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Distribution and Determinants of MERS-CoV, Kingdom of Saudi Arabia, 2012 – 2014

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Distribution and Determinants of Middle East Respiratory Syndrome Corona Virus (MERS-CoV), Kingdom of Saudi Arabia, 2012 – 2014

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Bachelor of Science in Nursing

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2011

An Abstract of

A thesis submitted to the Faculty of Rollins School of Public Health of Emory University in the fulfillment of the requirements of the degree of

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Abstract

Distribution and Determinants of MERS-CoV, Kingdom of Saudi Arabia, 2012 – 2014
By Hassan Aldosari

Introduction: MERS-CoV is a novel virus that predominately affects the Kingdom of Saudi Arabia (KSA). Little is known about its mode of transmission, so it is important to analyze reported data collected from infected patients to understand the distribution and determinants of morbidity and mortality.

Methods: Secondary, de-identified reported MERS-CoV data from the MoH in KSA were stratified by year, age, gender, nationality, and region. We analyzed these data with SAS and performed Chi-square and Fisher exact tests when appropriate.

Results: A total of 693 confirmed MERS-CoV cases were reported to the KSA MoH between June 2012 and 31 December 2014. The average age of MERS-CoV cases was 49.3 years and 35.8% were between 40 – 59 years. MERS-CoV cases were mostly male (64%) and Saudi (65%). Over 90% of MERS-CoV cases were reported from 4 regions. Of 693 cases, 13.1% were asymptomatic or had mild symptoms; 42% had severe symptoms but survived; and 45% had severe symptoms and died. The average age of patients who died was 59.3 years, and 79% were ≥ 60 years old. Those who died were mostly male (70%) and Saudi (78%). The number of MERS-CoV cases and deaths significantly increased in KSA across the study period, while the case fatality rate (CFR) decreased. Overall, 80% of cases were reported in 2014, and the number of cases increased each month, peaking in April.

Discussion: MERS-CoV is a global public health threat that must be addressed. The significant increase in 2014 case reports might be due to a real increase, the broadening of the case definition, or to hospital-associated outbreaks. The CFR was very high, but there might be bias due to the greater attention paid to severe cases than asymptomatic/mild ones. To properly identify MERS-CoV cases, we recommend the following: training for healthcare workers, public health surveillance evaluation and strengthening (including adopting e-Surveillance), standardization of reporting, and conducting studies involving both human subjects and camels. Improvements in compliance to current infection control protocols are also needed. To control this disease, attention must also be paid to cultural beliefs and denial.

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My success at Emory University would be impossible without their standing with me during my study. I am writing these acknowledgments with tears in my eyes.

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Chapter I

Introduction

Middle East Respiratory Syndrome Corona Virus (MERS-CoV) is a global public heath threat affecting many countries; the Kingdom of Saudi Arabia (KSA) is most affected. MERS-CoV is a novel virus first isolated in KSA in June 2012 by an Egyptian virologist in Jeddah [1]. This first patient was a 60-year old man admitted to Suliman Fakeeh Hospital in Jeddah with acute pneumonia and renal failure. After isolating the virus, the virologist sent the virus to the Erasmus Institute in the Netherlands, and only in September 2012 notified the KSA Ministry of Health and World Health Organization (WHO).

Following the first human patient, a second occurred in a Qatari man later transferred to the United Kingdom for care [1-3]. This infection had originated in Alzarqa, Jordan, because earlier (April 2012) there was an outbreak of an unknown respiratory illness among healthcare workers; two died [4]. After the first case in Jeddah, the Jordanian outbreak was traced back and MERS-CoV was retrospectively confirmed from stored specimens [4].

In 2012, this infectious isolate was named novel corona virus (nCoV) or Human Corona Virus-Erasmus Medical Centre (HCoV-EMC) [1, 3] and was later renamed MERS-CoV because of its origin in the Middle East. The number of MERS CoV cases has continued to increase worldwide and (as of 23 February 2015) now stands at 1,026 confirmed cases with 376 deaths. [5]. By 2015, the virus had spread to 23 countries, including the United States. [5, 6] However, the most-affected countries are located in the Arabian Peninsula (particularly KSA) where the greatest number of cases have been reported (912 of 1026) through 23 Feb 2015 [6, 7].

MERS-CoV transmission is not fully understood. Some studies show that MERS-CoV antibodies are found in the blood of dromedary camels living in the Arabian Peninsula as well as other areas [8-15]. Surprisingly, these studies also found MERS-CoV antibodies in stored camel blood collected before the awareness of MERS-CoV in 2012 [14-16]. MERS-CoV antibodies were found in 97.7% of stored camel specimens from 2003 – 2013 in the United Arab Emirates (UAE) and 93% of the stored camel specimens from 1983 –1997 in other African countries [14, 16]. This suggests that MERS-CoV may have circulated in camels for a long period of time.

Camel-to-human transmission has been confirmed; Azhar *et* al., found the strongest evidence for this in KSA [8]. MERS-CoV was isolated in a camel, and the full genomic sequence was identical to that of a MERS-CoV patient who had direct contact with the infected camel [8]. However, it is not known whether camels are the only animals that transmit to humans. We do know that many other livestock (e.g., horses, chicken, sheep, goats, monkeys, swine, cows) have been tested, but no MERS-CoV antibodies were found [9, 17-20].

MERS-CoV antibodies have been detected in bats. Several studies have shown bat MERS-CoV short sequences to be identical to human MERS-CoV [21-23]. However, the human cases denied any contact with bats. Many denied contact with any animal at all; they may indeed be secondary cases. Human-to-human transmission has occurred among healthcare workers and within households [5, 17, 24-27], but the majority of transmission occurs in healthcare settings. There is still no evidence of sustained human-to-human transmission in the community [17, 26-29].

Saudis own and raise most of the camels in the world. It is not uncommon for a Saudi to own 100 camels. Many Saudis come into close contact with camels in the course of caring for them or visiting others who own them. Respect and regard for these animals is part of the national culture, and people express their warmth and affection for them with kisses and poetry. They also drink unpasteurized camel milk and eat camel meat, which is distributed in many Saudi supermarkets. In addition, there are annual camel races and pageants that attract many thousands of Saudis and non-Saudis. Millions of Saudi riyals are spent for the fastest or the most beautiful camels, and some Saudis use camels as a source of livelihood. If camels are the main source of MERS-CoV, this puts Saudis at an increased risk of infection.

Another public health concern is the role played by KSA as a destination of annual pilgrimage for millions of Muslims. As the home of the two holy mosques in Mecca and Madinah, KSA is a special place for millions of Muslims. Every year, the Kingdom hosts millions of visitors from many different countries around the world during the pilgrimage (Hajj) period. Hajj is considered the largest mass gathering in the world. Millions of Muslims gather in one small area in Mecca; this makes it very easy for illness to spread and be communicated to other countries.

MERS-CoV risk factors are not fully understood. For example, when first recognized it affected mainly the elderly and proved fatal to those with comorbidities such as renal disease [30-32]. However, as time went on, MERS-CoV has affected younger, healthier people, as shown in a number of clusters occurring in April 2014 in KSA [26]. Some young people infected with MERS-CoV died. Additionally, laboratory-confirmed MERS-CoV patients have been asymptomatic or mildly symptomatic [25, 30, 32-34].

While the majority of confirmed MERS-CoV cases have been male [30, 32, 33, 35, 36], other risk factors (e.g., age, associated comorbidities) are still being determined. Therefore, it is important to analyze the most recently collected data to see if any predictors might increase or decrease morbidity or mortality rates of MERS-CoV infection. Until now, there is neither a vaccine nor treatment for MERS-CoV [17]. The unavailability of antivirals and vaccines puts the Saudi population at a high risk of being infected and even dying. The incidence and prevalence of this disease will increase until its source is known and controlled.

