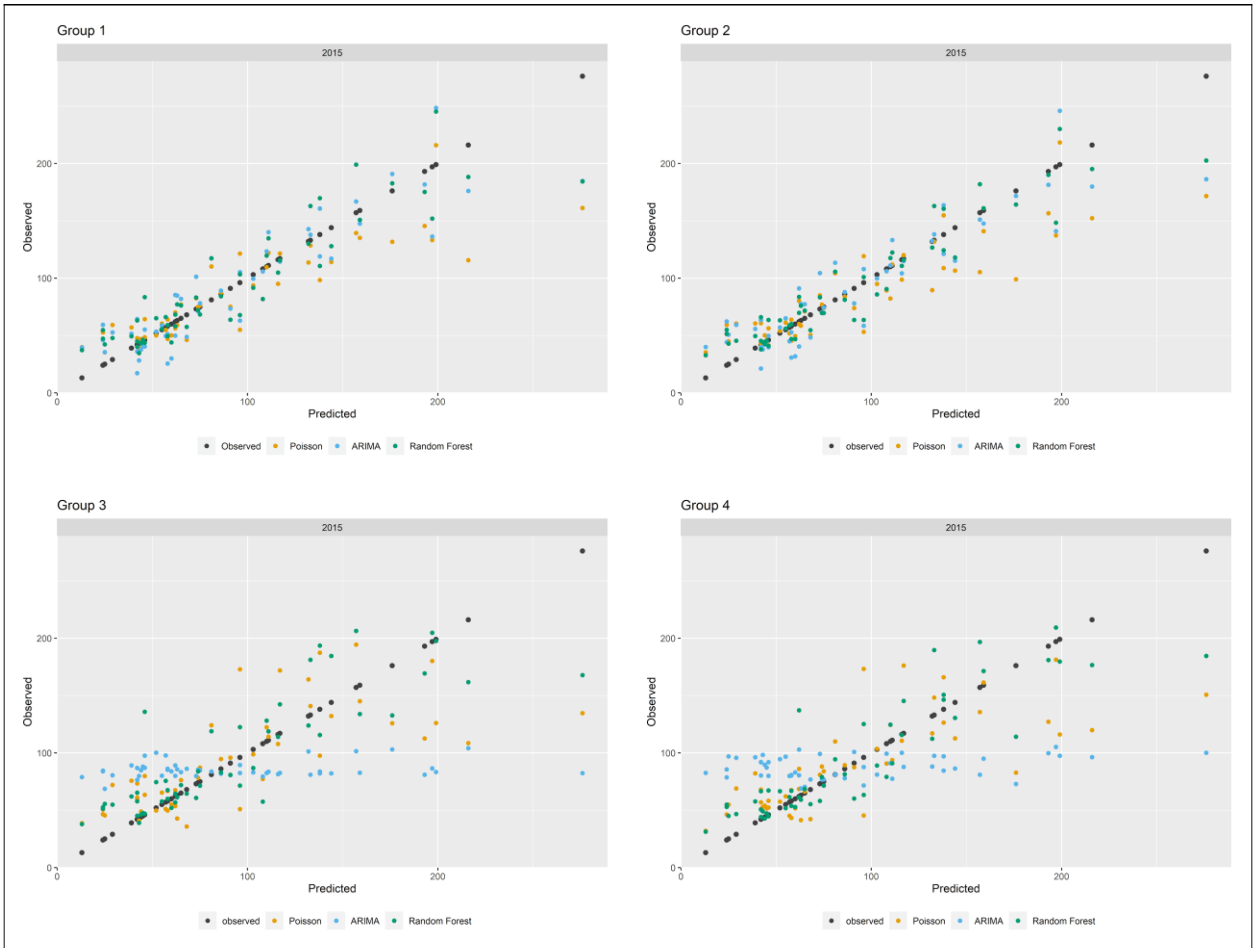

Group 4
2014
Observed
Predicted
observed
Poisson
ARIMA
Random Forest


Group 1
2014
Observed
Predicted
Observed
Poisson
ARIMA
Random Forest

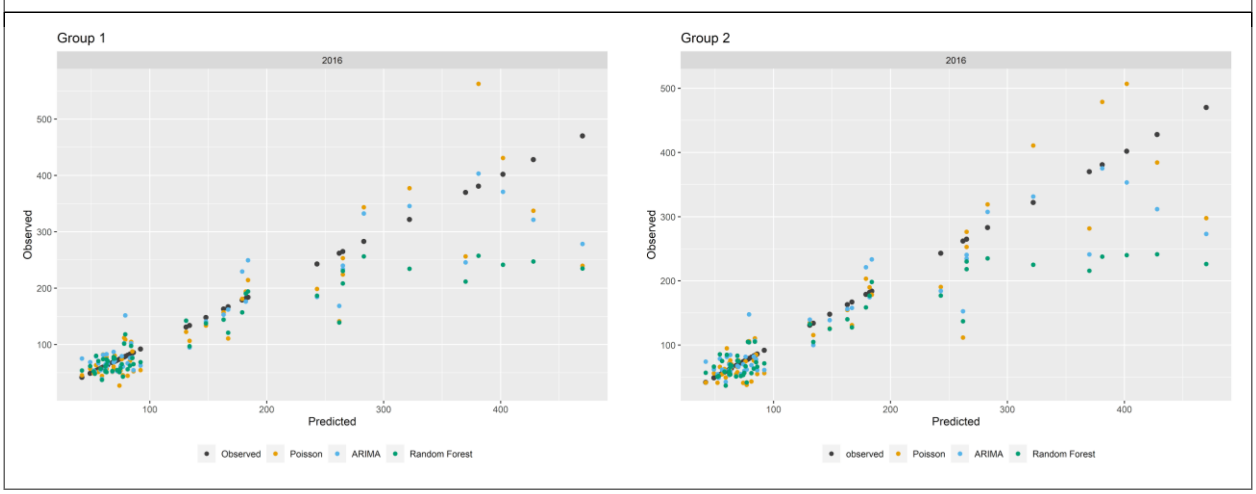

Group 3
2014
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

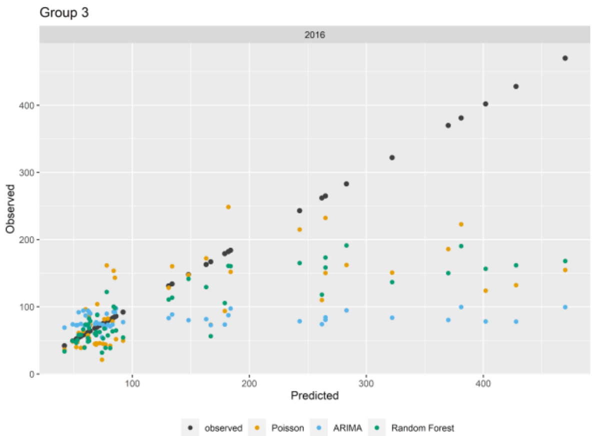

Group 2
2014
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

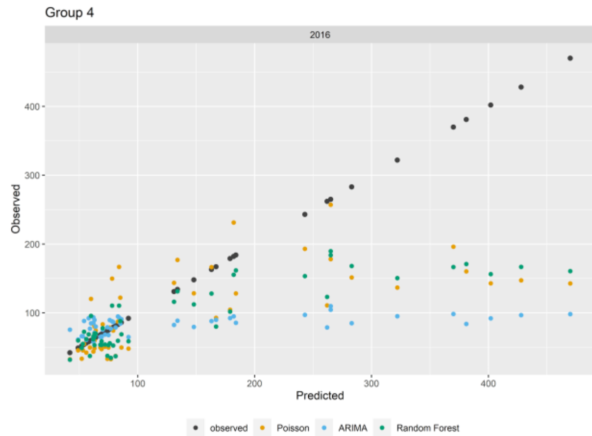
2015


Group 1
2015
Observed
Predicted
Observed Poisson ARIMA Random Forest
Group 2
2015
Observed
Predicted
observed Poisson ARIMA Random Forest
Group 3
2015
Observed
Predicted
observed Poisson ARIMA Random Forest
Group 4
2015
Observed
Predicted
observed Poisson ARIMA Random Forest

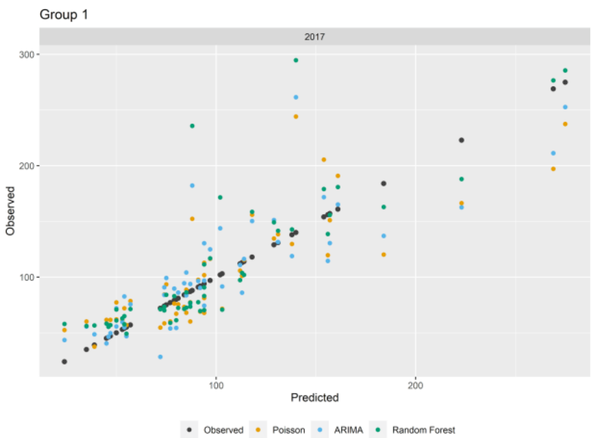
2016

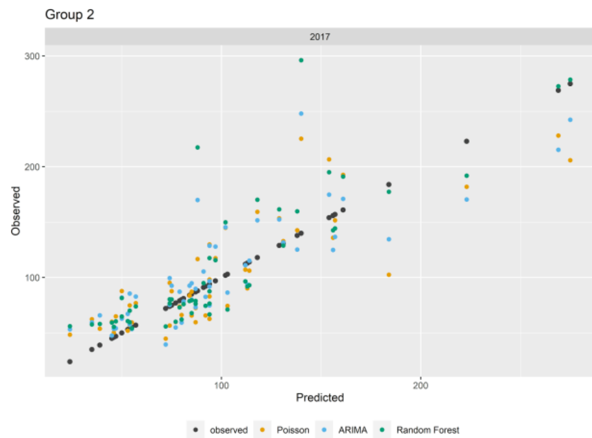

Group 1
2016
Observed
Predicted
Observed Poisson ARIMA Random Forest
Group 2
2016
Observed
Predicted
observed Poisson ARIMA Random Forest

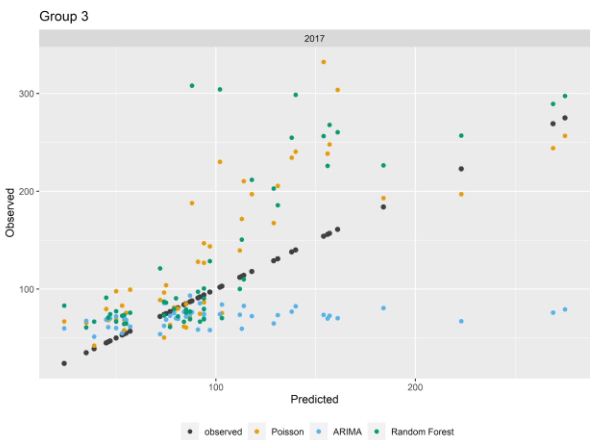

Group 3
2016
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

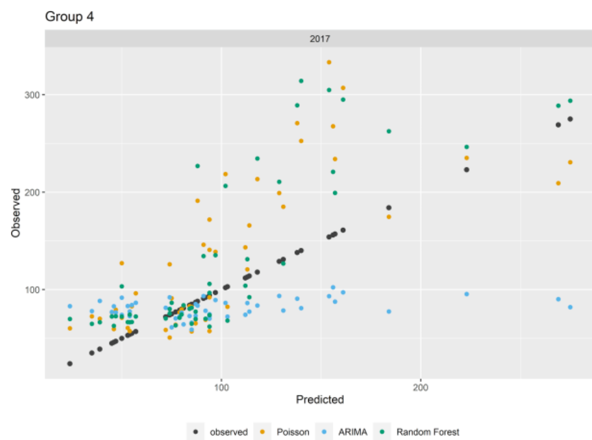

Group 4
2016
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

2017


Group 1
2017
Observed
Predicted
Observed
Poisson
ARIMA
Random Forest


Group 2
2017
Observed
Predicted
observed
Poisson
ARIMA
Random Forest


Group 3
2017
Observed
Predicted
observed
Poisson
ARIMA
Random Forest


Group 4
2017
Observed
Predicted
observed
Poisson
ARIMA
Random Forest

2018

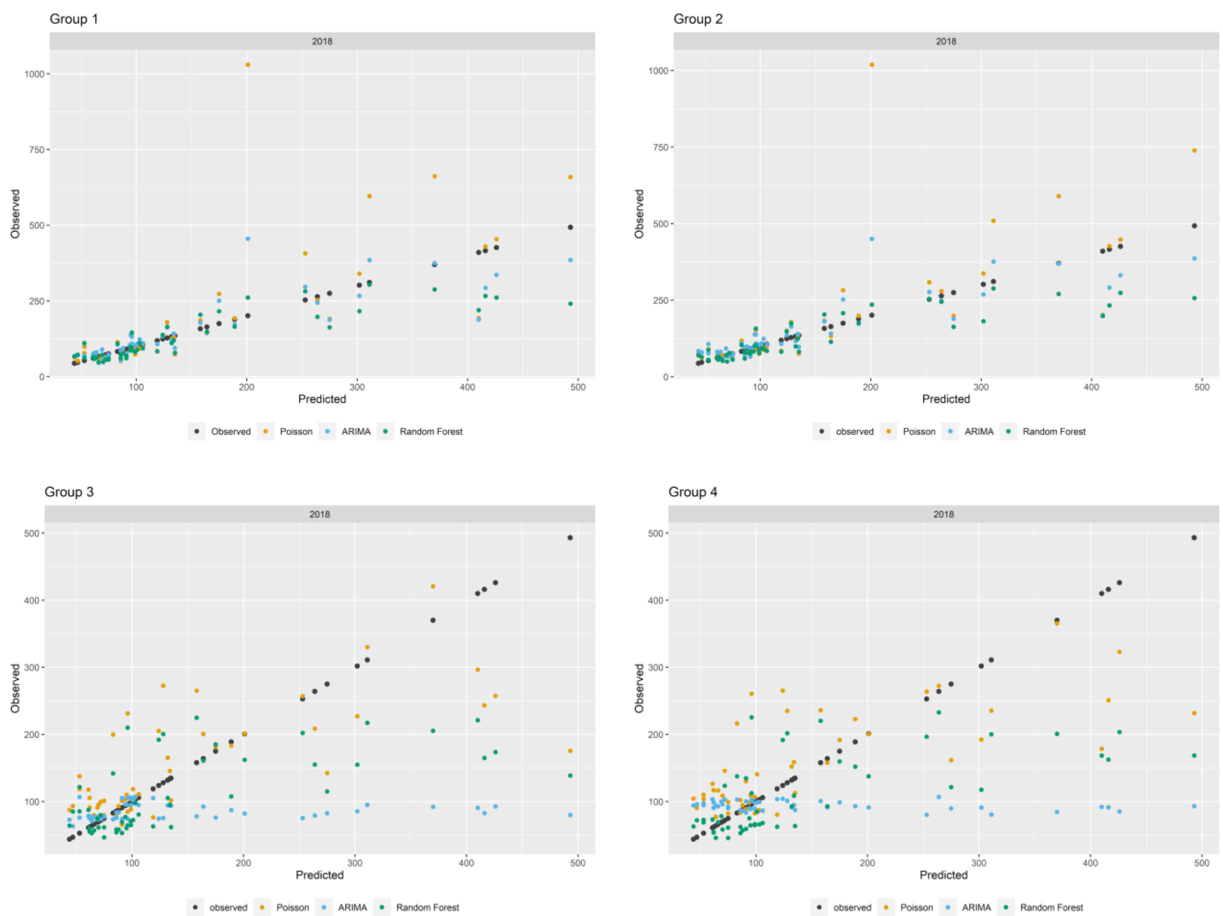
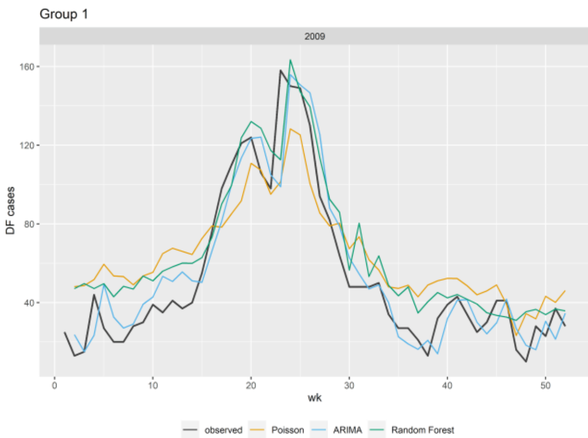
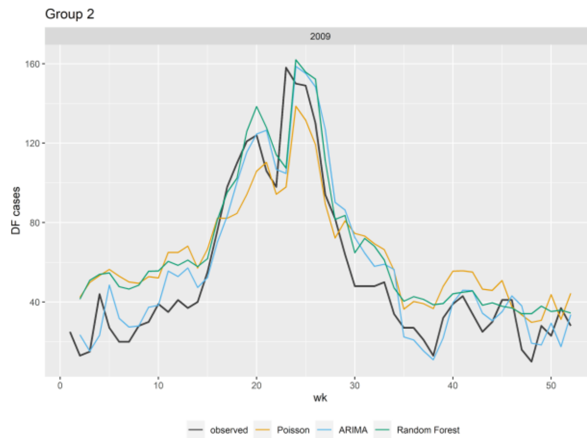
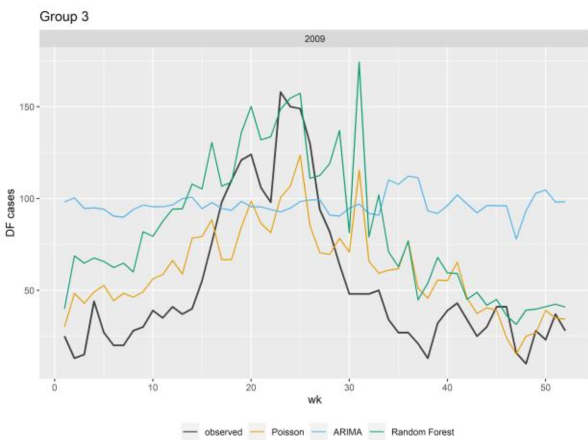


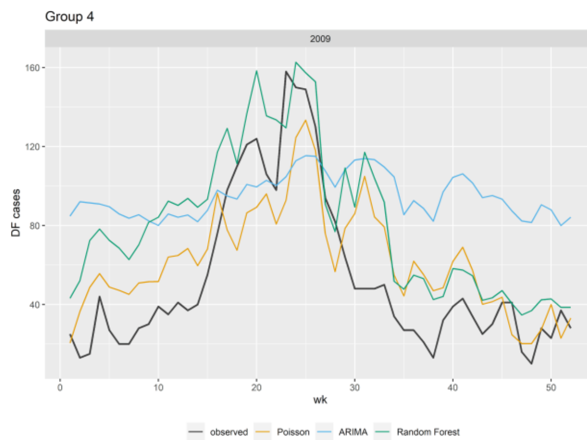
Figure 5(b). Correlation between observed and model predicted DF cases in Jeddah as predicted by poisson, ARIMA, and Random Forest regression models. Model validation on the one year excluded from the training dataset (a-j). Group number refers to the group of covariates used in the models.

2009

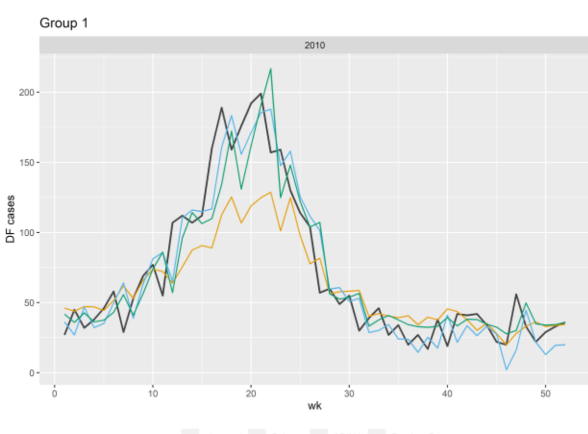

Group 1
2009
DF cases
wk
observed
Poisson
ARIMA
Random Forest

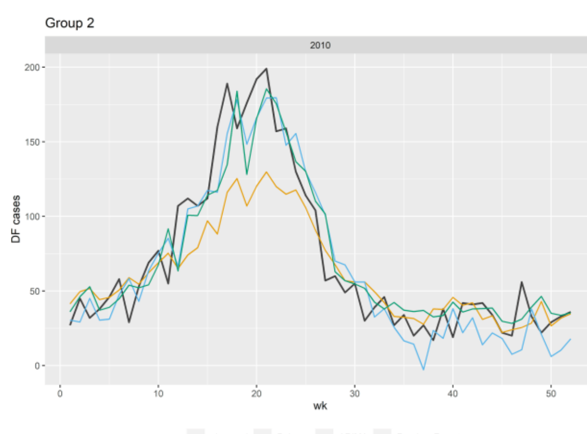

Group 2
2009
DF cases
wk
observed
Poisson
ARIMA
Random Forest

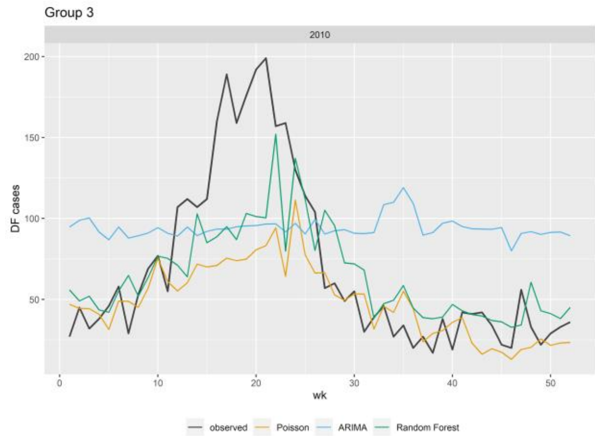

Group 3
2009
DF cases
wk
observed
Poisson
ARIMA
Random Forest

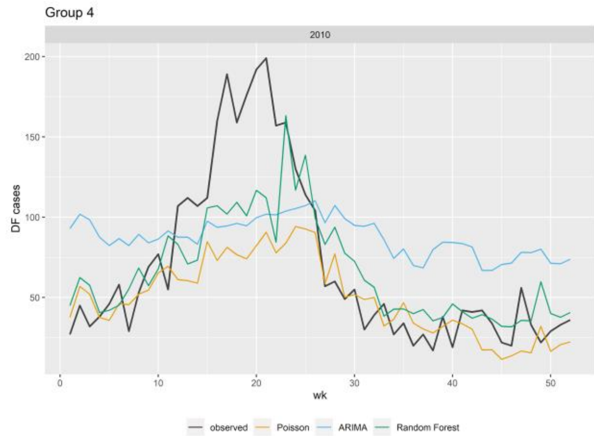

Group 4
2009
DF cases
wk
observed
Poisson
ARIMA
Random Forest

2010

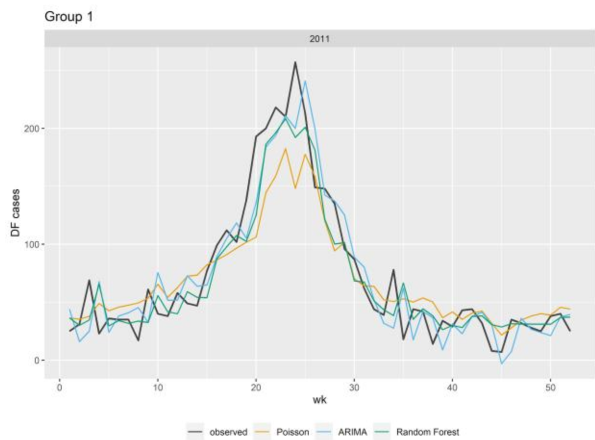

Group 1
2010
DF cases
wk
observed
Poisson
ARIMA
Random Forest

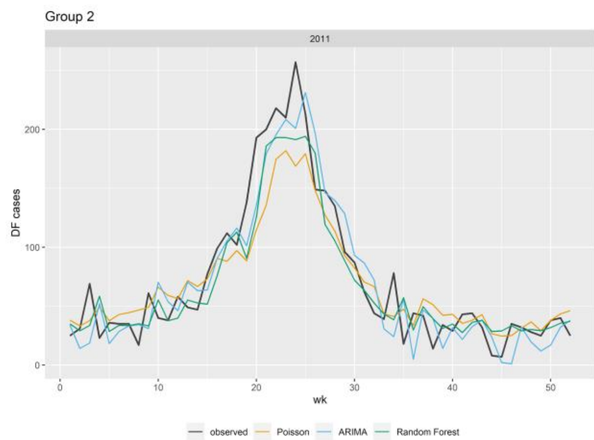

Group 2
2010
DF cases
wk
observed
Poisson
ARIMA
Random Forest

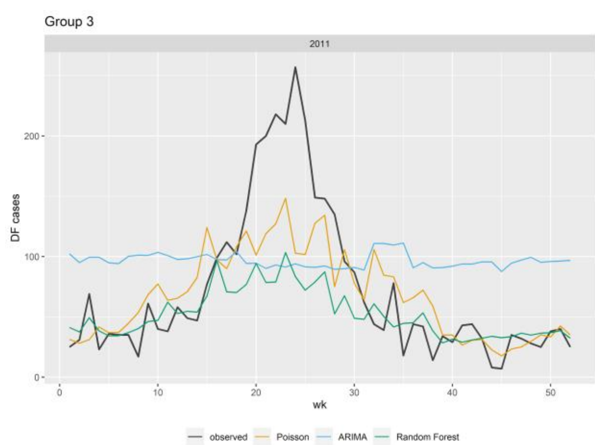

Group 3
2010
DF cases
0
10
20
30
40
50
50
100
150
200
wk
observed
Poisson
ARIMA
Random Forest

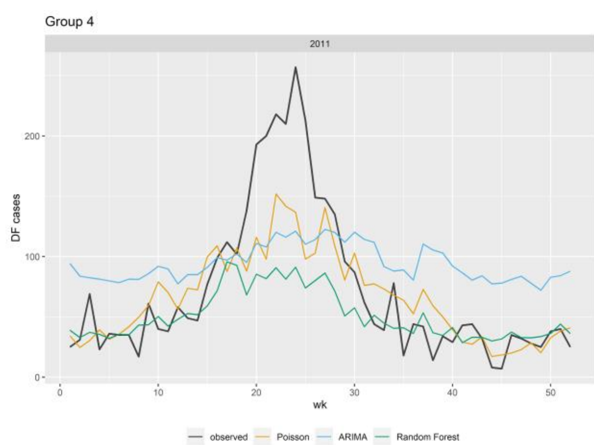

Group 4
2010
DF cases
0
10
20
30
40
50
50
100
150
200
wk
observed
Poisson
ARIMA
Random Forest

2011

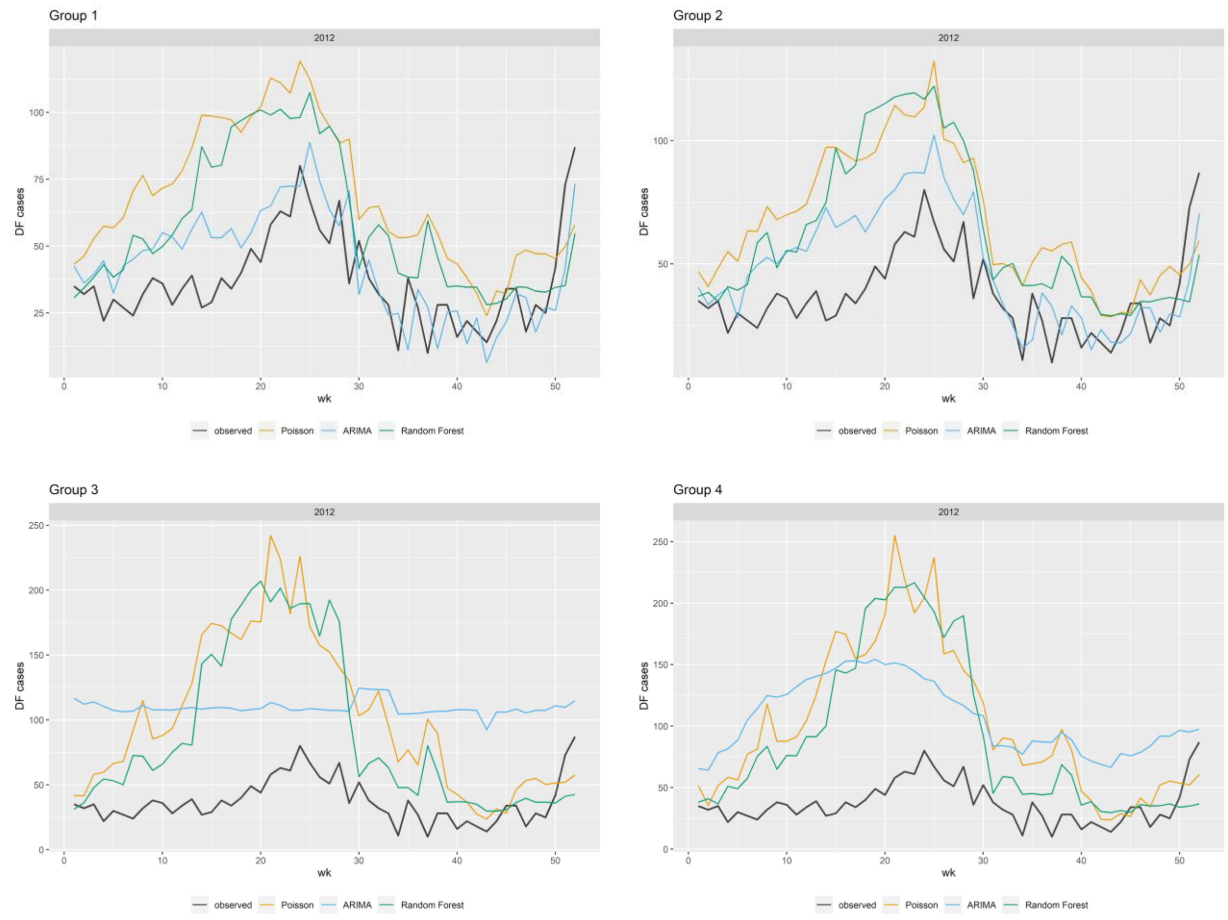

Group 1
2011
DF cases
0
10
20
30
40
50
0
100
200
wk
observed
Poisson
ARIMA
Random Forest


Group 2
2011
DF cases
0
10
20
30
40
50
0
100
200
wk
observed
Poisson
ARIMA
Random Forest

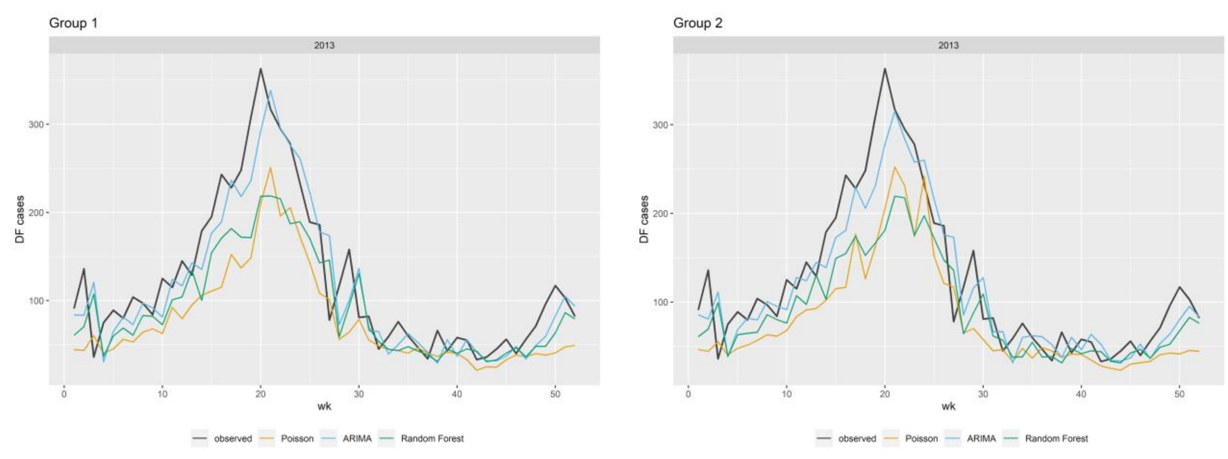

Group 3
2011
DF cases
0
10
20
30
40
50
0
100
200
wk
observed
Poisson
ARIMA
Random Forest