In spite of the ongoing rise in the incidence rates (IRs) of MERS-CoV, there is a paucity of descriptive epidemiologic data that describe all affected cases, both symptomatic and asymptomatic. Intermittent studies have been performed on clusters or single cases. It is crucial to study all reported MERS-CoV cases in KSA beginning from its recognition in 2012 and provide an epidemiologic description.

For these reasons, we analyzed the IRs and predictors of MERS-CoV to identify groups at risk. It is crucial to explore and analyze reported data to identify changes in the person, time, or place of MERS-CoV infection. This analysis of the incidence of MERS-CoV will improve the health authority's ability to identify most-affected groups and target prevention programs. This will also stimulate research. Therefore, we analyzed all MERS-CoV cases reported to the KSA Ministry of Health (MoH) from 2012 – 2014 and described the epidemiology of MERS-CoV infection.

Chapter II

Literature Review

The first recognized case of novel coronavirus (n-CoV) –"the index case" – was reported to the Ministry of Health, KSA September 2012. The patient was a 60-year old man admitted to a hospital in Jeddah with pneumonia and acute renal disease in June 2012 [1]. He later died due to multi-organ failure [1]. Shortly afterwards, another man was admitted to a hospital in Qatar with a respiratory syndrome and acute renal failure. He was later transferred to the United Kingdom for advanced care [1, 37]. A novel virus was isolated that identically matched the one infecting the first patient; this was reported to the WHO [3, 37]. The second patient visited KSA three weeks prior to becoming ill but denied any contact with the first; the second patient survived [1, 3, 37].

Subsequently, other cases and clusters were identified and reported and the number of MERS-CoV cases in KSA increased through 2013. In April 2014, the number of MERS-CoV reported cases spiked when several clusters occurred of MERS-CoV hospital outbreaks involving healthcare workers. By mid-May 2014, reported MERS-CoV cases decreased [38-40], but the virus persisted and has spread to other countries.

A respiratory disease caused by a novel beta coronavirus, MERS-CoV is one of a large family of coronaviruses that causes illnesses ranging from mild (e.g., the common cold) to severe (e.g., , Severe Acute Respiratory Syndrome [SARS]) [17]. According to the World Health Organization (WHO), MERS-CoV is found in countries located in or near the Arabian Peninsula (e.g., KSA, UAE, Qatar, Oman, Jordan, Kuwait, Yemen, and Lebanon) [6]. As of February 2015, 971 confirmed cases were reported to WHO from 23 countries; overwhelmingly (>85%) from

KSA [6]. The distribution of reported MERS-CoV cases has been sporadic, with clusters occurring in KSA communities and healthcare settings in several regions.

According to published reports, the median incubation period for MERS-CoV infection is 5.2 days, with a range of 2 – 14 days [41, 42]. One report showed the signs and symptoms to appear in 95% of 47 MERS-CoV confirmed cases within 12.4 days [30]. Another study in France estimated the incubation period in a patient who became infected from his hospital roommate to be 9 – 12 days [24].

MERS-CoV initially appears as a flu-like illness or lower respiratory tract infection, with fever, fatigue, chills, rhinorrhea, and myalgia [17, 30, 35, 36, 38, 43]. In addition, shortness of breath, dyspnea, and cough have been reported in many cases [30, 32, 36, 41, 42]. A number of people have developed severe pneumonia or respiratory failure requiring mechanical ventilation and extracorporeal membrane oxygenation [32, 36, 42, 44]. Gastrointestinal symptoms (e.g., anorexia, nausea, diarrhea, abdominal pain) were reported in some cases [30, 36, 41, 42]. Several severe MERS-CoV cases have developed lymphopenia, thrombocytopenia, intravascular coagulation, and pericarditis [30, 36, 42, 45]. Some developed multi-organ failure including renal failure and respiratory failure, which led to death [32, 36]. Viral and bacterial co-infections were also reported in many cases. These infections have included para-influenza, rhinovirus, influenza A and B, pneumococcus, and ventilator-associated pneumonia.

However, many confirmed MERS-CoV cases remained asymptomatic until the end of the incubation period (14 days) or only had mild symptoms and did not require hospitalization [30, 32]. For example, among a group of 3,000 routinely screened healthcare workers who had close contact with patients, seven had no symptoms and only five had mild symptoms such as an upper respiratory tract infection [33]. Among another group, 21% (27 of 130) were found to be asymptomatic or having mild symptoms [34]. In the United States, one MERS-CoV patient presented with only mild symptoms, namely malaise, myalgias, low-grade fever, dry cough, dyspnea, and hypoxia [25].

The disproportionality of MERS-CoV severity remains unclear and might be associated with underlying comorbidities (e.g., chronic renal disease, diabetes). A descriptive study of 47 confirmed MERS-CoV cases in KSA found that 68% had diabetes mellitus, 49% chronic renal illness, 34% hypertension, and 28% chronic cardiac illness [30]. Of those, 89% were admitted to the intensive care units; 72% required mechanical ventilation. A case-control study conducted in Al-Ahasa reported that the exposed MERS-CoV confirmed cases (numbering 17) were more likely than the control group (82 cases) to have diabetes mellitus, end-stage renal disease, and be overweight [31]. Another study on 12 severe MERS-CoV cases showed that all patients had at least one other disease, some having as many six [32].

However, those studies have limitations. For example, 96% of the included participants in the first study had comorbidities and only two were healthy [30]. In addition, the majority of the included patients had a disease that was considered a predictor for others. For example, 68% had diabetes and 49% had chronic renal disease requiring hemodialysis. This means that they could be expected to have at least two diseases: chronic renal disease and hypertension [30]. Also, hospital-acquired clusters such as in the hemodialysis unit outbreak in KSA's Eastern province were included in this study.

Many healthy, young people have experienced severe MERS-CoV illnesses and have required intensive care; a few died. This is similar to what happened to healthcare workers in the hospital outbreaks [26]. Therefore, there is no strong evidence to prove the relationship between comorbidities and the severity of MERS-CoV; there might be selection bias or confounding. We should interpret theses findings with caution. A case-control study would provide evidence for any association between comorbidities and the severity of MERS-CoV illness.

MERS-CoV sources and modes-of-transmission are not fully understood. Some research indicates the source to be bats; numerous studies done in Asia, Africa, and Europe have found the coronavirus sequences in bats and some of these were related to human infection with MERS-CoV [21-23, 46]. One study examining isolated coronaviruses from 823 fecal and rectal samples, revealed that short genome sequences of MERS-CoV were found in some bats that were identical to human MERS-CoV [21]. In spite of the possibility of bats being a reservoir, it is unlikely that they are the intermediate link between MERS-CoV and human, as most confirmed cases deny contact with bats.

Another suspected reservoir has been the dromedary camel, also called the Arabian camel [8]. A study isolated MERS-CoV from a 43-year old admitted to the intensive care unit in a hospital in Jeddah. This patient owned nine camels, four of which were ill and had nasal discharge. This patient was breeding camels and came into contact with them every day prior to his admission to the hospital. He was treating one ill camel with a topical homemade remedy that he applied to its nose. Nasal and rectal swabs as well as milk and urine specimens were collected from the nine camels. The camel that was treated by the patient was found to have MERS-CoV in the nasal swabs and the blood serum in both samples. In addition, this study showed that the full genome sequences of MERS-CoV in this patient were 100% identical to those found in the infected camel that he treated. No MERS-CoV antibodies were detected in the other eight camels, but the blood serum results showed an increase in the MERS-CoV antibodies titers. Four camels had an increase in the MERS-CoV antibodies titers in the second samples, and they remained high in the other four.

Prior studies support these findings. One study compared MERS-CoV in humans and camels and found that 74% (150 of 203) of camel serum samples had MERS-CoV antibodies [9]. In addition, the same antibodies were also found in the blood of dromedary camels in other Arabian Peninsula countries including Oman (100%), and United Arab Emirates (97%) [11, 16]. MERS-CoV antibodies were also found in camels living outside the Arabian Peninsula (e.g., Spain, Ethiopia, Egypt, Tunisia, Nigeria, Somalia, Sudan, and Kenya) [11-15, 47]. However, MERS-CoV antibody levels in dromedary camels that live in or near to Arabian Peninsula were higher than those living farther away. The MERS-CoV neutralizing antibodies titers in Omani camels were greater (1:320 to 1:2560) than in Spanish camels (1:20 to 1:320) [11]. In addition, only 14% of Spanish camels had MERS antibodies compared to 74% to 100% of those in the countries of the Arabian Peninsula [11].

Interestingly, MERS-CoV antibodies were found in stored serum blood samples in many countries before the recognition of MERS-CoV disease. An Emirati study found MERS-CoV antibodies in 59.8% of the stored serum samples from 2003, long before the MERS-CoV outbreak in 2012 [16]. In addition, MERS-CoV antibodies were found in 84.1% of stored blood serum samples taken from 1983 – 1997 from camels living in African countries (e.g., Sudan and Somalia) [15]. These findings suggest that MERS-CoV may circulate in camels for a long period of time. In addition, there may have been people infected before 2012 that were asymptomatic or died from this disease without its having been detected. Other potential zoonotic reservoirs tested include chicken, sheep, donkeys, horses, goats, swine, cows, water buffalos, and mules. However, MERS antibodies have not been found in these animals [9, 17-20].

The literature indicates that MERS-CoV can be transmitted from camels to humans, yet there are likely other transmission routes, as many confirmed cases have denied coming into contact with camels. Human-to-human transmission, among family members and healthcare workers, has been documented in many clusters in KSA. The reported confirmed cases in countries such as KSA, United States, Turkey, Tunisia, Italy, France, the U.K., and Iran suggest that MERS-CoV is communicated from human-to-human [17, 24-27, 48]. Approximately 50% of human-to-human transmissions has occurred in healthcare settings and among healthcare workers and patients, with the highest occurrence in Jeddah in April 2014 [26, 27]. The virus might be transmitted through droplets or direct contact with infected persons in which there was no strict infection control procedure followed [17, 26].

In addition, human-to-human transmission has occurred in household settings among family members, but this mode of transmission has been limited in number and there is no evidence of sustained transmission in the community [17, 28, 29]. In a study that involved 26 index cases and their 280 households, about 4% of households were detected with confirmed MERS-CoV [29]. This study supported other findings showing that the disease's severity is less in secondary cases than primary ones for the most part. However, this study had a high percentage of loss to follow up for serological tests three weeks after contact with the index cases. This may result in not identifying other cases, so the findings should be interpreted with caution.

The human-to-human transmissibility of MERS-CoV was estimated in a study in 2013 by using the basic reproduction number (R0) as an indicator of inter-human transmissibility. The study found that the MERS R0 is 0.60 (95%CI= 0.42 – 0.80) compared to 0.80 (95%CI= 0.54 – 1.13) for SARS [49]. According to this study, if this number is higher than one, an epidemic has been reached. Although MERS-CoV is not easily transmitted between humans and usually happens only among close contacts, it has a higher fatality rate (about 37 – 40%) than SARS, which is transmitted more easily [17]. However, the severe MERS cases have higher detection rate than those with no signs or symptoms, which may leads to biases in estimating the fatality rate of this disease [50]. In addition, it is sometimes difficult to detect MERS-CoV cases, especially among patients with mild symptoms, because its clinical features and symptoms are nonspecific [17].

There is currently no antiviral therapy or vaccine for MERS-CoV illness, but there are efforts to develop both in the future [51]. Treatment focuses on supporting the vital organs, managing the signs and symptoms, and preventing complications [51]. However, studies suggest that the combination of two antivirals, namely interferon (IFN)-alpha-2b and ribavirin, are effective and inhibit the viral replication more than the use of a single antiviral alone [52, 53]. This antiviral regime has been tested in KSA with MERS-CoV patients in many studies [54, 55]. However, this combination was promising if the regimen commenced early in the clinical stage.

One of the studies showed that this combination had no significant effect and that MERS-CoV patients receiving this combination died a median of 19 days after admission [54]. In addition, this study's findings suggest that this combination was not beneficial for patients with comorbidities [54]. Another cohort study showed a significant improvement in health and protection of life when this combination was used early (three days post diagnosis) in comparison to those who received only supportive care, but there was no huge difference when those patients received this regimen 28 days after diagnosis [55]. A randomized control study is needed to test the effectiveness of this regimen or any other antiviral agents.

Licensed vaccination is not available. However, Novavax developed an experimental MERS-CoV vaccine that targets the major surface spike protein by using nanoparticle technology [56-58]. In addition, there are other vaccines candidates suggested in many studies.

For example, “the construction of an infectious cDNA clones of MERS-CoV using a bacterial artificial chromosome (BAC)” [59]. Modified vaccinia virus Ankara is another candidate that targets the full-length MERS-CoV spike (S) protein [60]. However, these vaccinations are in stage one of development and will take a long time, maybe years, to be licensed and released. In addition, as MERS-CoV is not fully understood and many things remain unclear such as its original source and its transmission modes, so the question about who should receive the MERS-CoV vaccination remains a public health issue.

Chapter III: Manuscript

Abstract

Introduction: MERS-CoV is a novel virus that predominately affects the Kingdom of Saudi Arabia (KSA). Little is known about its mode of transmission, so it is important to analyze reported data collected from infected patients to understand the distribution and determinants of morbidity and mortality.

Methods: Secondary, de-identified reported MERS-CoV data from the MoH in KSA were stratified by year, age, gender, nationality, and region. We analyzed these data with SAS and performed Chi-square and Fisher exact tests when appropriate.

Results: A total of 693 confirmed MERS-CoV cases were reported to the KSA MoH between June 2012 and 31 December 2014. The average age of MERS-CoV cases was 49.3 years and 35.8% were between 40 – 59 years. MERS-CoV cases were mostly male (64%) and Saudi (65%). Over 90% of MERS-CoV cases were reported from 4 regions. Of 693 cases, 13.1% were asymptomatic or had mild symptoms; 42% had severe symptoms but survived; and 45% had severe symptoms and died. The average age of patients who died was 59.3 years, and 79% were ≥ 60 years old. Those who died were mostly male (70%) and Saudi (78%). The number of MERS-CoV cases and deaths significantly increased in KSA across the study period, while the case fatality rate (CFR) decreased. Overall, 80% of cases were reported in 2014, and the number of cases increased each month, peaking in April.

Discussion: MERS-CoV is a global public health threat that must be addressed. The significant increase in 2014 case reports might be due to a real increase, the broadening of the case definition, or to hospital-associated outbreaks. The CFR was very high, but there might be bias due to the greater attention paid to severe cases than asymptomatic/mild ones. To properly identify MERS-CoV cases, we recommend the following: training for healthcare workers, public health surveillance evaluation and strengthening (including adopting e-Surveillance), standardization of reporting, and conducting studies involving both human subjects and camels. Improvements in compliance to current infection control protocols are also needed. To control this disease, attention must also be paid to cultural beliefs and denial.