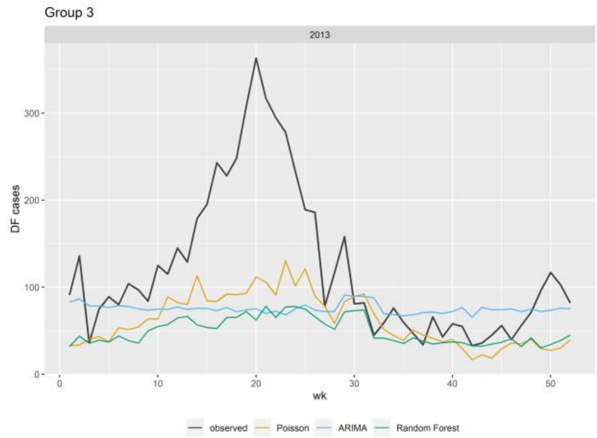

Group 4
2011
DF cases
0
10
20
30
40
50
0
100
200
wk
observed
Poisson
ARIMA
Random Forest

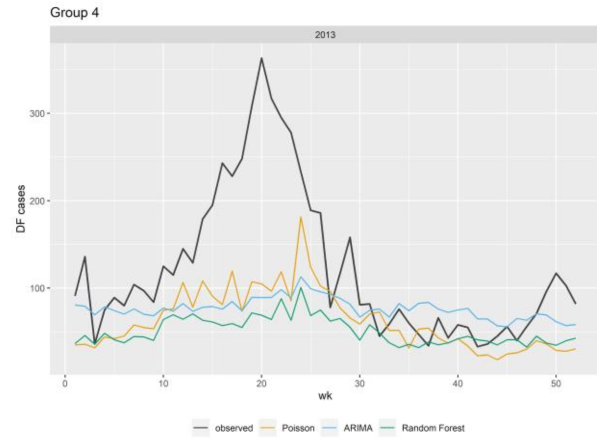
2012


Group 1
2012
DF cases
wk
observed Poisson ARIMA Random Forest
Group 2
2012
DF cases
wk
observed Poisson ARIMA Random Forest
Group 3
2012
DF cases
wk
observed Poisson ARIMA Random Forest
Group 4
2012
DF cases
wk
observed Poisson ARIMA Random Forest

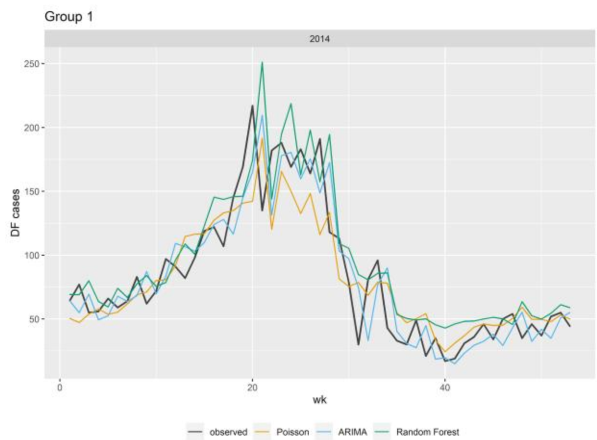
2013

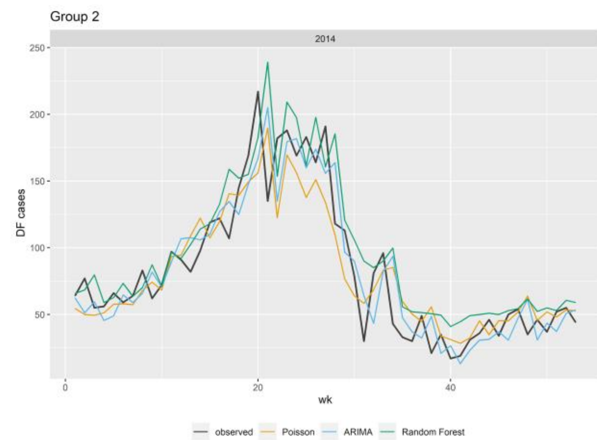

Group 1
2013
DF cases
wk
observed Poisson ARIMA Random Forest
Group 2
2013
DF cases
wk
observed Poisson ARIMA Random Forest

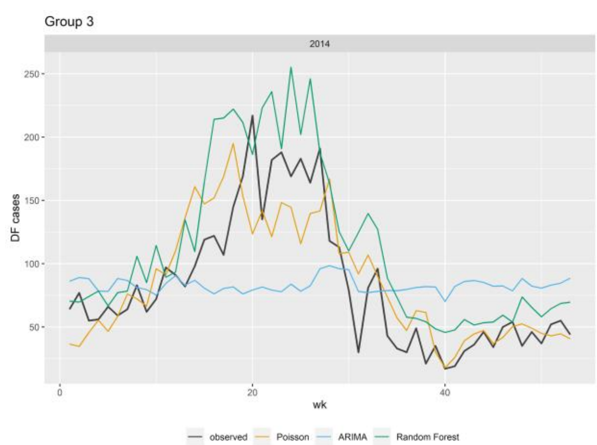

Group 3
2013
DF cases
wk
observed
Poisson
ARIMA
Random Forest

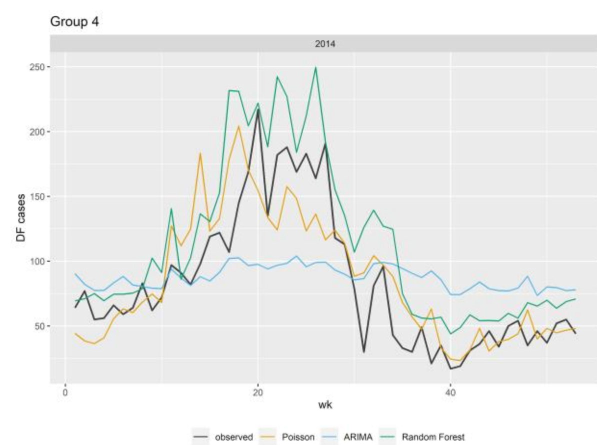

Group 4
2013
DF cases
wk
observed
Poisson
ARIMA
Random Forest

2014

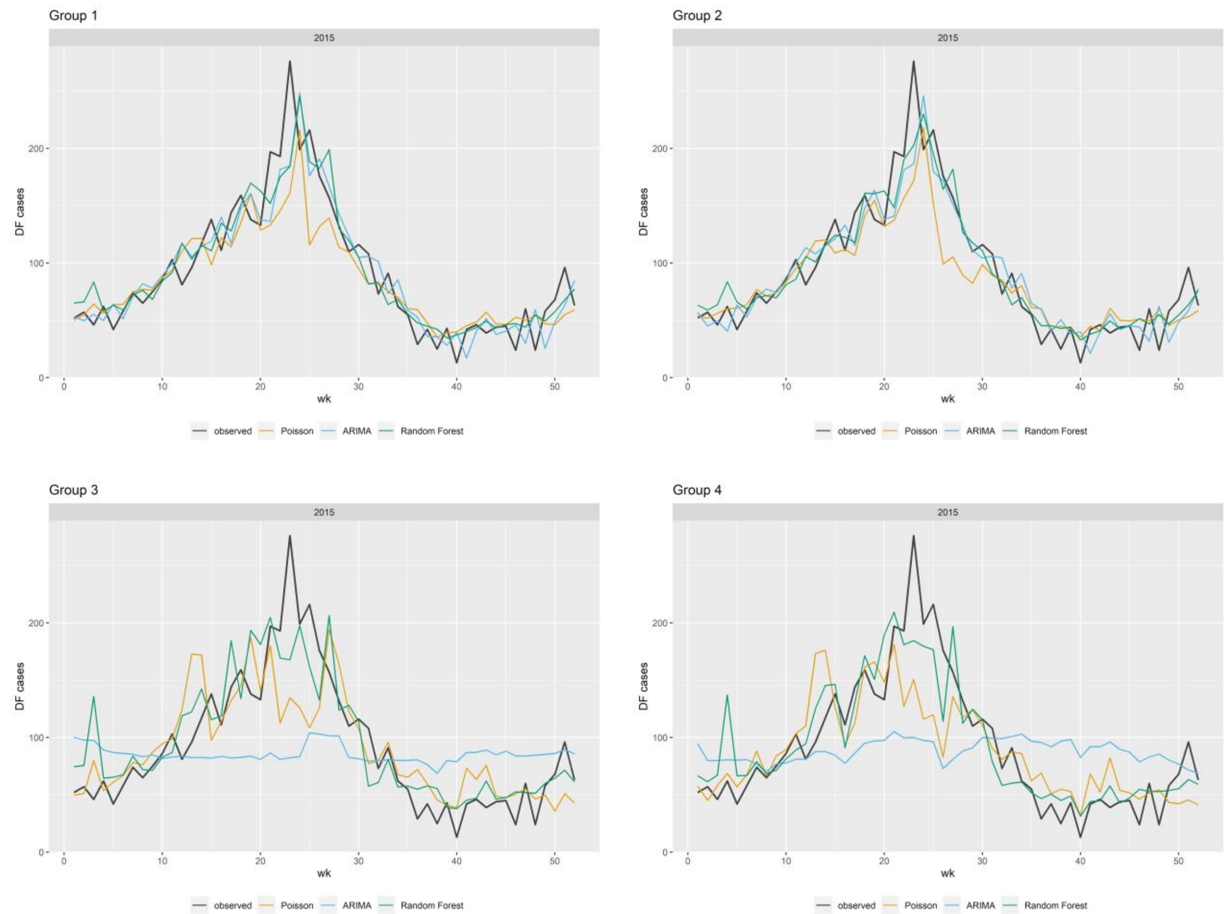

Group 1
2014
DF cases
wk
observed
Poisson
ARIMA
Random Forest


Group 2
2014
DF cases
wk
observed
Poisson
ARIMA
Random Forest

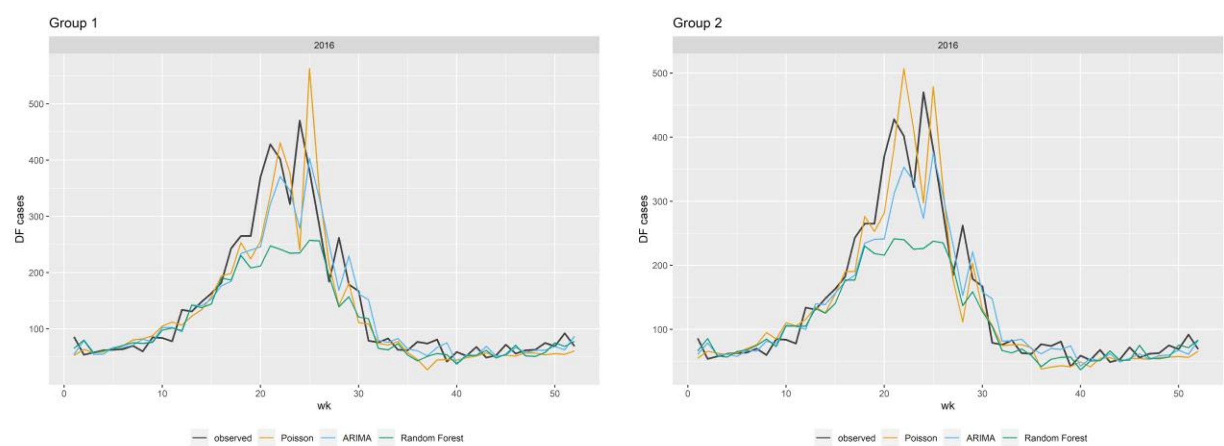

Group 3
2014
DF cases
wk
observed
Poisson
ARIMA
Random Forest

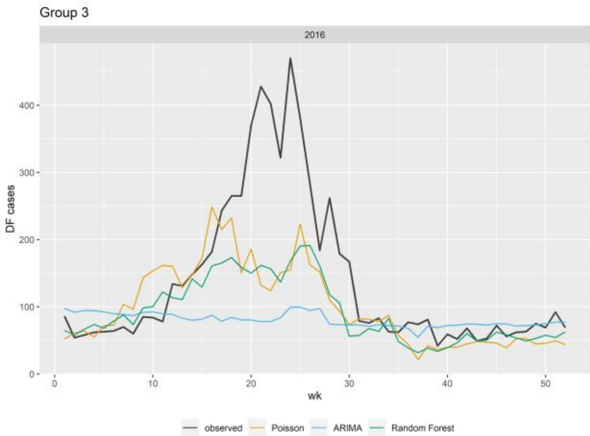

Group 4
2014
DF cases
wk
observed
Poisson
ARIMA
Random Forest

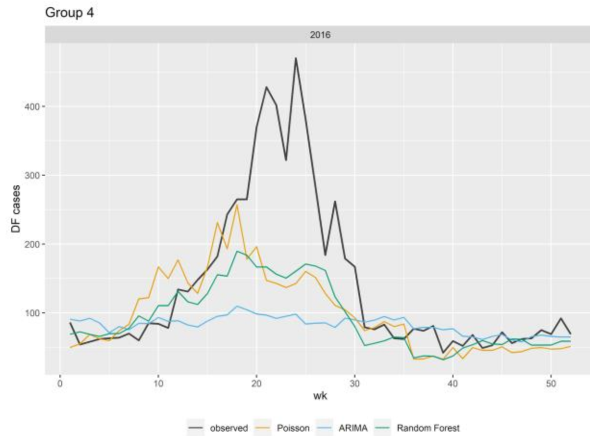
2015


Group 1
2015
DF cases
wk
observed
Poisson
ARIMA
Random Forest
Group 2
2015
DF cases
wk
observed
Poisson
ARIMA
Random Forest
Group 3
2015
DF cases
wk
observed
Poisson
ARIMA
Random Forest
Group 4
2015
DF cases
wk
observed
Poisson
ARIMA
Random Forest

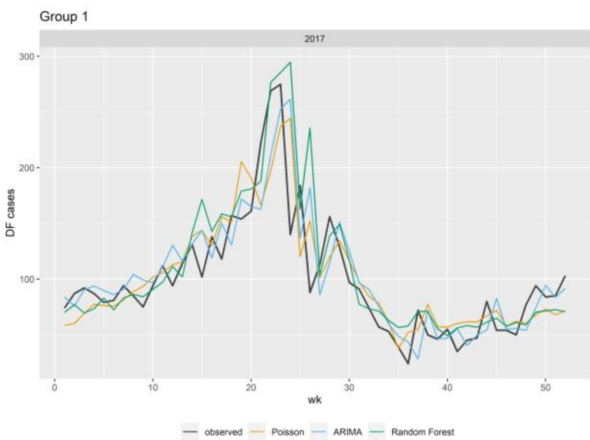
2016

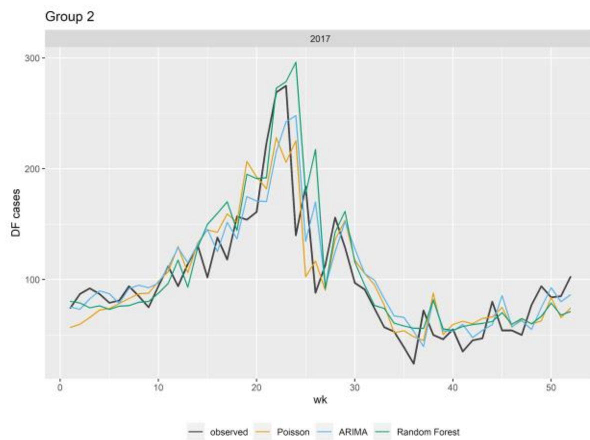

Group 1
2016
DF cases
wk
observed
Poisson
ARIMA
Random Forest
Group 2
2016
DF cases
wk
observed
Poisson
ARIMA
Random Forest