Introduction

Middle East Respiratory Syndrome Corona Virus (MERS-CoV) is a global public health threat affecting many countries; the Kingdom of Saudi Arabia (KSA) is most affected. MERS-CoV is a novel virus first isolated in KSA in June 2012 by a virologist in Jeddah [1]. This infectious isolate was named novel corona virus (nCoV) or Human Corona Virus-Erasmus Medical Centre (HCoV-EMC) [1, 3] and was later renamed MERS-CoV because of its origin in the Middle East. The number of MERS-CoV cases has continued to increase worldwide (as of 23 February 2015) and now stands at 1,026 confirmed cases with 376 deaths [5]. By 2015, the virus had spread to 23 countries, including the United States [5, 6]. However, the most affected countries are those located in the Arabian Peninsula (particularly KSA), where the greatest number of cases have been reported (912 of 1,026 reported cases of MERS-CoV through 23 Feb 2015) [6].

MERS-CoV transmission is not fully understood. Some studies show that MERS-CoV antibodies are found in the blood of dromedary camels living in the Arabian Peninsula as well as in other areas [8-15]. Surprisingly, these studies also found MERS-CoV antibodies in stored camel blood collected before the discovery of MERS-CoV in 2012 [14-16]. Camel-to-human transmission has been confirmed; Azhar et al. found the strongest evidence for this in KSA [8]. However, it is not known whether camels are the only animals that transmit to humans. MERS-CoV antibodies have been detected in bats. Several studies have shown that the MERS-CoV short sequences in bats are identical to that in humans [21-23]. Human-to-human transmission has occurred among healthcare workers and within households [5, 17, 24-27], but the majority of transmission occurs in healthcare settings. There is still no evidence of sustained transmission in the community [17, 26-29].

MERS-CoV risk factors are not fully understood. For example, when first recognized, it affected mainly the elderly and proved fatal to those with comorbidities such as renal disease [30-32]. However, as time went on, MERS-CoV has affected younger, healthier people, as shown in a number of clusters occurring in April 2014 in KSA [26]. Some young people infected with MERS-CoV died. Additionally, laboratory-confirmed MERS-CoV patients have been asymptomatic or mildly symptomatic [25, 30, 32-34]. While the majority of confirmed MERS-CoV cases have been male [30, 32, 33, 35, 36], other risk factors (e.g., age, associated comorbidities) are still being determined. Therefore, it is important to analyze the most recently collected data to see if any changes in risk factors might increase or decrease the MERS-CoV morbidity or mortality rates.

Until now, there is neither a vaccine nor treatment for MERS-CoV [17]. The unavailability of antivirals and vaccines puts the Saudi population at a high risk of infection and death. The incidence and prevalence of this disease will increase until its source is known and controlled. In KSA, camel ownership is a popular mark of status that has financial and cultural significance. The regard that people have for the animals and some people's denial of their being a source of an infection could be an impediment to controlling the disease. Another public health concern is the role played by KSA as an annual pilgrimage destination for millions of Muslims. Hajj is considered the largest mass gathering in the world. Millions of Muslims gather in one small area in Mecca, and this makes it very easy for illness to spread and be communicated to other countries.

In spite of the ongoing rise in the incidence rates (IRs) of MERS-CoV, there is a paucity of descriptive epidemiologic data that describes all affected cases, both symptomatic and asymptomatic. Intermittent studies have been performed on clusters or single cases. It is crucial to study all reported MERS-CoV cases in KSA beginning at the point of its recognition in 2012 and provide an epidemiologic description. For these reasons, we analyzed IRs and predictors of MERS-CoV to identify groups at greater risk. This analysis of the incidence of MERS-CoV will improve the health authority's ability to identify most-affected groups and target prevention programs. This will also stimulate research in other countries to compare results. We analyzed all MERS-CoV cases reported to the KSA Ministry of Health (MoH) from 2012 – 2014 and described the epidemiology of MERS-CoV infection.

Methods

Data Sources

Secondary, de-identified MERS-CoV data was obtained from the KSA MoH. In accordance with the WHO MERS-CoV case definition, every healthcare facility in KSA is required to immediately report all probable and confirmed MERS-CoV cases to the MoH. Saudi population data were obtained from the Central Department of Statistics and Information (CDSI) in the Ministry of Economy and Planning in KSA. CDSI collects data including age, gender, and nationality for all Saudi and non-Saudi citizens.

Study Variables

The case report includes demographic variables (i.e., age, gender, city, region, and nationality), as well as hospital/healthcare facility. It also includes report date, symptom onset date, final outcome, probable infection source, and comorbidities. However, some variables were excluded from our analysis. In the reports, >20% of the variables were missing or incomplete (not at random), including MERS-CoV infection source and comorbidities.

We created new variable groups including the final outcome, age group, and nationality. We combined the final outcome variable into two (died or survived) and combined nationality into two (Saudi and non-Saudi). We initially grouped the age variable into WHO's standard 10 age categories (i.e., 0-9, 10-19, up to 90-99). Due to the small number in some age groups (e.g., <5), we used Chi-square analysis and Fisher exact tests to recombine the age groups into four categories (0-19, 20-39, 40-59, and 60+).

Due to the variance in the number of cases across regions, we only selected the four regions (Makkah, Riyadh, Eastern Region, and Madinah) that made up over 90% of all cases for all years combined.

Data Analysis

Using SAS 9.4, data were analyzed for all confirmed cases collected from the emergence of MERS-CoV in June 2012 to the end of December 2014. The case fatality rate (CFR) was defined as the proportion of persons with confirmed MERS-CoV over the 2-1/2 year study period who had died. The CFR was presented as a percentage in our analysis. We performed a Chi-square or Fisher exact test when required for equal proportions and association between age groups, regions, gender, and nationality. We also performed Chi-Square trend tests to investigate the CFR by year and age group. All tests were conducted with a significance of 0.05.

Ethical Considerations

We applied to the IRB at Emory University for expedited/exempt review as these data analyses were conducted using secondary, aggregate de-identified data. Our analysis was determined to be IRB-exempt because it used secondary data and all data were de-identified prior to analysis. Prior to data collection, all portions of the study were reviewed by Emory's IRB and determined to meet the criteria for exemption.

Results

A total of 693 confirmed MERS-CoV cases were reported to the KSA MoH between 1 June 2012 and 31 Dec 2014, with approximately 80% reported in 2014 (Table 1). The mean age of confirmed MERS-CoV cases averaged 49.3 years and 36% were 40 to 59 years of age. Those who had MERS-CoV were mostly males (64%) and Saudis (65%). Over 90% of MERS-CoV cases were reported from 4 regions: Makkah, Riyadh, Eastern Region, and Madinah (Figure 1). Eastern Region had experienced the highest CFR and was the only major region where the number of reported cases was reduced in 2014 than the year before (Figure 2).

Of 693 cases, 310 died, indicating the overall CFR of 45% (Table 1). A full 75% of deaths occurred in 2014. Those who died from MERS-CoV were an average of 59.3 years old and 79% were ≥ 60 years old (Table 1). Of those who died, 70% were male and 78% were Saudi. The number of MERS-CoV cases and deaths significantly increased in KSA across the study period, while the CFR decreased (Table 1).

Overall and in each year, the number of cases increased as age increased ($p<.001$), except for the ≥60 age group, for which the number of cases decreased (Table 1). The CFR was greater among males than females and greater among Saudis than non-Saudis ($p<.001$) (Table 1). The analysis of cases stratified by age group and years revealed that the CFR decreased across years in each age group except for those aged 0-19 (Table 2).