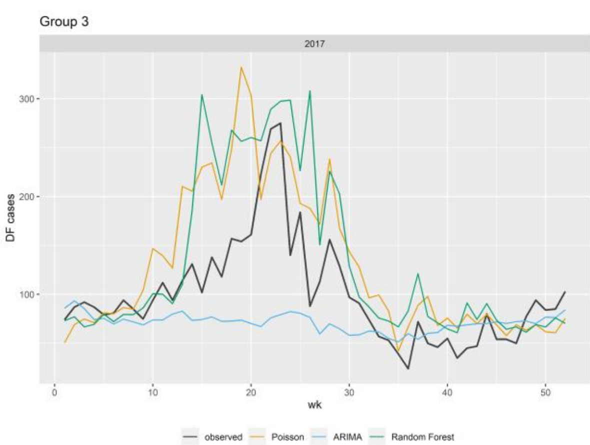

Group 3
2016
DF cases
wk
observed
Poisson
ARIMA
Random Forest

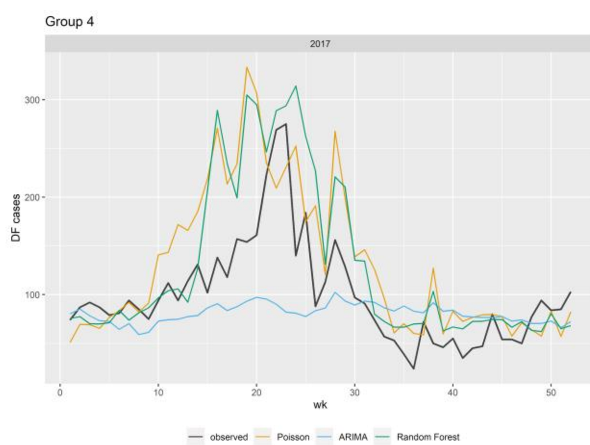

Group 4
2016
DF cases
wk
observed
Poisson
ARIMA
Random Forest

2017


Group 1
2017
DF cases
wk
observed
Poisson
ARIMA
Random Forest


Group 2
2017
DF cases
wk
observed
Poisson
ARIMA
Random Forest


Group 3
2017
DF cases
wk
observed
Poisson
ARIMA
Random Forest


Group 4
2017
DF cases
wk
observed
Poisson
ARIMA
Random Forest

2018

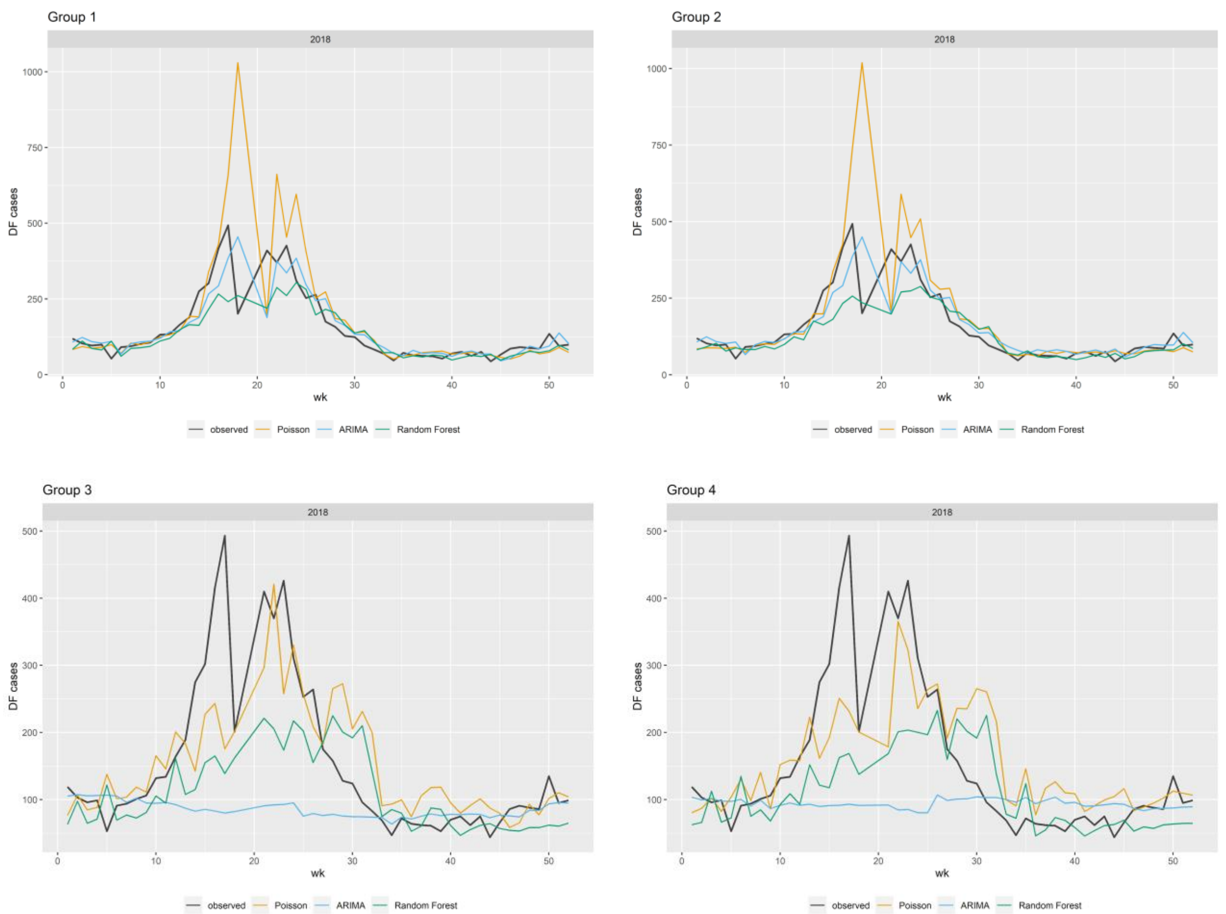


Figure 6(b). Line graph of observed vs. model predicted DF cases in Jeddah as predicted by poisson, ARIMA, and Random Forest regression models. Model validation on the one year excluded from the training dataset (a-j). Group number refers to the group of covariates used in the models.

Appendix B. Figures describing both weather patterns and the results of the bivariate analyses for the cities of Makkah and Jizan.

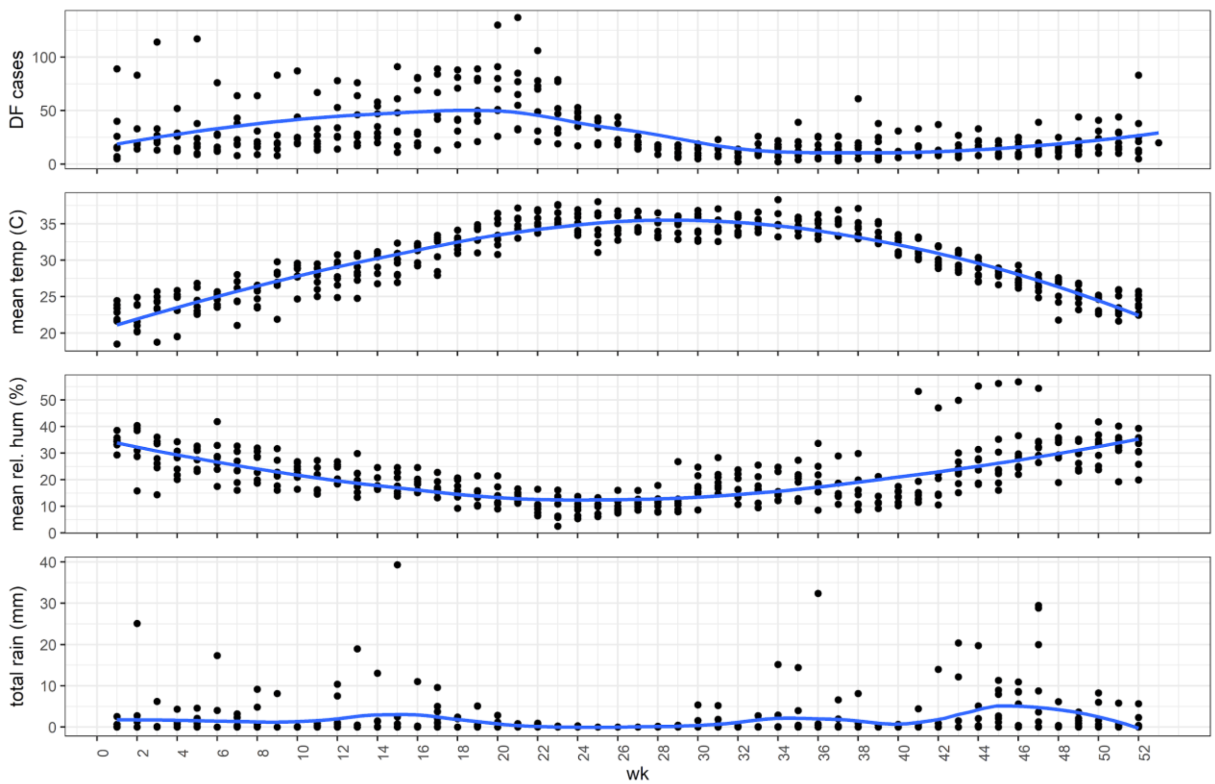


Figure 2(b). Distribution of DF cases, temperature, humidity, and rainfall throughout the year in Makkah, based on average measurements for 2012 to 2018.

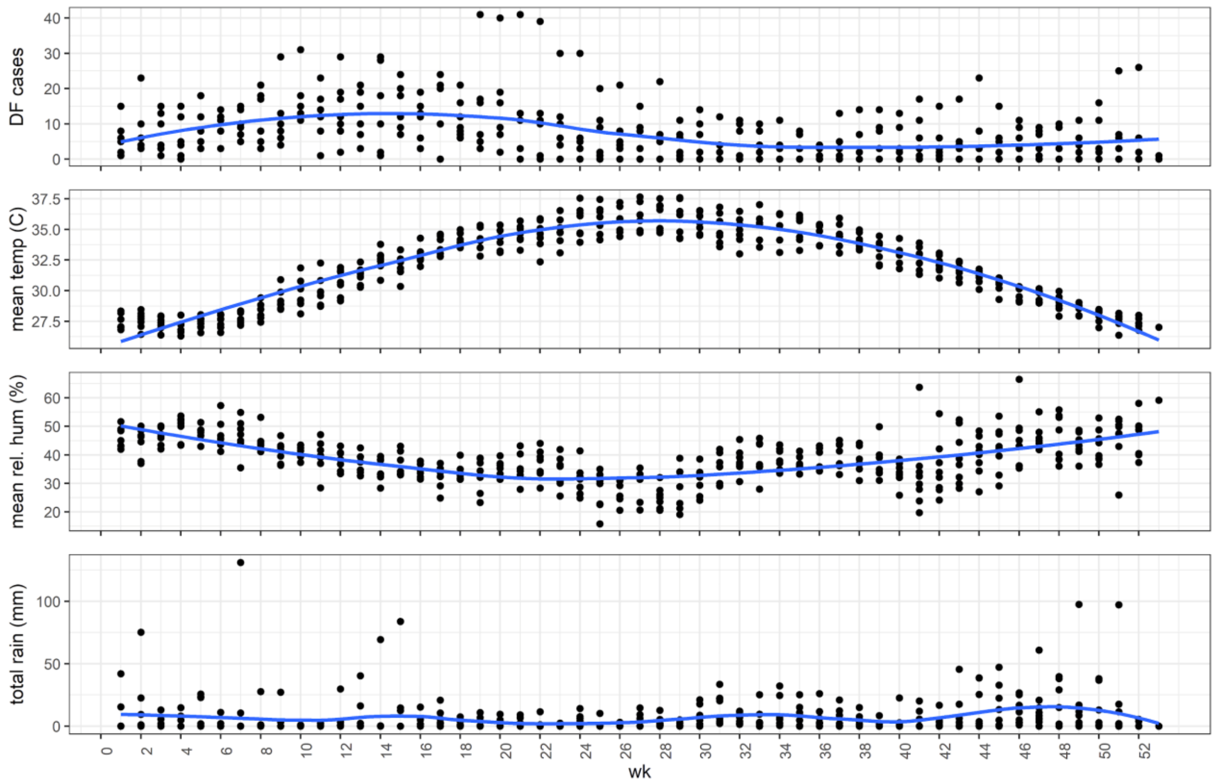
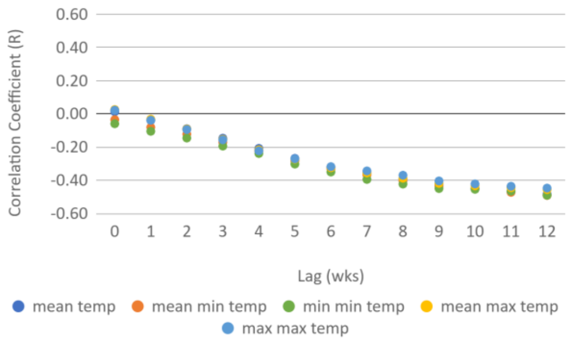
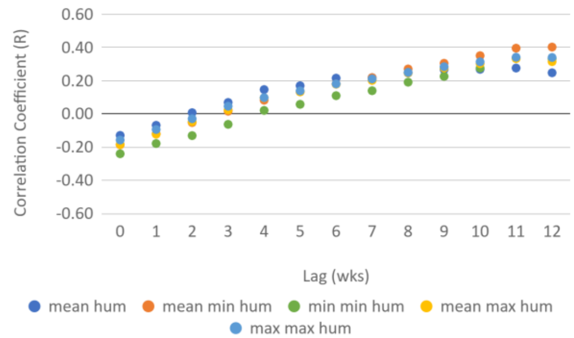


Figure 2(c). Distribution of DF cases, temperature, humidity, and rainfall throughout the year in Jizan, based on average measurements for 2012 to 2018.

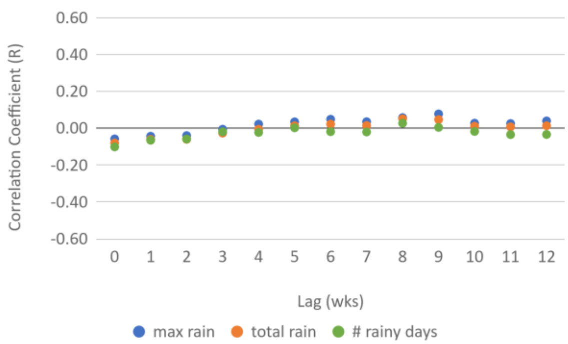
(a) Correlation with temperature variables.



(b) Correlation with humidity variables.



(c) Correlation with precipitation variables.



(d) Correlation with pilgrimage variables.

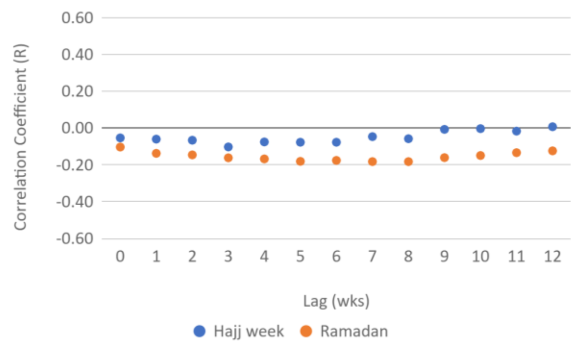


Figure 5(a-d). Results of the univariate analysis between DF cases and weather and population variables in the city of Makkah between 2012 to 2018.

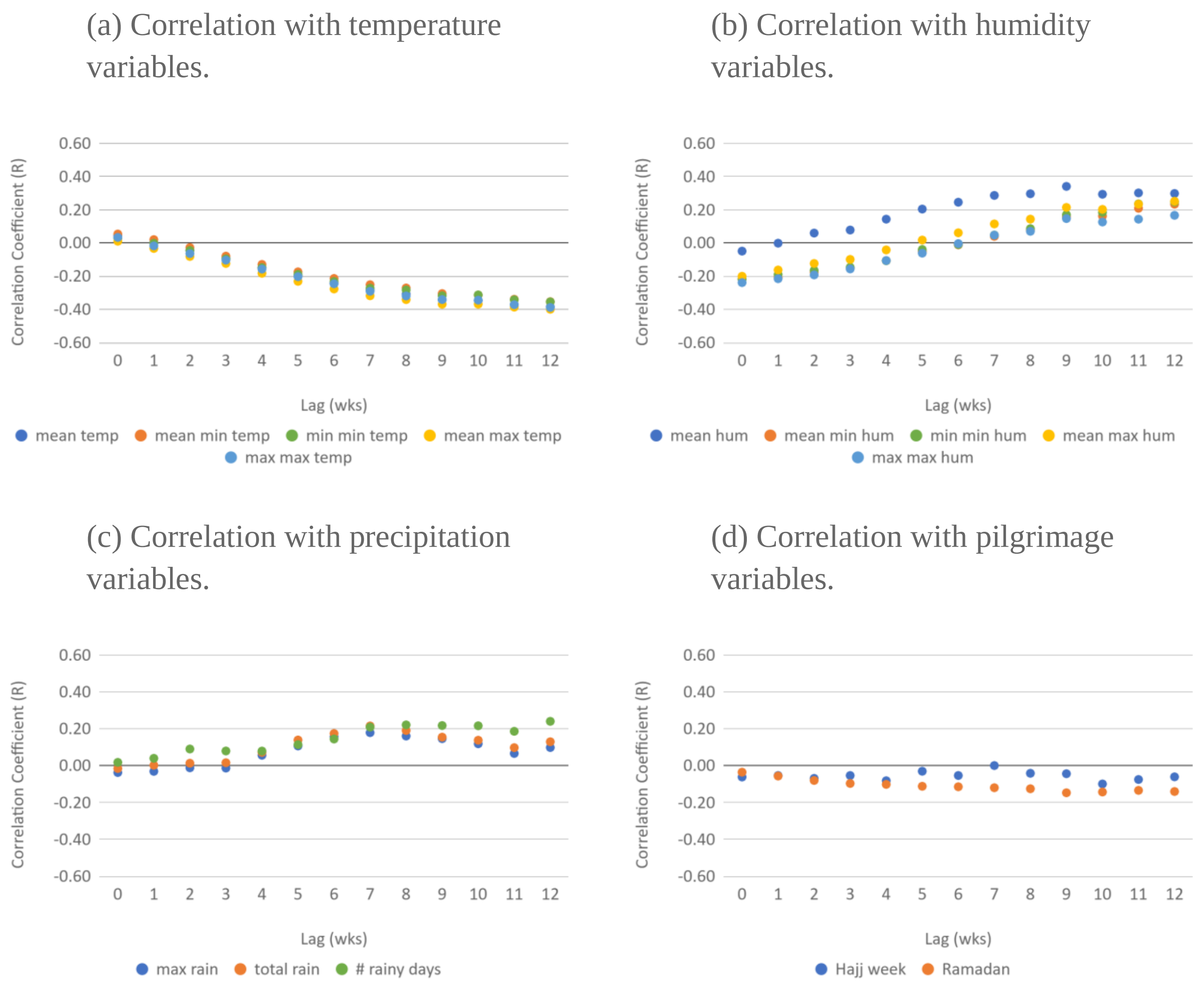


Figure 6(a-d). Results of the univariate analysis between DF cases and weather and population variables in the city of Jizan between 2012 to 2018.