Of 693 confirmed MERS-CoV cases, 91 cases were asymptomatic or had mild symptoms (13%), 602 had severe symptoms and were admitted to hospitals, of which 292 survived (42%), and 310 died (45%) (Table 3). Most of those who were asymptomatic or had mild symptoms were between 20-39 years old (63%), female (59%) and non-Saudi (59%). A sizeable proportion of those who had severe symptoms and survived were between 40-59 years old (46%), male (64%) and Saudi (58%).

The number of MERS-CoV cases among males was greater than among females in all age groups (Table 4). In addition, the highest proportion of MERS-CoV cases among males occurred in 40-50 age group, while among females, it occurred in the 20-39 age group (Table 4).

Saudis had a greater number of MERS-CoV cases than non-Saudis across all age groups except the 20-39 age group, in which non-Saudis had almost double the number of cases of Saudis (46% vs. 20%) (Table 4). Among Saudis, the highest proportion of MERS-CoV cases occurred in ≥ 60 age group, and among non-Saudis, in the 30-39 year old age group (Table 4).

MERS-CoV cases among males significantly differed by nationality (P<.0001) (Table 5). From 2013 to 2014, the number of cases among non-Saudis increased by more than 7-fold, compared to a 3-fold increase among Saudis in that time period (Table 5). In terms of gender, rates are about equal by nationality for females but significantly different for males. Males proportion higher among Saudis with males making up about 68% and about equal in both gender among non-Saudis. The number of cases among Saudis was more than double that among non-Saudis in 3 of the 4 most affected regions, but the number by nationality was approximately equal in Makkah, the region with the highest number of reported cases (Table 5).

Among Saudis, the greatest proportion of MERS-CoV deaths occurred in the ≥60 age group (59%) and among non-Saudis, in the 40-59 age group (46%) (Table 6). The number of deaths in the ≥60 age group was higher among females (60%) than males (51%) (Table 6).

The number of reported cases in 2013 was fairly stable between April and September (Figure 3). In 2014, the number of cases increased monthly through a peak in April, then fell until August, then increased again, rising through October (Figure 3).

Discussion

Our results showed that MERS-CoV dramatically increased across the study period, and that the majority of MERS-CoV cases were reported in 2014. This might be due to a real increase in the disease epidemic in KSA, but other potential explanations of this sharp increase should be considered.

The impact of changes to and the expansion of the case definition should be considered, as it was adjusted to better target probable cases or those who should be investigated for MERS-CoV, including those who are asymptomatic or have mild symptoms.

Another potential explanation of this increase was the improvement of laboratory technology and the new guidance revisions for MERS laboratory investigations.

In addition, the major hospital-associated outbreak occurring in April 2014, which involved health care workers and patients, might also explain this increase. The outbreak resulted in the deaths of some young Saudi healthcare workers, provoking greater fear, and special attention was paid to MERS-CoV afterwards. Following this, many sectors of KSA became more involved, including the media, healthcare agencies, the MoH, and international agencies such as CDC and WHO. Altogether, this might have led to an increase in MERS case reporting.

KSA has more than 85% of all global MERS-CoV cases. In addition, our results showed a higher rate of MERS-CoV cases among males, especially Saudi males. This might be due to men's higher exposure to the MERS-CoV reservoir or to camels. Moreover, more Saudi females had asymptomatic cases compared to Saudis males, and overall non-Saudis had more asymptomatic cases than Saudis. This might be due to the fact that Saudi males come into contact with camels more often and therefore make up most of the primary cases. However, the

MoH data is missing information from case reports on the source of MERS infections that could help confirm our hypothesis.

The fact that camels are one of the main suspected sources of the disease is an important issue in terms of control and prevention in KSA, as camels are well-regarded animals, especially among their male owners and shepherds, and many Saudis believe that their milk is a source of treatment, not a source of disease. People’s frequent contact with camels and their consumption of camel meat and milk raises risk levels and, coupled with these attitudes, could hinder control efforts.

Previously, it was hypothesized that the number of MERS-CoV cases was highest among those age 60 and above. Our study showed that the highest number of cases occurred in the 40-59 age. In fact, we found that the number of MERS-CoV cases among younger adults (aged 20-39) was approximately equal to the number of cases among those aged 60 and above.

By nationality, our analysis showed that the number of MERS-CoV cases was greater among Saudis than non-Saudis for every age group except 20-39. Most health workers in KSA fall into this age group. The number of non-Saudi cases increased 7-fold from 2013 to 2014. Studies suggest that clusters have spread from patients to healthcare workers and vice versa in many health care settings in KSA.

The vast majority of MERS-CoV cases were reported from the most developed regions in KSA, the ones that have the best technology and employ the most highly qualified and educated clinicians and healthcare professionals. Therefore, reporting might be superior in these areas, and this might explain the higher numbers. In contrast, there might be many unidentified cases in other regions or smaller cities that are less equipped to identify the disease.

It has been hypothesized that the case number peak in April 2014 was related to the camel birth cycle, which occurs in the mid-spring in KSA, between March and April. However, this may not be so. According to WHO, healthcare-acquired infections among patients and healthcare workers were mainly responsible for the rise in MERS cases in April and May of 2014, so the increase might have been due to MERS nosocomial infections and the limited infection control in many KSA hospitals.

Our study had several limitations. First, it was a secondary analysis with missing data such as the source of infection, comorbidities, and occupation. These variables are very important in determining or predicting the final outcome and the associated causes of deaths. In addition, there is the potential for underreporting of asymptomatic cases and therefore bias the true CFR. Since we only had data on confirmed MERS cases, the probable or suspected cases were not available and therefore limited further analysis on the incidence and prevalence.

To improve the control and prevention of MERS-CoV, comprehensive and standardized reporting forms should be developed and distributed by the MoH to all healthcare settings to collect data on all probable and confirmed cases; training should be provided to healthcare workers on the identification of cases and the risk environment in clinical settings; studies incorporating the random testing of Saudi and non-Saudi residents should be conducted to identify the asymptomatic cases; random testing of camels should also be conducted in different regions (possibly as a requirement for entering races or pageants) to identify the infected camels and store samples for future investigation if required; and current infection control protocols and guidelines should be improved, emphasizing infection restrictions for probable cases, and reinforcing infection control protocols. Finally, it is crucial to quantify the incidence and prevalence of MERS-CoV in KSA, which can be done when all suspected cases are reported to the MoH. This will help in assessing the programs that have been established to fight this disease.

Chapter 4: Conclusion and Recommendations

MERS-CoV is a pandemic infectious disease predominately affecting the population of KSA. The number of cases as well as deaths increases every year; it is a major public health threat that needs to be addressed. MERS-CoV and its severity are still not fully understood, and the transmission modes are still unclear. Neither treatment nor vaccine is available for this illness.

Our recommendations start with the surveillance system. It is of the utmost importance that sufficient data be collected for studying and understanding this new novel disease. There should be comprehensive standardized forms to collect MERS-CoV data from all affected cases. We recommend that the government, MoH, Saudi healthcare settings, all healthcare professionals, researchers, and patients cooperate and improve the surveillance system by collecting and reporting the full information from MERS cases, including the probable source of infection, health history, and all probable cases. The surveillance system should be evaluated, and the sensitivity and specificity of reporting should be assessed.

Since asymptomatic cases may be vastly underreported, we also recommend further studies that randomly test Saudi and non-Saudi residents to identify the asymptomatic cases.

Also, it is important to conduct random investigations of camels in many different regions to identify the infected camels and store samples for future investigation if required. These investigations can take place during annual camel races and pageants. Also, the government should make these random animal investigations compulsory or a requirement for entering these races or pageants.

Many challenges related to infection control exist in governmental and private health care facilities. Therefore, we recommend that the MoH improve infection control protocols and guidelines, emphasize infection restrictions for probable cases, and reinforce infection control protocols through the adoption of new sanctions against healthcare workers who do not follow these protocols. Training for healthcare workers on MERS-CoV case identification as well as on the protective measures that can be taken against this disease are also needed.

Cultural beliefs and denial in regard to the MERS-CoV reservoir is another public health issue that needs to be addressed, so health education should be provided for all concerned parties including patients, healthcare professionals, camel owners, and butchers.

Finally, further studies are needed utilizing more data to investigate other possible confounders associated with CFR such as the source of infection and comorbidities. In addition, it is crucial to quantify the incidence and prevalence of MERS-CoV in KSA, which can be done by reporting all suspected cases to the MoH. This will help in assessing the programs that have been established to fight this disease.

Table 1. Demographic Characteristics of Reported MERS-CoV Cases and Deaths, Kingdom of Saudi Arabia, 2012 – 2014

Characteristic	# Cases	# Deaths (%)	p-value
Year			*<.01*
2012	5	3 (60)	
2013	136	76 (56)	
2014	552	231 (42)	
Age			*<.001*
0 – 19 y	32	4 (12)	
20 – 39 y	201	37 (18)	
40 – 59 y	248	102 (42)	
≥ 60 y	212	167 (79)	
Gender			*<.01*
Male	442	217 (49)	
Female	251	93 (37)	
Nationality			*<.0001*
Saudi	449	243 (54)	
Non-Saudi	244	67 (28)	
Total	693	310 (45)	

Table 2: Reported Cases of MERS-CoV and Proportion of Deaths, by Age Group and Year, Kingdom of Saudi Arabia, 2012 – 2014

Age Group	2012 # cases (% deaths)	*2013 # cases (% deaths)	*2014 # cases (% deaths)
0 – 19	0 (0)	12 (8)	20 (15)
20 – 39	2 (50)	24 (25)	175 (17)
40 – 59	1 (0)	55 (51)	192 (38)
≥ **60**	2 (100)	45 (91)	165 (65)
Total	5 (60)	136 (56)	552 (42)

* p-value <0.05

Table 3. Severity of Reported MERS-CoV Cases, by Age Group, Gender, and Nationality, Kingdom of Saudi Arabia, 2012 – 2014

Characteristic	# Asymptomatic or Mild Symptoms (%)	Severe Symptoms and #Survived (%)	Severe Symptoms and #Died (%)	p-value
Age				*<.0001*
0 – 19 y	16 (50)	12 (37)	4 (12)	
20 – 39 y	57 (28)	107 (53)	37 (18)	
40 – 59 y	16 (6)	130 (52)	102 (41)	
≥ 60 y	2 (1)	43 (20)	167 (79)	
Gender				*<.0001*
Male	37 (8)	188 (49)	217 (43)	
Female	54 (22)	104 (41)	93 (37)	
Nationality				*<.0001*
Saudi	37 (8)	169 (38)	243 (54)	
Non-Saudi	54 (22)	123 (50)	67 (27)	
Total	**91 (13)**	**292 (42)**	**310 (45)**	

Table 4. Reported Cases of MERS-CoV, by Gender, Nationality, and Age Group, Kingdom of Saudi Arabia, 2012 – 2014

Characteristic	Age Group			
	0 – 19	20 – 39	40 – 59	≥ 60
	# (%)	# (%)	# (%)	# (%)
***Gender**				
Male	19 (4)	112 (25)	164 (37)	147 (33)
Female	13 (5)	89 (35)	84 (34)	65 (26)
***Nationality**				
Saudi	27 (6)	90 (20)	151 (34)	181 (40)
Non-Saudi	5 (2)	111 (46)	97 (40)	31 (13)

* p-value <.0001

Table 5. Reported Cases of MERS-CoV, by Year, Gender, Region, and Nationality, Kingdom of Saudi Arabia, 2012 – 2014

Characteristics		Nationality		
		Saudi # Cases (%)	Non-Saudi # Cases (%)	p-value
*Year				<.0001
	2012	5 (100)	0 (0)	
	2013	108 (79)	28 (21)	
	2014	336 (61)	216 (39)	
*Gender				<.0001
	Male	313 (71)	129 (29)	
	Female	136 (54)	115 (46)	
*Region				<.0001
	Makkah	154 (57)	117 (43)	
	Riyadh	171 (69)	78 (31)	
	Eastern Region	61 (86)	10 (14)	
	Madinah	31(70)	13 (30)	

* p-value <.0001

Table 6. Reported MERS-CoV Deaths, by Gender, Nationality. and Age Group, Kingdom of Saudi Arabia, 2012 – 2014

Characteristic	Age Group			
	0 – 19	20 – 39	40 – 59	≥ 60
	# (%)	# (%)	# (%)	# (%)
***Gender**				
Male	4 (2)	26 (12)	76 (35)	111 (51)
Female	0 (0)	11 (12)	26 (28)	56 (60)
***Nationality**				
Saudi	4 (2)	25 (10)	71 (29)	143 (59)
Non-Saudi	0 (0)	12 (18)	31 (46)	24 (36)

* p-value <.05

Figure 1. Reported Cases and Deaths of MERS-CoV, by Region, Kingdom of Saudi Arabia, 2012 — 2014

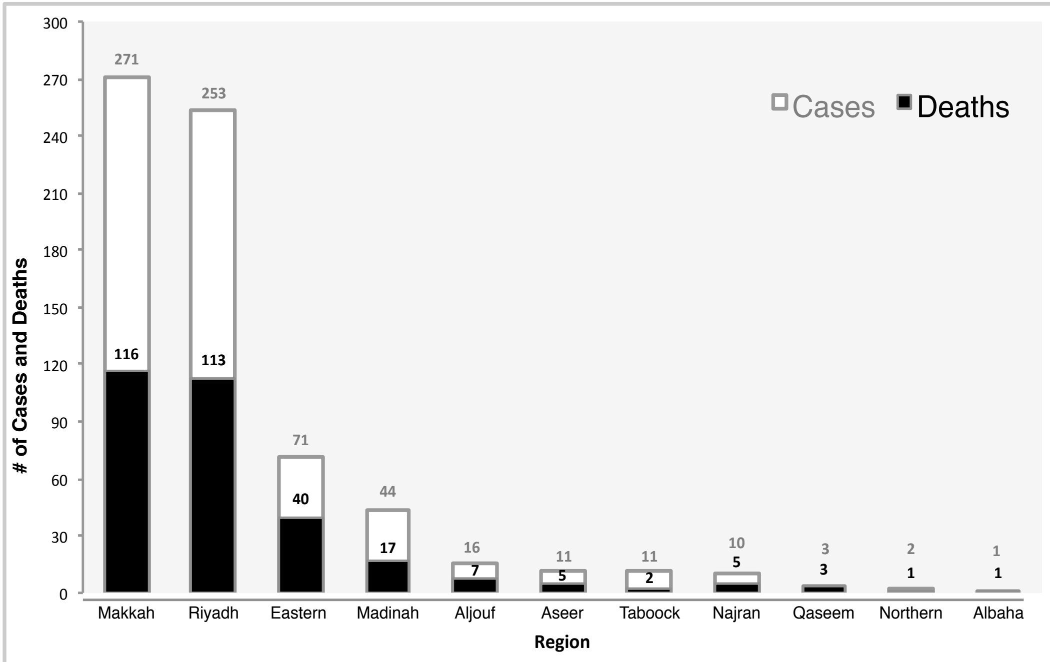


Figure 2. Reported Cases of MERS-CoV, by Region and Year, Kingdom of Saudi Arabia, 2012 – 2014