Chapter 3

Simulating Dengue Fever in Saudi Arabia Using a Process-Based Modelling Approach

1. Introduction

Dengue Fever (DF) is the most common mosquito borne viral illness (Williams et al. 2016), transmitted by *Aedes Aegypti* and *Aedes Albopictus* mosquitoes. Although DF can often manifest as mild non-specific illness (Andraud et al. 2012), it causes a large burden of disease globally, estimated at 390 million infections a year, and 21,000 deaths (Naish et al. 2014), generally as a result of severe variants of the disease; Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) (Andraud et al. 2012).

A current review of the literature shows strong evidence to support the relationship between weather variables and DF epidemiology, specifically temperature, humidity and in some geographic areas rainfall (Naish et al. 2014). Several studies have shown the role of temperature and humidity on mosquito feeding and breeding, as well as on viral replication within the vector, and thus on DF incidence. Investigations in certain tropical areas have also described the role rainfall collections may play in creating mosquito breeding habitats. The seasonal pattern exhibited by disease further supports the hypothesis of DF as a climate driven disease.

Although a vaccine has recently been developed it has limited application, and prevention approaches still largely depend on vector control measures. Novel approaches to curb disease incidence should focus primarily on preparedness and early warning systems that target the environmental and population factors that play a role in DF epidemiology.

Dengue Fever was first introduced to Saudi Arabia in December 1993 as a case of Dengue hemorrhagic fever in the city of Jeddah. For a decade afterwards the disease caused small sporadic outbreaks of no more than a few hundred people. In 2004 the number of cases grew resulting in a large epidemic with over a thousand cases and had spread to nearby cities. Since then yearly outbreaks have occurred in several cities in the western region of Saudi Arabia leading the Ministry of Health to declare the region endemic for dengue fever. DF fever in Saudi Arabia, has also demonstrated a seasonal pattern of distribution and sensitivity to weather factors, particularly temperature and humidity (Altassan, Morin, and Hess 2020).

The Hajj is one of the largest mass gatherings in the world where 1.5 to 2.5 million Muslims from over 180 different countries gather to participate in the week-long event (Aleeban and Mackey 2016). The majority of these pilgrims arrive from countries in Eastern Asia and Africa, which are endemic for DF (El-Kafrawy et al. 2016; Almutairi et al. 2018). Several studies have suggested that inter-regional population movement, particularly during the Hajj, may play a role in disease importation. The mass gathering event can further drive serotype mixing and transmission (Humphrey et al. 2016) as evidenced by phylogenetic analysis of circulating DENV serotypes (El-Kafrawy et al. 2016; Zaki et al. 2008). Altassan et al. (2020) identified both weather variables and pilgrimage factors as potentially influencing DF incidence (Altassan, Morin, and Hess 2020).

DF prevention more recently has focused on anticipating DF incidence patterns through disease prediction. Two approaches are commonly referenced in the literature; statistical modelling methods, and process based dynamic models. Statistical methods utilize historical data and measured associations with specific covariates to train a model to predict future disease based on estimated measurements of covariates. In contrast, process based models are based on the use of known mathematical relationships between environmental factors and different aspects of ecological dynamics of the disease. Models that incorporate an entomological component, representing the disease vector, have demonstrated success in simulating vector-borne diseases (Bannister-Tyrrell et al. 2013; Morin et al. 2015). Because DF ecology is complex, utilizing a dynamic process based model can help gain a better understanding of the interactions between the various components of the system. Additionally, the ability to perform multiple simulations under varying conditions, is another benefit, as oftentimes data on the parameters involved in DF ecology is unavailable (Morin et al. 2015). Furthermore, while statistical models are location specific, process based models can be generalizable as they rely on equations formulated from lab based associations.

Our main objectives in this study is 1) to validate the DyMSiM model developed by Morin et al 2015 in Saudi Arabia, 2) to expand on the DyMSiM model with the incorporation of an SEIR model that describes the unique pilgrimage event that takes place in Saudi Arabia and 3) to compare between the performance of both.

To our knowledge this is the first attempt to apply a process based model for DF prediction in Saudi Arabia. This effort is also the first time an SEIR model describing Hajj pilgrims has been included into a dynamic model for infectious disease simulations.

2. Methods

2.1 Process based model

The process based model utilized in this study is the dynamic simulation model (DyMSiM) created by Morin et al. (2015). This deterministic model builds on the previously developed DyMSiM model with specific parametrization for Ae. aegypti mosquitoes and incorporates an epidemiological SEIR model to describe the vector-human dynamic relationship.

SEIR Model: Susceptible >>> Exposed >>> Infected >>> Recovered

We assume that reinfection only occurs in hyper endemic areas therefore we neglect the Recovered >>> Susceptible relationship in the SEIR model.

We further expand on this model to include an SEIR model specific to Hajj pilgrims visiting from abroad to describe the infection dynamics amongst this population and to account for this unique factor on DF epidemiology.

$\text{Susceptible}_{[\text{pilgrims}]}$ >>> $\text{Exposed}_{[\text{pilgrims}]}$ >>> $\text{Infected}_{[\text{pilgrims}]}$ >>> $\text{Recovered}_{[\text{pilgrims}]}$

We will refer to this variation on the DyMSiM model as DyMSiM(P).

2.2 Data sourcing

a) Dynamic daily variables

Weather data: We used the *GLDAS Noah Land Surface Model L4 3 Hourly 0.25 x 0.25 degree* data subsets provided by Goddard Earth Sciences Data and Information Services Center. Daily measurements of minimum and maximum temperature (°C), average relative humidity (%), and total rainfall (mm), were calculated by aggregating the GLDAS 3-hourly measurements of temperature, rainfall, surface pressure, and specific humidity. The geographical coordinates selected for the city of Jeddah, as per Google search results, were 21.375°, 39.375°.

Pilgrims: We estimated daily numbers of infected pilgrims based a combination of data sources and assumptions. First we obtained the number of visiting non-resident pilgrims from the Saudi General Authority for Statistics' publicly available online data (author 2015). We assumed the distribution of these pilgrims country of origin using the Saudi government's Hajj visa quota of 1 per 1000 Muslim residents for each country (Aleeban and Mackey

2016), multiplied by the populations of the top 24 countries with largest Muslim populations from the Pew-Templeton Global Religious Futures Project (Pew-Templeton n.d.). We then estimated daily numbers of pilgrims based on arrival and departure estimates of visiting pilgrims informed by Hajj visa guidelines (“Visas - Hajj” n.d.), rough statistical data from the General Authority for Statistics(author 2015), and expert advice from Saudi passport authorities.

b) Parameter values

Parameters with known values: These include latitude (21.375°), and annual population. Population was calculated based on census data for the city of Jeddah for 2007, 2010, and 2016 and an annual population growth rate.

Parameters with unknown values: These include dimensions of outdoor water containers (e.g. old tires) which are subject to evaporation and filled by rainwater; *container area* and *container height*, amount of water stored in household containers; *permanent water*, the number of larvae/pupae per area of water necessary to sustain the mosquito population; *suitability index*, and the *field mortality* rate of the mosquitoes. We estimated the proportion of DF *infected pilgrims* by applying the country-specific DF prevalence rate obtained from IHME (cite) to the estimated number of pilgrims visiting from that country and aggregated the values for the total. The equation used:

$$\text{Infected}_{[\text{pilgrims}]} = \sum((\text{Muslims per country} / 1000\ [\text{hajj quota}]) * \text{DF prevalence per country})$$

Population and DF prevalence for missing years was calculated based on an annual growth rate. We assume no infected domestic pilgrims as DF prevalence outside Jeddah is very low. Finally, the *background infection* rate which is the minimum number of weekly cases divided by the total population. To increase the probability of capturing the true value of these non-measured parameters we used a range of values, with each simulation run changing one parameter value, thus eventually all the values would be tested. The parameters pertaining to mosquito lifecycle dynamics are based on either lab derived or field based evidence from the literature (cite?), while the range of values for the rest of the parameters are determined based on our best judgement. For instance, for *infected pilgrims* the upper and lower values of the country-specific DF prevalence rates were used as additional parameter values, and for *background infection* we opted to double and triple the calculated value to account for possible underreporting. Parameters with non-measured values are summarized in Table 1.

2.3 Analysis

We applied both variations of the DyMSiM model: the original Morin et al. developed DyMSiM model with the parameter values specific to the city of Jeddah, and the expanded DyMSiM model that includes the pilgrims SEIR equations. We ran the models for each year individually but included the previous year to provide spin up time for the purpose of creating the infection and immunity vector-host relationship dynamic. We converted daily DF case counts to weekly numbers based on epidemiological calendar.

2.4 Model Performance Assessment

We assessed model performance for each year by comparing the observed weekly DF incidence to the simulated weekly numbers after standardization using the following formula:

(weekly DF cases $_{[Sim]}$ / annual DF cases $_{[Sim]}$) * annual DF cases $_{[obs.]}$

The top 2% best-fit models were selected for each year based on the correlation R^2 value and an ensemble mean, minimum, and maximum DF case distribution plotted. We noted R^2 and RMSE values and inspected the ensemble DF weekly distribution pattern alongside the observed DF distribution.

We used Spyder (3.3.6) to run the DyMSiM model in Python, and RStudio Data Analytics Software (1.2.1335) to analyze the generated output in R.

3. Results

We first describe the weather, pilgrimage, and DF patterns in Jeddah from 2008 to 2009, as illustrated in Figure 1. Temperature is seen to increase significantly after mid 2010 from no recorded highs over 40 ℃ to a third of the year recording highs of over 40 ℃. Consequently, humidity is also found to change over time beginning in 2011, where it changes from averages between 50 - 70 % relative humidity in 2008, 2009, and 2010, to recording several weeks of levels between 20 - 40% relative humidity. Overall, precipitation is quite sparse, apart from a few extreme rainfall events, usually occurring at the end of the year. The pattern of arrival and departure of Hajj pilgrims from abroad demonstrates the slight shift of the pilgrimage season every year from the end of the year in 2008 to the late summer period in 2018. We also note the decreased number of pilgrims between 2013 and 2017. DF cases follow a seasonal pattern peaking between the weeks of 13 and 26. DF distribution also exhibits an overall annual increase in magnitude.

To evaluate the performance of the models we looked at both the correlation measure R2 and the error measure RMSE. Because our DF output results were standardized the RMSE is not a good objective measure of performance, but it is useful in combination with the R2 as a comparative measure between the two variants of the dynamic model. Both DyMSiM and DYMSiM(P) performed very well for the years 2009 and 2010 with R2 between 0.67 - 0.83 and RMSE between 37.2 and 51.5. Both models also performed moderately well for 2013 and 2018 with R2 between 0.35 - 0.46. When comparing between the two models overall DyMSiM(P) performed better with an average R2 = 0.37 and an average RMSE = 78.2. The DyMSiM(P) significantly improved the performance measures for 2012, 2015, and 2017 where the increase in correlation R2 was 0.08, 0.31, and 0.28 respectively and the decrease in the RMSE was 33.8, 85.4, and 42.8. There was slight improvement for 2009 with the difference in correlation and error measures of 0.05 and 7.8 respectively. There was no difference in the performance of the two models for 2010 and 2018. For 2014 although the DyMSiM(P) had a slightly lower R2, there was a significant improvement to the RMSE of 29.7. For 2011, 2013, and 2016 the DyMSiM model had slightly higher R2 and lower RMSE. The R2 and RMSE measures for each year using DyMSiM and DyMSiM(P) are summarized in Table 2.

Plots depicting the mean, minimum, and maximum of the simulation ensembles, along with the observed cases for each year is demonstrated in Figure 2, and Figure 3 (Appendix C). Although the correlation between observed and simulated cases is strong for the years 2009 and 2010 the simulation ensemble overestimates the peak of the epidemic and underestimates the periods of lower DF incidence. A similar pattern is noted for 2013 and 2018, while in 2011 and 2016 the simulation ensemble also predicts the peak of the epidemic earlier than observed. This pattern of overestimating the peak, underestimating the off-peak, and starting the peak earlier is also noted for the 2014 simulation ensemble produced by DyMSiM. For the same year DyMSiM(P) was less able to accurately replicate the pattern of the disease incidence, but more closely mimicked the magnitude of the epidemic. The DyMSiM simulation ensemble for 2015 was not able to capture the variability in case distribution nor the peak of the epidemic. Yet, with the addition of pilgrims into the model the peak of the epidemic better replicated, albeit slightly delayed. A similar improvement in the pattern of the simulations ensemble between DyMSiM and DyMSiM(P) was also noted for 2017 and 2012.

We also considered the number of times different values for parameters were selected in the top 2% of simulations for both models (Figure 4). Overall, no significant variation was noted in the number of times the parameter values for *container height*, *permanent water*, and *suitability index* were selected among different years and between the two models. A discrepancy was noted for *container area* and *mosquito mortality*. In the DyMSiM(P), 2016 was the only year where the highest value (810 cm2) was not selected for *container area*, and in the DyMSiM, 2015 was the only year where the highest value for *mosquito mortality* (0.18) was exclusively selected.

4. Discussion

Overall, both DyMSiM and DyMSiM(P) performed well for 2009 and 2010. Performance for the rest of the years varied among the years and between the models ranging from correlation R2 = 0.004 to 0.37. The variability in performance between years can be ascribed to the effect of extreme temperatures on mosquito survival. The entomological component of the model is sensitive to weather variables, particularly temperature, and humidity. From the middle of 2010 to the end of the study period temperatures over 40°C were recorded during at least one third of the year. As several studies show mosquito mortality increases at such extreme heat, with the optimal temperature for Aedes breeding and survival between 20 and 30°C. In fact, studies have found increasing temperatures over 32°C are detrimental to the mosquitoes. The Aedes vector is also sensitive to increasing humidity, favoring moderately high levels, between 50 - 70% relative humidity. Between 2008 and 2010 relative humidity in Jeddah maintained this moderately high range, never going above 70% or below 30%. Starting in 2011 relative humidity levels began to decrease with a large portion of the year recording levels below 30%. The changes in these two variables and the consequent effect on the entomological component of the dynamic models likely led to very high rates of mosquito mortality resulting in wipe out of the population of adult mosquitoes. While the model has the capacity to recover with the development of new pupae when the environmental factors are suitable, in the meantime the vector that transmits the virus between the human hosts is no longer available, leading to a standstill in disease transmission. This phenomenon can be seen in Figure 5, which shows the distribution of the vector population and its relationship to the DyMSiM simulated cases. In contrast, rainfall does not seem to play as significant a role on simulated DF cases. This may be due to several factors. First, the precipitation events, which are few and far between, are occurring at a time when the peak of the epidemic has already passed. According to Altassan et al. (2020), rainfall in this region has a significant association with DF with no lag period to lags of 7 weeks. Further, the rare rainfall events which often result in flooding (Youssef et al. 2016), could cause washout of mosquito habitat. Finally, it is most likely that because this is an arid environment with very little rainfall, and thus very few areas of standing water resulting from rain, mosquito habitat is limited to permanent water sources in or around homes such as household containers, water fountains, etc.. Kholedi et al. (2012) suggested that water storage behaviors in response to water shortages is the most likely source of mosquito breeding habitat in Jeddah (Kholedi et al. 2012).

Addition of pilgrims to the dynamic model in the DyMSiM(P), improved the performance of the models for 2009, 2010, 2012, 2015 and 2017. The remaining years either no difference in performance was detected or the DyMSiM performed worse. This can be explained at least partially by the previously mentioned effect of extreme weather on mosquito mortality. Similarly, when the adult mosquito population decreases to zero, the dengue viruses potentially introduced by infectious pilgrims have no vector to transmit them to human hosts. Thus, adding infectious pilgrims should result in no affect. This observation needs to be considered in the context of timing of the Hajj period. In 2008 and 2009 the pilgrimage occurred at the end of the year so the effect of having infectious pilgrims come in while there is a mosquito population is reflected in the number of simulated cases at the beginning of the following year. This is especially demonstrated in 2012, 2015, 2017, where pilgrims' arrivals coincided with the depletion of the mosquito population, yet those years still saw improvement in model performance with the addition of pilgrims (Figure 6). This was likely a benefit from coinciding pilgrims with a robust mosquito population during 2014 and 2016. These patterns are summarized in Figure 7 (Appendix C).

For the most part we do not believe the choice of parameters played any significant role on the output of the dynamic models. The two standout associations in Figure 4, previously referenced in the results section, do not appear to reflect any true mechanistic association with these parameter values, especially as the DyMSiM for these two years, 2015 and 2016, was not performing particularly well and are thus unreliable.

The pattern of the simulated cases described earlier, with an exaggerated peak and minimal variability in the number of cases during the off peak period, is largely a result of the standardization process applied to the simulated cases. To appropriately assess the performance of the model in a like-with-like comparison, standardization was necessary by applying a minimum number of annual cases equal to that of the observed. By doing so, even during years where the mosquito population eventually became zero, this minimum number of cases needed to be maintained when there were cases, generally during the peak, resulting in overrepresentation of the number of cases in a short time period. The lack of variability in the number of simulated cases is likely a result of the model utilizing a limited number of influencing factors. If the model parameters have little to no effect on the model outputs, then the model is relying largely on weather alone to determine the pattern of disease. This may not reflect the reality in which there are many other environmental and population factors playing a role in altering DF vector-host dynamics.

We note several limitations to this study. First, the entomological component of the DyMSiM is very sensitive to extremes of temperature and humidity, which are a hallmark of this geographic region. This has often resulted in total elimination of the adult mosquito population in the simulated results. Further, the method in which we collect weather data does not capture the spatial variability often seen in an urban environment. Weather data was obtained from the GLDAS dataset, which utilizes weather station data in combination with modeling techniques, to produce reanalysis data. This approach also utilizes a grid system with each two by two cell representing an area of roughly 750 km2. The result is a very homogenous picture of weather that fails to reflect microclimates in which the vector population can thrive such as gardens, shaded entrances, swimming pools and water features. This is particularly problematic during years where there are extremes of weather leading to death of the entire mosquito population from the models. For years where the weather variables are within the ideal window for mosquito survival this limitation is not as evident. Second, the previous issues resulting in a false representation of a non-existent mosquito population, makes it difficult to assess the utility of incorporating a pilgrim SEIR model when developing a process based model for DF in Saudi

Arabia. Finally, the need to standardize the model outputs to be able to compare them to the observed cases, is more likely a reflection of inaccuracies in the observed data than issues with the model itself. DF surveillance systems globally, often suffer from issues of underreporting due to asymptomatic or mildly symptomatic infections, misdiagnosis, and lack of diagnostic equipment. This results in an observed number of cases estimated to represent approximately a third of the true number of infections (Bhatt et al. 2013).

The model might perform better in areas where this is not so much variability between overall weather measurements and microclimates such as tropical areas. One way to make this model more applicable to areas of extreme weather is to modify our approach to the collection of weather variables by obtaining on the ground measurements that reflect the variability present in an urban environment including microclimates. Given that it appears DF in Saudi Arabia is more influenced by water storage behaviors than rainfall accumulation, the model would also benefit from more accurate data regarding these ecological parameters, which are modifiable through public health interventions. Finally, having better estimates of disease incidence would limit the need for standardization, allowing the model to accurately simulate the magnitude of disease epidemiology in addition to the pattern.

5. Conclusion

More recently, DF prevention methods have centered on utilizing predictive models to anticipate disease incidence patterns. Using a dynamic process-based modelling approach provides insights into disease ecology by allowing the study of the effects of various factors on the multiple processes involved in DF transmission. Both dynamic models evaluated in this study, DyMSiM and DyMSiM(P), performed well, particularly during the years where temperature and humidity were relatively more moderate. The effect of extreme temperature and humidity on the simulated mosquito populations points to a probable discrepancy between captured weather data and actual weather measurements in areas where mosquitoes are likely flourishing. This finding emphasizes the need for on the ground data that accurately reflects the heterogeneous nature of climate in an urban environment which would allow us to better assess the performance of both models. Furthermore, it highlights the importance of targeted spraying in or around homes in areas of mosquito congregation. While process based models are generalizable, they also provide opportunities to evaluate unique regional. This was demonstrated in our study through the incorporation of pilgrimage data points in DyMSiM(P), which not only improved the accuracy of the dynamic model, but also allowed us to evaluate the effect of the arrival of pilgrims on patterns of disease incidence. This association can be further explored with additional data on pilgrims and more detailed description of their movement patterns in and out of the study area. Additional studies addressing DF in Saudi Arabia utilizing process based models can better illuminate many of the complex relationships between the disease and the various environmental factors involved in its transmission.

6. Tables and Figures

Parameter	**Description**	**Values**
Container area (cm^2)	Average water storage area*	270, 540, 810
Container height (cm)	Average water storage container height*	8, 16
Water storage (cm^2)	Amount of standing water*	58, 116, 174
Background infection	Lowest number of weekly cases divided by population calculated as a rate per 1000	calculated, doubled, tripled
Suitability index (pupae/cm^2)	Number of larvae/pupae per area of water	0.25, 0.5, 1
Field mortality	Rate of mosquito death*	0.06, 0.12, 0.18
Infected pilgrims	Proportion of infected foreign pilgrims visiting during the Hajj	3 values; number of infected foreign pilgrims divided by total number of foreign pilgrims each year, in addition to upper limit, and lower limit of prevalence data

Table 1. Parameter values applied to the DyMSiM model.

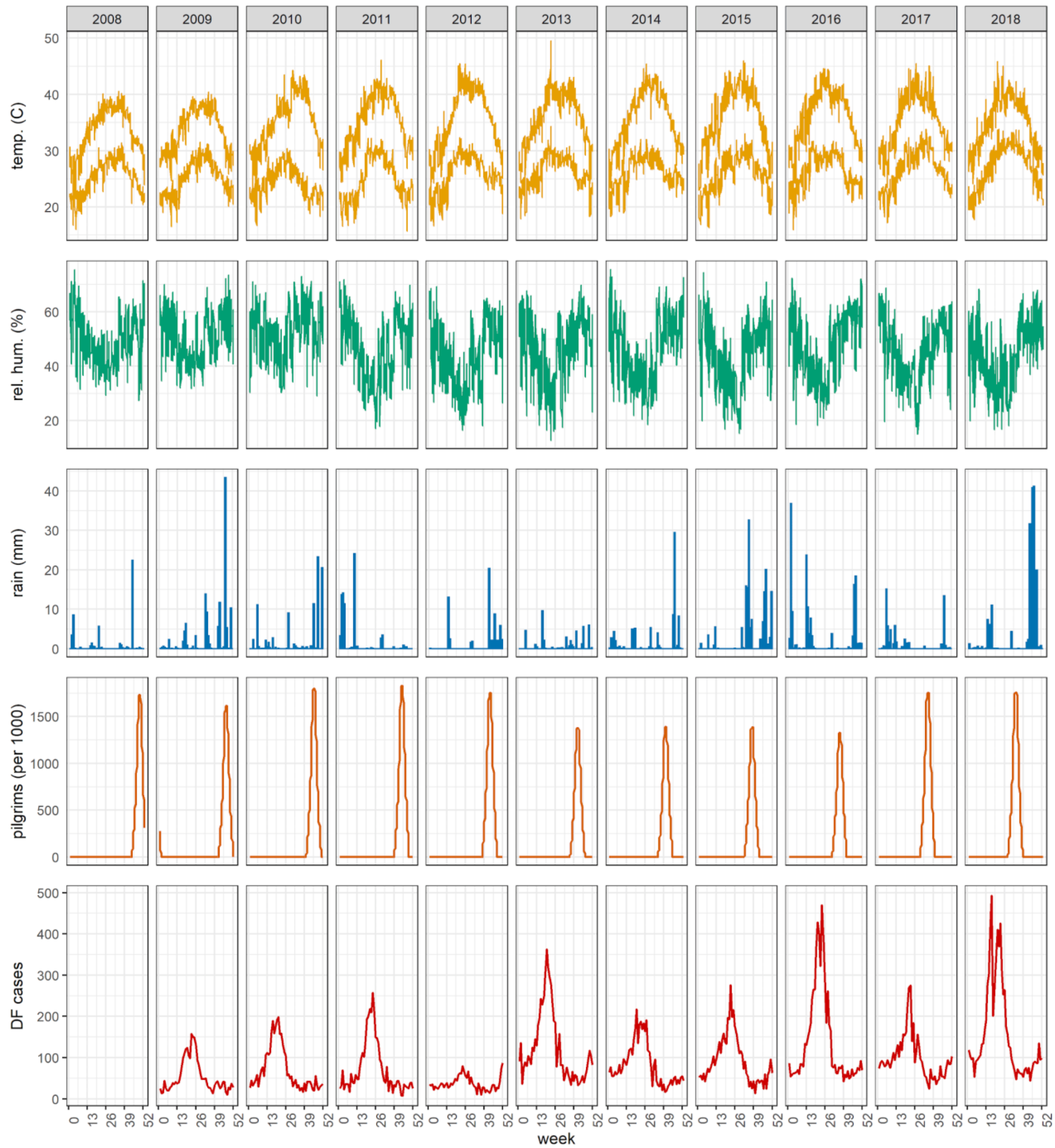


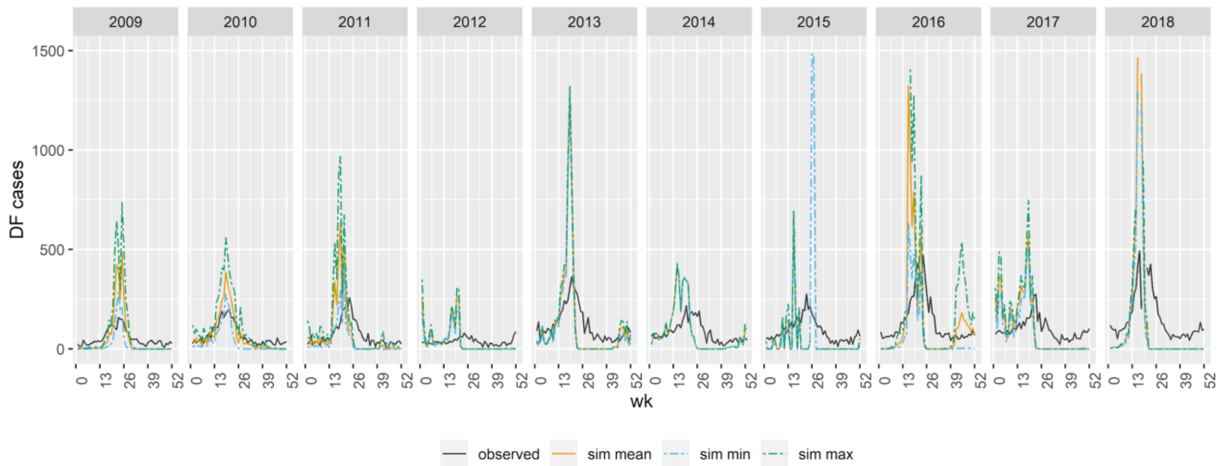
Figure 1. Weekly measurements of minimum and maximum temperature, average relative humidity, and total rainfall, as well as number of Hajj pilgrims and number of observed DF cases in the city of Jeddah from 2008 - 2018. Note: There is no electronic reporting of DF cases for 2008.

Year	**DyMSiM**	**DyMSiM(P)**

	R^2	RMSE	R^2	RMSE
2009	0.67	51.5	0.72	43.7
2010	0.83	37.4	0.83	37.2
2011	0.26	69.6	0.18	71.4
2012	0.004	48.1	0.08	14.3
2013	0.46	112.7	0.41	122.4
2014	0.25	72.3	0.2	42.6
2015	0.08	137.9	0.39	52.5
2016	0.16	141.9	0.12	148.1
2017	0.1	106.4	0.38	63.6
2018	0.35	186.6	0.35	186.6
Average (all years)	0.32	96.4	0.37	78.2

Table 2. Summary of performance measures R2 and RMSE for each year using both DyMSiM, and DyMSiM(P).

DyMSiM



DyMSiM(P)