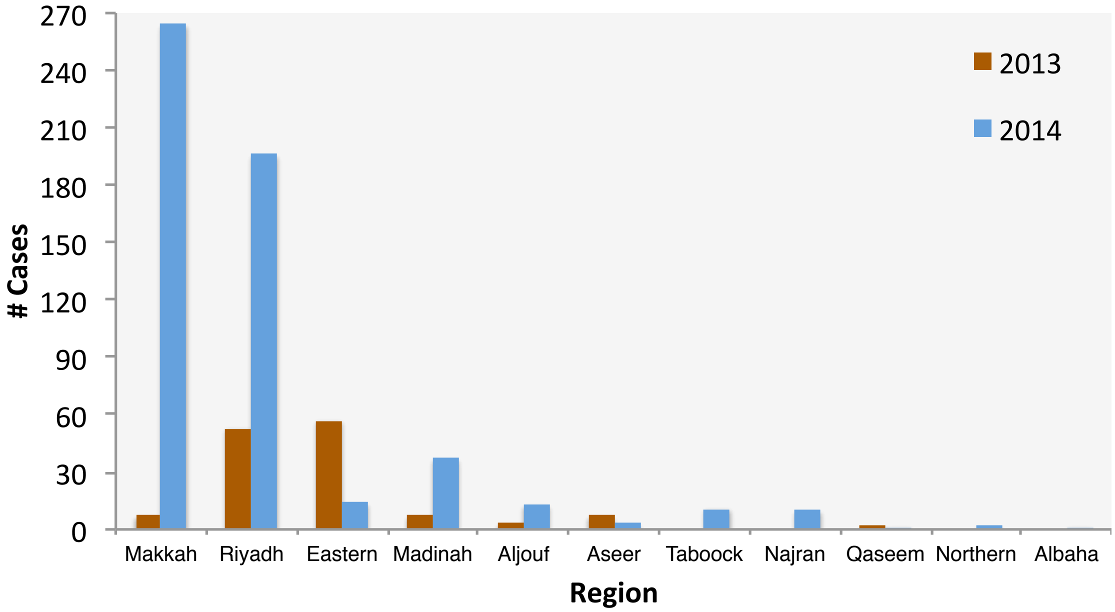
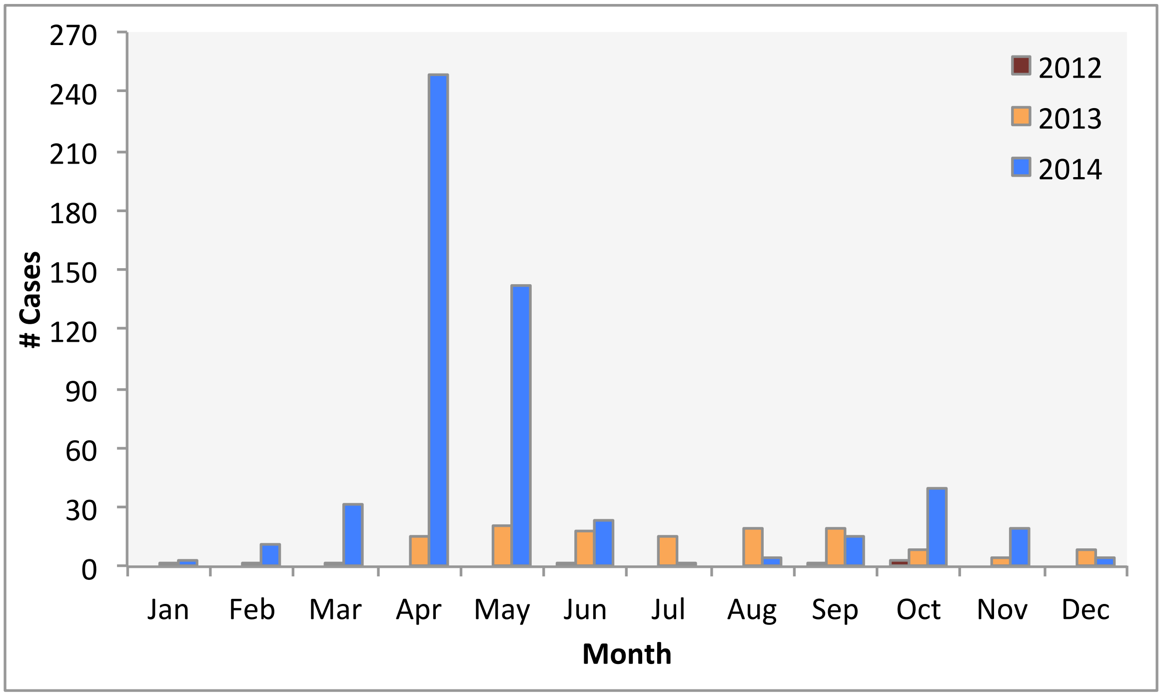


Figure 3. Reported Cases of MERS-CoV, by Month and Year, Kingdom of Saudi Arabia, 2012 – 2014



Referernces List

1. Zaki, A.M., et al., *Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia.* New England Journal of Medicine, 2012. **367**(19): p. 1814-1820.
2. Bermingham, A., et al., *Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012.* Euro Surveill, 2012. **17**(40): p. 20290.
3. World Health Organization, *Novel coronavirus infection in the United Kingdom*. 2012.
4. Hijawi, B., et al., *Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation.* 2013.
5. World Health Organization. *Global Alert and Response. Middle East respiratory syndrome coronavirus (MERS-CoV) – Saudi Arabia- 23 February 2015*. 2015 [cited 2015 Feb 23]; Available from: http://www.who.int/csr/don/23-february-2015-mers-saudi-arabia/en/.
6. World Health Organization, *Middle East respiratory syndrome coronavirus (MERS-CoV): summary of current situation, literature update and risk assessment–as of 5 February 2015 [cited 2015 Feb 25]*.
7. Command and Control Center of Ministry of Health in the Kingdom of Saudi Arabia. *New Confirmed Corona Cases Recorded*. 2015 [cited 2015 Feb 30, 2015]; Available from: http://www.moh.gov.sa/en/CCC/PressReleases/Pages/Statistics-2015-02-24-001.aspx.
8. Azhar, E.I., et al., *Evidence for camel-to-human transmission of MERS coronavirus.* New England Journal of Medicine, 2014. **370**(26): p. 2499-2505.

9. Alagaili, A.N., et al., *Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia.* MBio, 2014. **5**(2): p. e00884-14.

10. Reusken, C., B.L. Haagmans, and M.P. Koopmans, *[Dromedary camels and Middle East respiratory syndrome: MERS coronavirus in the 'ship of the desert'].* Ned Tijdschr Geneeskd, 2014. **158**: p. A7806.

11. Reusken, C.B., et al., *Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study.* The Lancet infectious diseases, 2013. **13**(10): p. 859-866.

12. Perera, R., et al., *Seroepidemiology for MERS coronavirus using microneutralisation and pseudoparticle virus neutralisation assays reveal a high prevalence of antibody in dromedary camels in Egypt, June 2013.* Euro Surveill, 2013. **18**(36): p. 20574.

13. Chu, D.K., et al., *MERS coronaviruses in dromedary camels, Egypt.* Emerg Infect Dis, 2014. **20**(6): p. 1049-1053.

14. Corman, V.M., et al., *Antibodies against MERS coronavirus in dromedary camels, Kenya, 1992–2013.* Emerging infectious diseases, 2014. **20**(8): p. 1319.

15. Muller, M.A., et al., *MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983-1997.* Emerg Infect Dis, 2014. **20**(12): p. 2093-5.