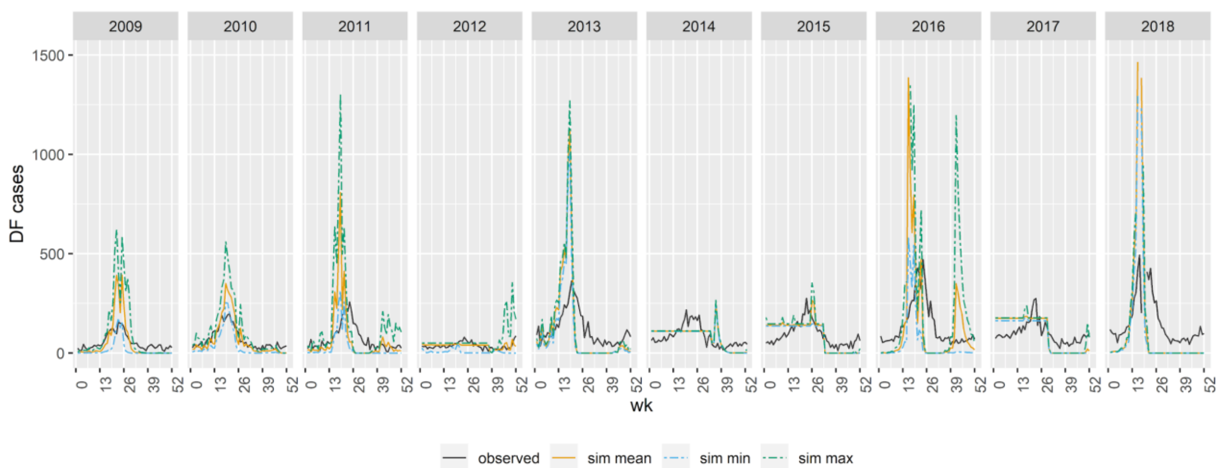
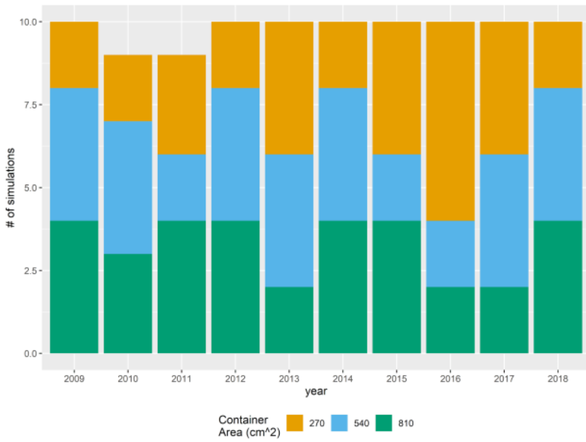
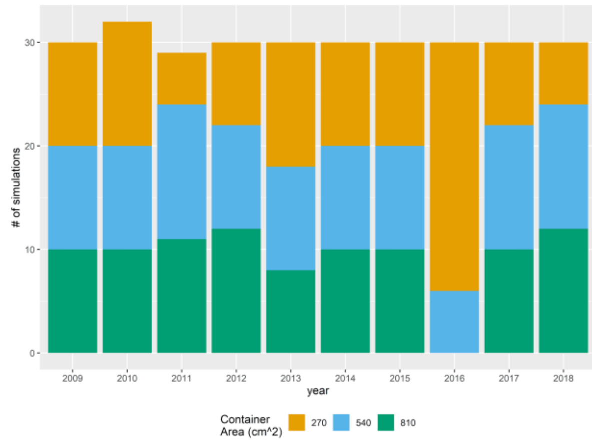
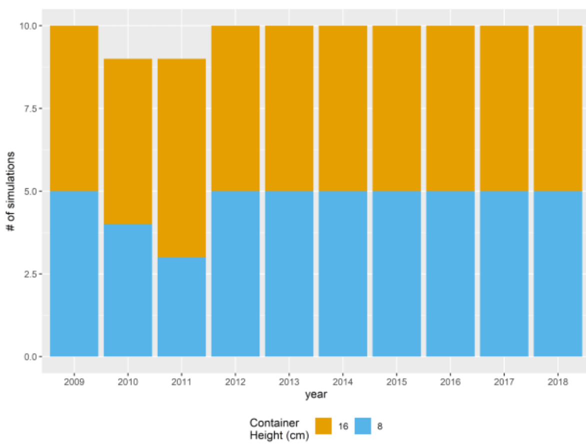
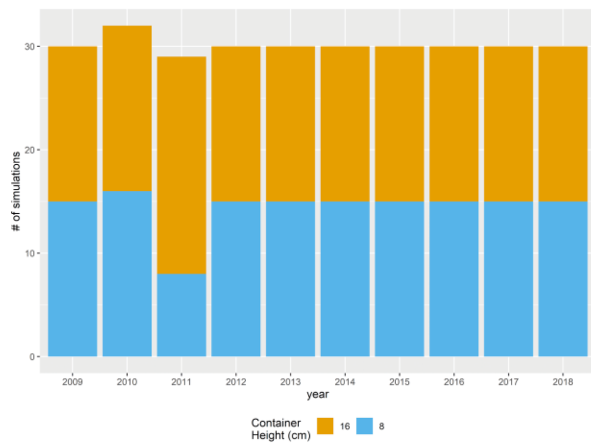
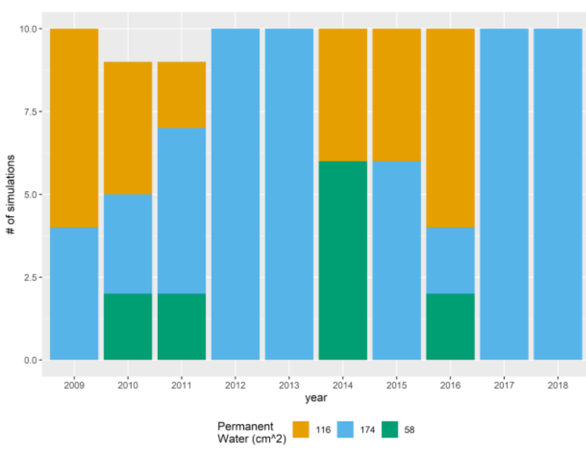
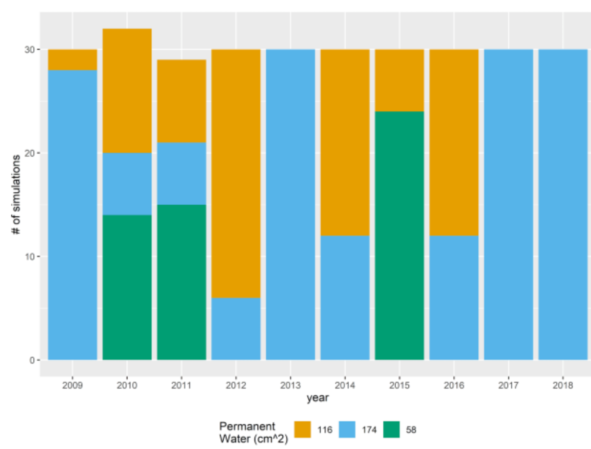


Figure 2. Distribution of observed DF cases and average, minimum and maximum DF cases predicted by top 2% of simulations for 2009 to 2018. (a) Simulation based on DyMSiM model. (b) Simulation based on DyMSiM(P). Note: For the purpose of visual clarity the number of cases was capped at 1500.

DyMSiM	DyMSiM(P)
	
	
	

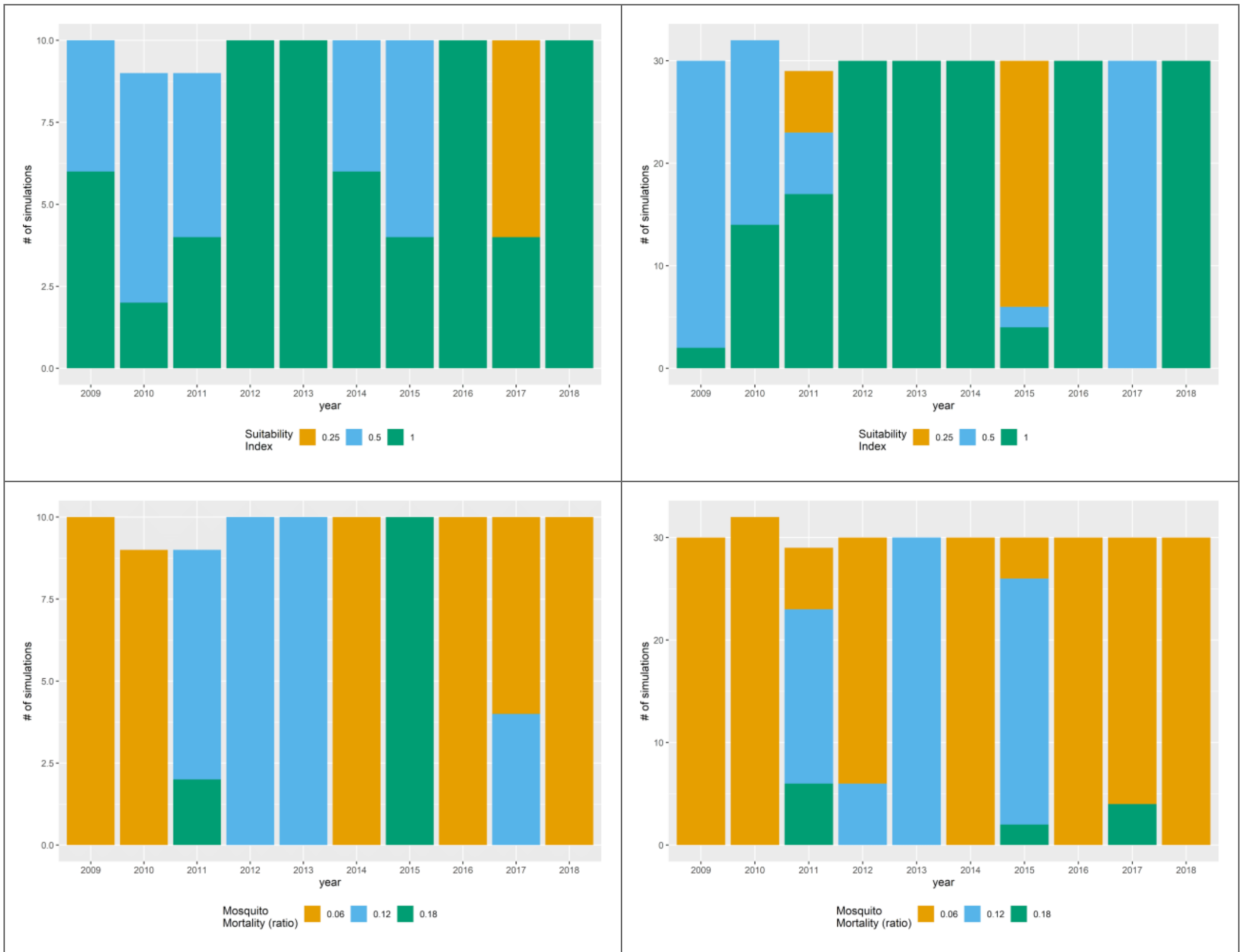


Figure 4. Number of times parameters (container area, container height, mosquito mortality, permanent water, and suitability index) were selected in the top 2% of simulations. (a) Simulation based on DyMSiM model. (b) Simulation based on DyMSiM(P).

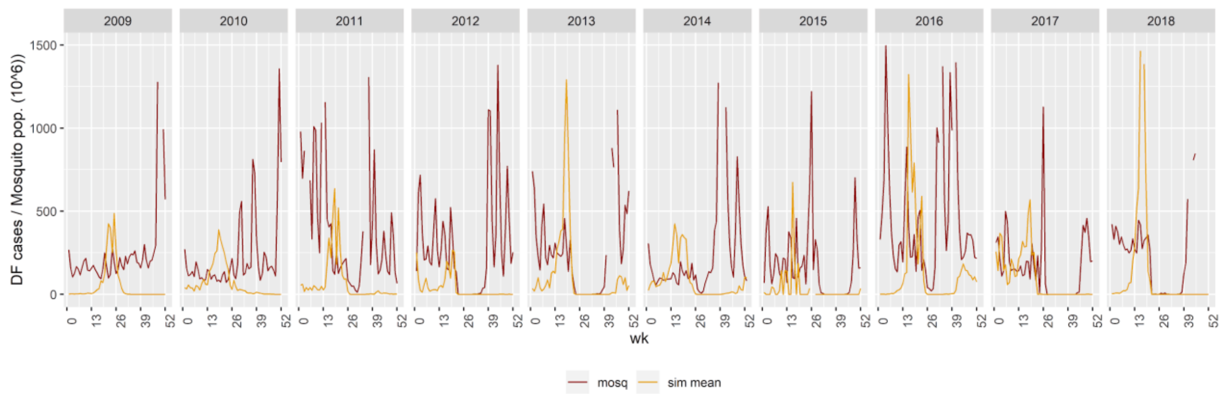


Figure 5. Distribution of average number of mosquitoes (in million) and average DF cases predicted by top 2% of DyMSiM simulations for 2009 to 2018. Note: Count capped at 1500.

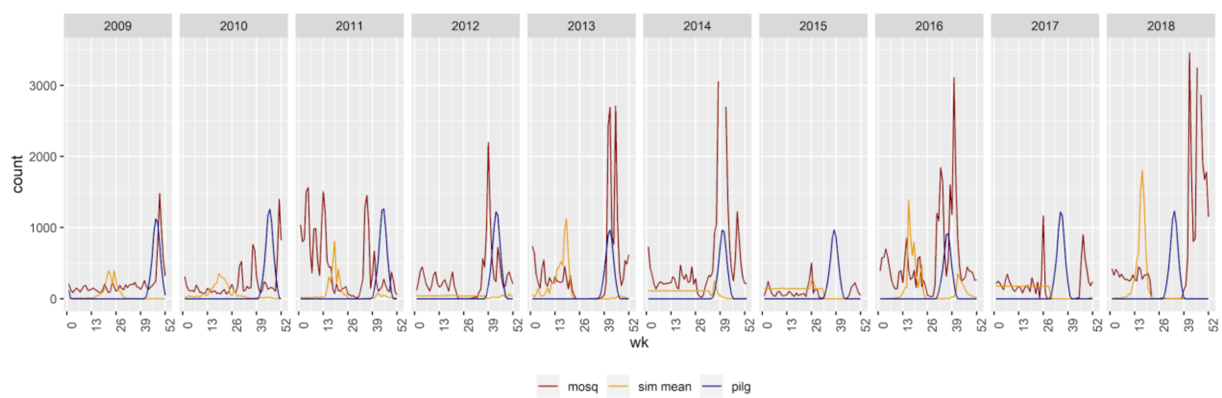


Figure 6. Distribution of average number of mosquitoes (in million) and average DF cases predicted by top 2% of DyMSiM(P) simulations, and number of pilgrims (in 10,000) for 2009 to 2018. Note: Count capped at 3500.

Appendix C: Figures comparing the performance of DyMSiM, and DyMSiM(P) for each year.

<table>
<tr><th>DyMSiM</th><th>DyMSiM(P)</th></tr>
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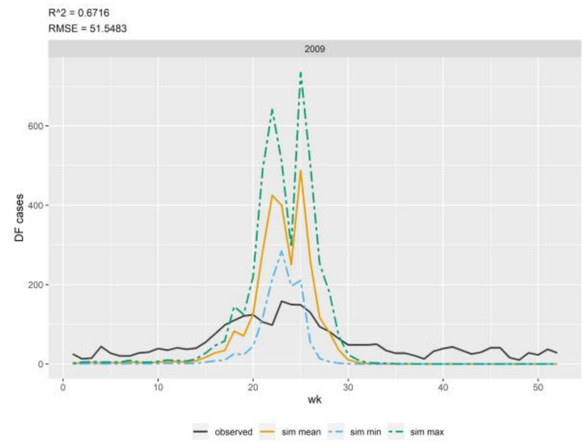

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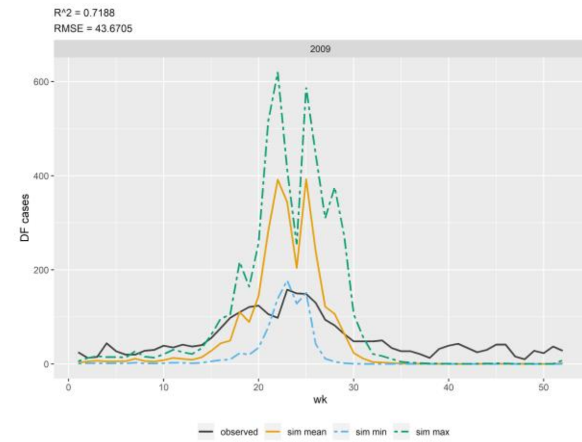

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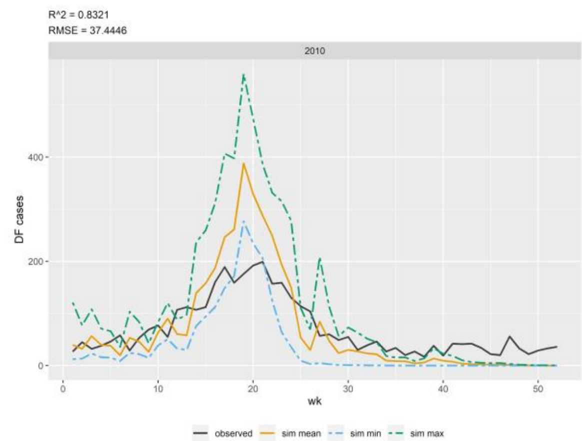

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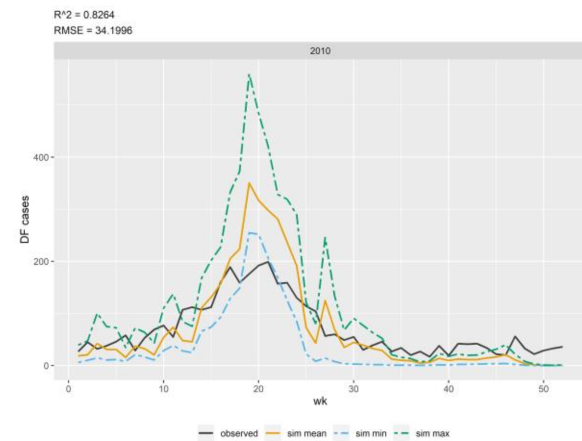

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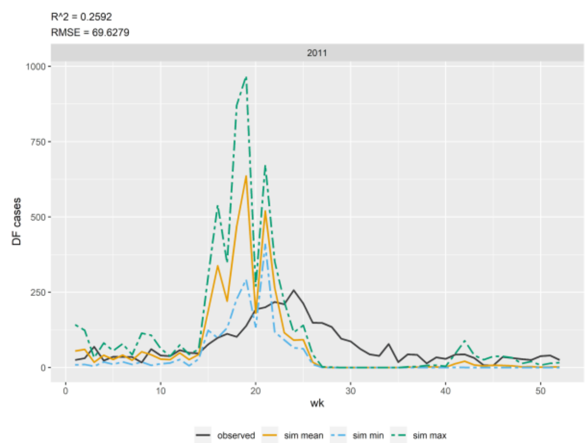

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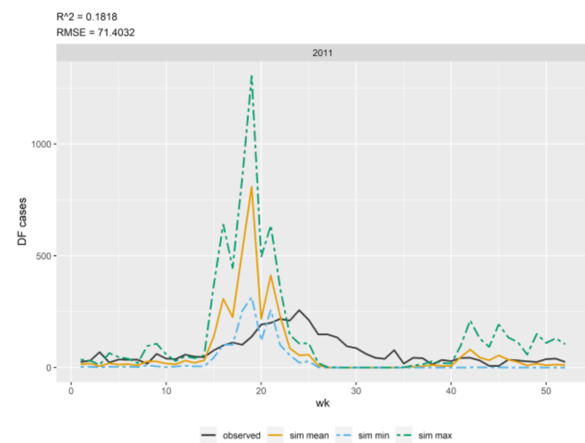

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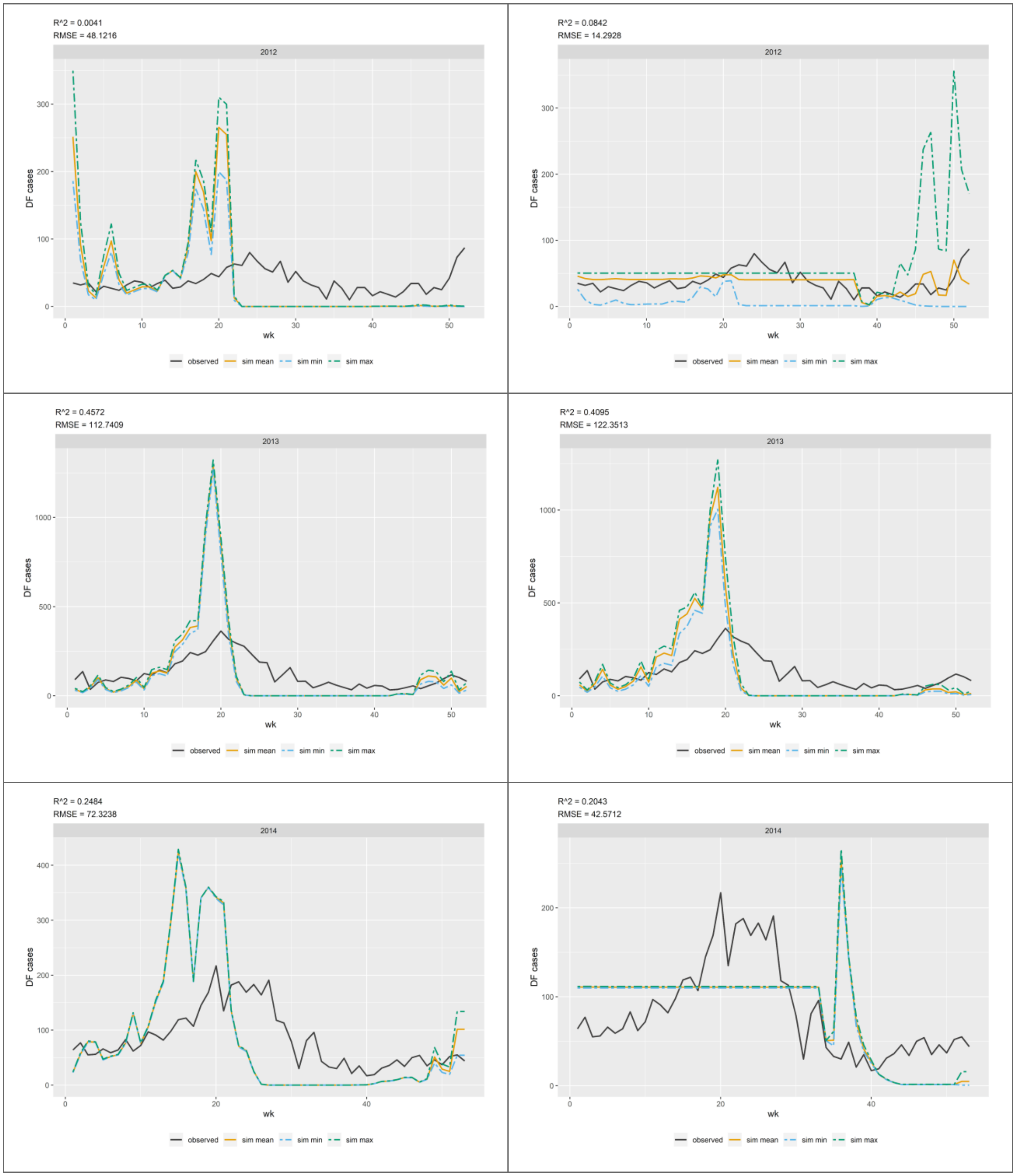

R^2 = 0.0041
RMSE = 48.1216
2012
R^2 = 0.0842
RMSE = 14.2928
2012
R^2 = 0.4572
RMSE = 112.7409
2013
R^2 = 0.4095
RMSE = 122.3513
2013
R^2 = 0.2484
RMSE = 72.3238
2014
R^2 = 0.2043
RMSE = 42.5712
2014
DF cases
wk
observed
sim mean
sim min
sim max


R^2 = 0.0826
RMSE = 137.8692
2015
R^2 = 0.385
RMSE = 52.4587
2015
R^2 = 0.1635
RMSE = 141.9406
2016
R^2 = 0.119
RMSE = 148.1429
2016
R^2 = 0.0973
RMSE = 106.4226
2017
R^2 = 0.375
RMSE = 63.5944
2017
DF cases
wk
observed
sim mean
sim min
sim max

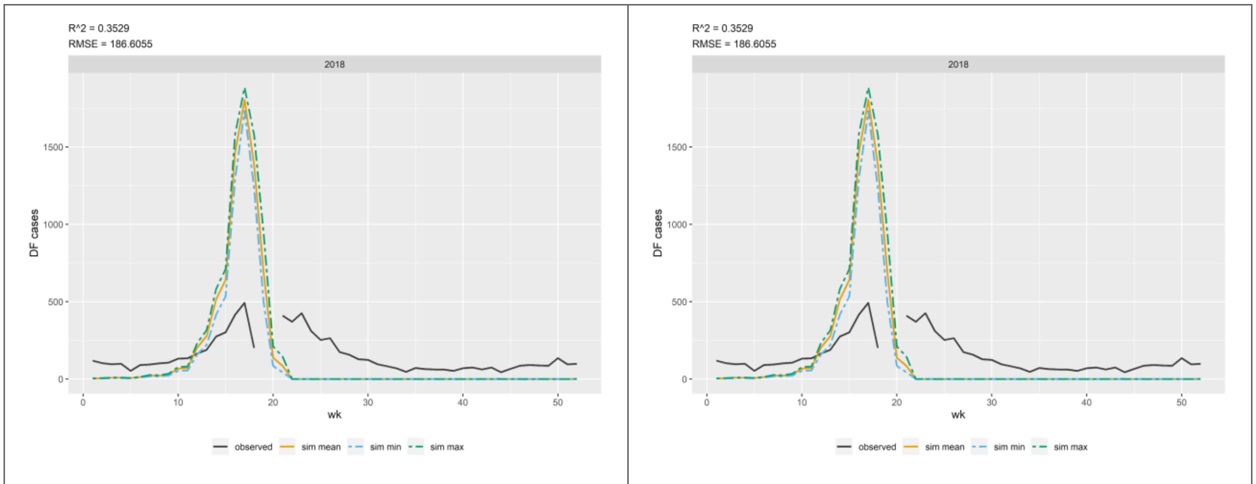
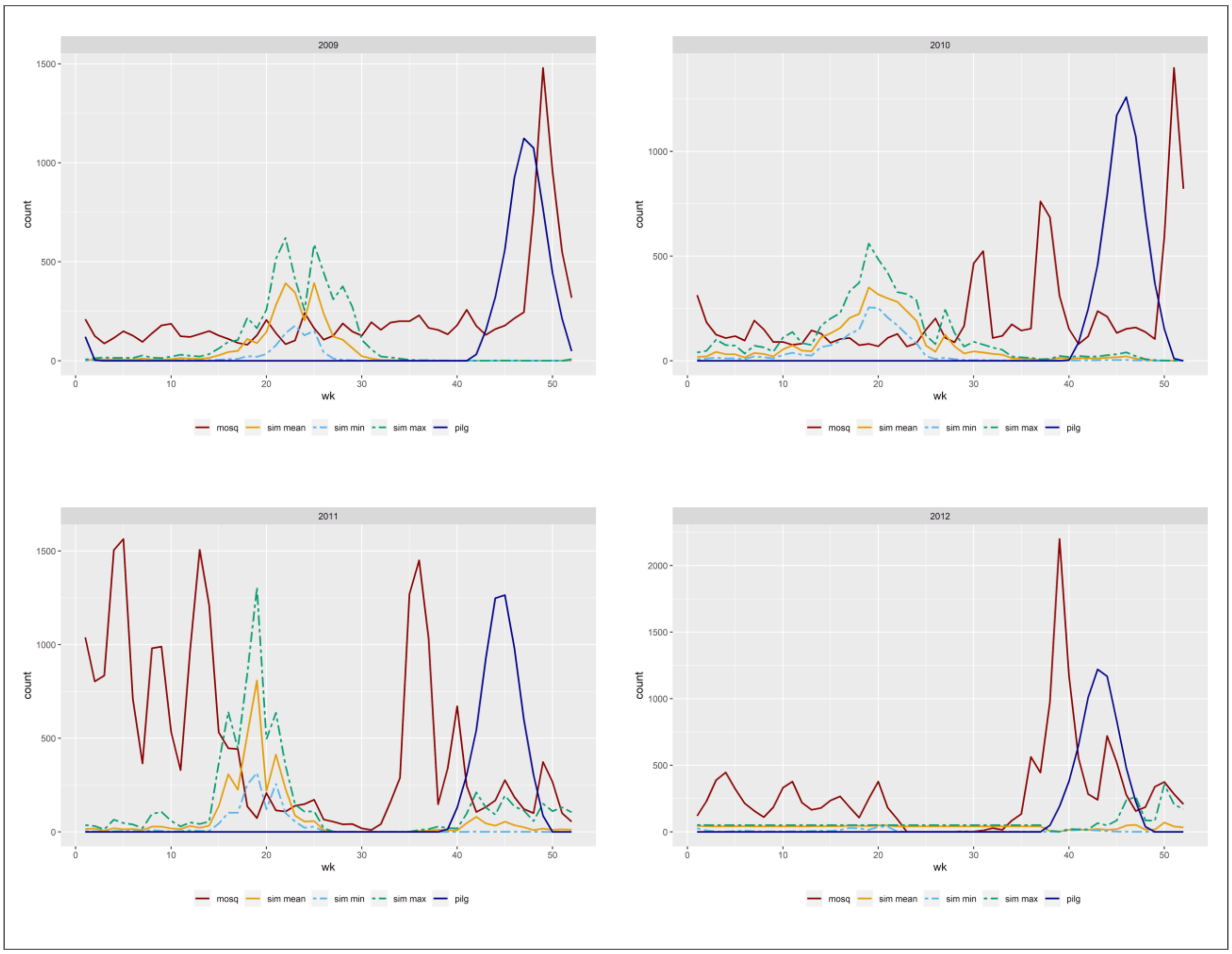


Figure 3. Distribution of observed DF cases and average, minimum and maximum DF cases predicted by top 2% of simulations. (a) Simulation based on DyMSiM model. (b) Simulation based on DyMSiM(P).



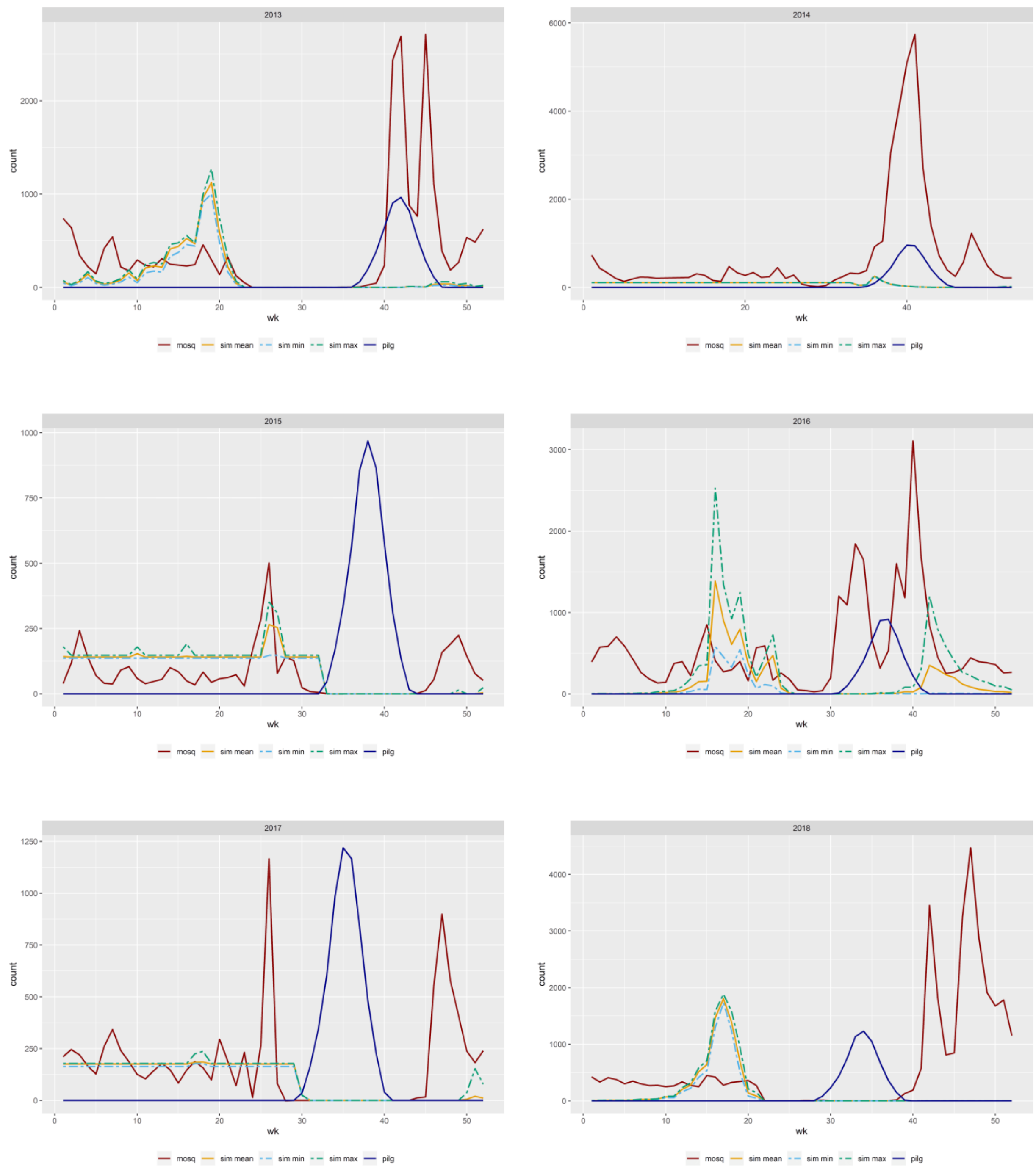


Figure 7. Distribution of average number of mosquitoes, and average, minimum and maximum DF cases predicted by top 2% of DyMSiM(P) simulations and number of pilgrims for 2009 to 2018.

Conclusion

DF is the most important climate-associated infectious disease in Saudi Arabia, and has been increasing in incidence since the end of the last century. All four serotypes of the virus are currently circulating in the western region of the country, where five administrative areas have been reporting recurrent annual cases since electronic reporting of DF began. The seasonal distribution of DF incidence in Saudi Arabia strongly suggests that weather variables likely play an important role in disease transmission and spread. The results from our statistical analyses further support this hypothesis, and specifically emphasize the importance of temperature and humidity on DF transmission through their effect of mosquito life cycle dynamics. This association is somewhat confused by the coarse spatial resolution of remote sensing weather data, which fails to capture the nuances of weather variability in urban areas and particularly in areas that experience extremes of temperature, such as desert regions. In these areas mosquitoes often flourish in pockets of comparatively more moderate temperatures, such as gardens, near fountains, and in shaded areas. Weather data that more accurately reflects on the ground mosquito habitat would help paint a better picture of the relationship between DF and weather in Saudi Arabia. Investigations of the influence of population factors, specifically, the role of the Hajj and Umrah pilgrimages on DF incidence, strongly suggest a link between these events and viral spread. Further studies are needed to better assess and accurately quantify this association. Additionally, exploring the roles of other population factors, such as population movement through the importation of foreign labor from regions with high dengue prevalence, would also help gain a better understanding of the role of such variables on the importation and dissemination of vector borne diseases in Saudi Arabia. Ultimately, this information can lead to accurate prediction of the timing and magnitude of DF epidemics, and more targeted disease prevention measures.

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