16. Meyer, B., et al., *Antibodies against MERS coronavirus in dromedary camels, United Arab Emirates, 2003 and 2013.* Emerg Infect Dis, 2014. **20**(4): p. 552-559.

17. World Health Organization. *Frequently asked questions on Middle East respiratory syndrome coronavirus (MERS‐CoV)*. 2014 [cited 2015 Feb 5].

18. Hemida, M., et al., *Middle East Respiratory Syndrome (MERS) coronavirus seroprevalence in domestic livestock in Saudi Arabia, 2010 to 2013.* Euro surveillance:

bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin, 2012. **18**(50): p. 20659-20659.

19. Engler, O., et al., *Middle East respiratory syndrome coronavirus (MERS-CoV) serology in major livestock species in an affected region in Jordan, June to September 2013.* 2013.

20. Meyer, B., et al., *Serologic Assessment of Possibility for MERS-CoV Infection in Equids.* Emerging infectious diseases, 2015. **21**(1): p. 181.

21. Memish, Z.A., et al., *Middle East respiratory syndrome coronavirus in bats, Saudi Arabia.* Emerg Infect Dis, 2013. **19**(11).

22. Wang, Q., et al., *Bat origins of MERS-CoV supported by bat coronavirus HKU4 usage of human receptor CD26.* Cell Host Microbe, 2014. **16**(3): p. 328-37.

23. Annan, A., et al., *Human betacoronavirus 2c EMC/2012–related viruses in bats, Ghana and Europe.* Emerging infectious diseases, 2013. **19**(3): p. 456.

24. Guery, B., et al., *Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission.* The Lancet, 2013. **381**(9885): p. 2265-2272.

25. Bialek, S.R., et al., *First Confirmed Cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection in the United States, Updated Information on the Epidemiology of MERS-CoV Infection, and Guidance for the Public, Clinicians, and Public Health Authorities-May 2014.* MMWR. Morbidity and mortality weekly report, 2014. **63**(19): p. 431-436.

26. World Health Organization, *Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update—as of 9 May 2014*. 2014.

27. Drosten, C., et al., *An observational, laboratory-based study of outbreaks of middle East respiratory syndrome coronavirus in jeddah and riyadh, kingdom of saudi arabia, 2014.* Clin Infect Dis, 2015. **60**(3): p. 369-77.

28. Centers for Diseases Control and Prevention. *MERS-CoV not spread to household members or health care contacts of the two U.S. cases*. [cited 2015 January 5,]; Available from: http://www.cdc.gov/media/releases/2014/p0617-Mers.html.

29. Drosten, C., et al., *Transmission of MERS-coronavirus in household contacts.* New England Journal of Medicine, 2014. **371**(9): p. 828-835.

30. Assiri, A., et al., *Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study.* The Lancet infectious diseases, 2013. **13**(9): p. 752-761.

31. Al-Tawfiq, J.A., et al., *Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients.* Clinical Infectious Diseases, 2014: p. ciu226.

32. Arabi, Y.M., et al., *Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection.* Annals of internal medicine, 2014. **160**(6): p. 389-397.

33. Memish, Z.A., A.I. Zumla, and A. Assiri, *Middle East respiratory syndrome coronavirus infections in health care workers.* New England Journal of Medicine, 2013. **369**(9): p. 884-886.

34. Control, C.f.D. and Prevention. *Updated information on the epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection and guidance for the public, clinicians, and public health authorities, 2012-2013*. MMWR. Morbidity and mortality weekly report 2013 [cited 62 38]; 793].

35. Saad, M., et al., *Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia.* Int J Infect Dis, 2014. **29**: p. 301-6.

36. Memish, Z.A., et al., *Family cluster of Middle East respiratory syndrome coronavirus infections.* New England Journal of Medicine, 2013. **368**(26): p. 2487-2494.

37. Wise, J., *Patient with new strain of coronavirus is treated in intensive care at London hospital.* BMJ, 2012. **345**.

38. World Health Organization, *Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update–as of 11 June 2014*.

39. World Health Organization, *WHO risk assessment: Middle East respiratory syndrome coronavirus (MERS-CoV). 24 April 2014. Geneva: WHO; Apr 2014*.

40. Alghamdi, I.G., et al., *The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health.* Int J Gen Med, 2014. **7**: p. 417-23.

41. Assiri, A., et al., *Hospital outbreak of Middle East respiratory syndrome coronavirus.* New England Journal of Medicine, 2013. **369**(5): p. 407-416.

42. Mackay, I.M. and K.E. Arden, *Middle East respiratory syndrome: An emerging coronavirus infection tracked by the crowd.* Virus Res, 2015.

43. Al-Tawfiq, J.A., A. Zumla, and Z.A. Memish, *Coronaviruses: severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus in travelers.* Curr Opin Infect Dis, 2014. **27**(5): p. 411-7.

44. Drosten, C., et al., *Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection.* The Lancet infectious diseases, 2013. **13**(9): p. 745-751.

45. World Health Organization, *Global Alert and Response (GAR). Background and summary of novel coronavirus infection—as of 21 December 2012*. 2012.

46. Ithete, N.L., et al., *Close relative of human Middle East respiratory syndrome coronavirus in bat, South Africa.* Emerging infectious diseases, 2013. **19**(10): p. 1697.

47. Reusken, C.B., et al., *Geographic distribution of MERS coronavirus among dromedary camels, Africa.* Emerging infectious diseases, 2014. **20**(8): p. 1370.

48. World Health Organization. *Global Alert and Response. Middle East respiratory syndrome coronavirus (MERS-CoV) – Saudi Arabia*. 2015 23 February 2015 [cited 2015 23 February 2015]; Available from: http://www.who.int/csr/don/23-february-2015-mers-saudi-arabia/en/.

49. Breban, R., J. Riou, and A. Fontanet, *Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk.* The Lancet, 2013. **382**(9893): p. 694-699.

50. Cauchemez, S., et al., *Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility.* The Lancet infectious diseases, 2014. **14**(1): p. 50-56.

51. World Health Organization, *Interim Guidance Document. Clinical management of severe acute respiratory infections when novel coronavirus is suspected: what to do and what not to do.* Avialable at: http://www. who. int/csr/disease/coronavirus_infections/en, 2014.

52. Falzarano, D., et al., *Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin.* Scientific reports, 2013. **3**.

53. Dyall, J., et al., *Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays.* Journal of General Virology, 2014. **95**(Pt 3): p. 571-577.

54. Al-Tawfiq, J.A., et al., *Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study.* International Journal of Infectious Diseases, 2014. **20**: p. 42-46.

55. Omrani, A.S., et al., *Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study.* The Lancet Infectious Diseases, 2014. **14**(11): p. 1090-1095.

56. Novavax. *Novavax Produces MERS-CoV Vaccine Candidate*. 2013 [cited 2015 January 18]; Available from: http://www.novavax.com/download/releases/2013-06-06 CoronaV FINAL PR.pdf.

57. Yelle, J., *MERS Coronavirus: Current Status.* J Hum Virol Retrovirol, 2014. **1**(3): p. 00010.

58. Coleman, C.M., et al., *Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice.* Vaccine, 2014. **32**(26): p. 3169-3174.

59. Almazán, F., et al., *Engineering a replication-competent, propagation-defective Middle East respiratory syndrome coronavirus as a vaccine candidate.* MBio, 2013. **4**(5): p. e00650-13.

60. Song, F., et al., *Middle East respiratory syndrome coronavirus spike protein delivered by modified vaccinia virus Ankara efficiently induces virus-neutralizing antibodies.* Journal of virology, 2013. **87**(21): p. 11950-11954.