Distribution Agreement

MERS-CoV Mortality by Region and Healthcare Provider,

Kingdom of Saudi Arabia, 2012 – 2015

By

Yasser Moneer Bakhsh
MPH

Global Health

____

Scott JN McNabb, PhD, MS
Committee Chair

MERS-CoV Mortality by Region and Healthcare Provider,

Kingdom of Saudi Arabia, 2012 – 2015

By

Yasser Moneer Bakhsh

MBBS
King Abdulaziz University
2008

Thesis Committee Chair: Scott JN McNabb, PhD, MS

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2016

Abstract

MERS-CoV Mortality by Region and Healthcare Provider,

Kingdom of Saudi Arabia, 2012 – 2015

By Yasser Moneer Bakhsh

Background: Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) has caused persistent outbreaks in the Kingdom of Saudi Arabia (KSA) since 2012. Of special concern has been the virus's transmission within healthcare facilities, affecting hospital patients, visitors, and healthcare workers. The objective of this study was to describe differences in the mortality rates of MERS patients among different regions and healthcare providers in KSA from 2012 to 2015 and to examine the relationship between patient mortality and predictors of interest using Generalized Estimating Equations accounting for clustering effect and correlation of outcome within hospital.

Methods: Data from the KSA Ministry of Health (MoH) were collected through the national MERS-CoV surveillance system. All confirmed, symptomatic MERS-CoV cases in KSA from September 2012 to December 2015 were included. We performed Chi-square tests for the association of outcome with all predictors, and we used cross-sectional multi-level analysis to generalize estimating equations (GEE). Cases were analyzed as observations within hospitals and hospitals were grouped into regions.

Results: A total of 1,283 cases of MERS-CoV infection were reported with an overall mortality rate of 43%. The probability of death for symptomatic MERS patients in Ministry of Health (MoH) hospitals (adjusted for age, gender, nationality, and infection source) was 39% in the Central division, 19% in the Eastern division, and 16% in the Western division. National Guard (NG) hospitals showed lower odds of death compared to MoH hospitals in the Central and Eastern divisions. Military hospitals showed higher odds of death compared to MoH hospitals only in the Western division.

Conclusion: Discrepancies were observed in the probability of death for MERS-CoV patients across different divisions and healthcare provider sectors in KSA. Patient age and source of infection are strong predictors of mortality in all regions. Inconsistent case reporting from some regions led to the inability to estimate probabilities and odds of mortality for those regions. Observed results reflect variability in standards of care across healthcare providers in KSA. Improving infection control protocols in hospitals could limit the transmission of MERS-CoV and improve the survival of patients.

MERS-CoV Mortality by Region and Healthcare Provider,

Kingdom of Saudi Arabia, 2012 – 2015

By

Yasser Moneer Bakhsh

MBBS
King Abdulaziz University
2008

Thesis Committee Chair: Scott JN McNabb, PhD, MS

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2016

Acknowledgements

I am extremely grateful to my Lord (Allah) for providing me the opportunity to learn and grow on personal and professional levels and for helping to make this thesis possible.

I would like to thank my wife, Samah, for standing by my side throughout this long journey and providing me with unlimited love and support. My daughter, Talah, has always been a source of happiness and joy to my heart and has given me the power to face all challenges. My parents have never stopped loving, encouraging, and supporting me all my life. I am thankful to have these amazing people around me.

I would like to thank my advisor, Dr. Scott McNabb, for his continuous guidance and support, Dr. Jose Binongo for his inspiration and mentoring, Natalie Schulhofer for helping with the editing and organization of this thesis, and the whole KAFP team.

Finally, special thanks to Dr. Abdullah Assiri who made this possible with his support, and to my dearest friend Abdulhameed Kashkary for his encouragement and brilliant ideas.

Table of Contents

Chapter 1 – Introduction

Problem Background

In September 2012, an Egyptian virologist in a private hospital in Jeddah, Kingdom of Saudi Arabia (KSA), reported the first case of a new coronavirus. At first, it was named novel coronavirus (nCoV) but later became known as Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV). By September of 2015, the number of MERS-CoV cases had grown rapidly, reaching 1,283 cases in Saudi Arabia and 1,493 cases worldwide [1]. The mortality rate among people infected with MERS-CoV was reported to be around 35%. Many ambiguities persist about the particulars of MERS-CoV transmission—both animal to human and human to human.

Several outbreaks of MERS-CoV infection have been observed within healthcare facilities and many cases have been hospital-acquired varying between hospital in-patients, visitors, and healthcare workers. Not every hospital treating MERS-CoV cases has observed a within-facility outbreak. Infection control issues are major factors in disease incidence, with many outbreaks limited to even certain units of hospitals and afflicting a high percentage of healthcare workers. There is the possibility of non-standardized care being delivered and this could be the cause of higher mortality rates in some hospitals.

Problem Statement

The high incidence of infection with high mortality rate is a source of concern in Saudi Arabia. Healthcare facilities have been stigmatized for being an infection source, which might cause people to refrain from seeking care at certain hospitals that observed outbreaks of infection[2]. With the still standing ambiguity around the epidemiology of

MERS-CoV, policy makers in Saudi Arabia are still in need of further information to direct preventive interventions.

The majority of studies have analyzed and reported MERS-CoV mortality rates in crude terms or adjusted for patient-related factors such as gender, age, and comorbidities. There is no information on whether hospital factors could affect mortality. This information is important to the public in order for them to make informed choices about where to seek medical care based on how hospitals perform in treating MERS-CoV infections reflected through case mortality rates. It would also direct the attention of policymakers to regions with higher mortality rates and sectors of hospitals that need further assessment and evaluation of infection control protocols and treatment procedures.

Significance

Looking at mortality rates across hospitals of different sectors in different regions of Saudi Arabia will reveal potential variations in mortality rates and may lead to insights about virulence of disease and gaps in hospital practices. By comparing means of mortality rates between different hospitals we can gain information on differences in health outcomes across hospitals that might be attributed to disease severity or healthcare quality. The multilevel modeling in this study will allow for multiple comparisons of higher statistical significance and the generalized estimating equations will provide estimates of population mean mortality rates for every region. With this information, policies can be focused on areas of need.

Study Purpose

Using patient-level and hospital-level data collected by the Ministry of Health (MoH), this study will be the first multilevel analysis of MERS-CoV with the intention of contributing to treatment and prevention strategies.

This study aims to answer the following questions: Are there significant differences in mortality between regions in Saudi Arabia? Are there significant differences in mortality between sectors of healthcare providers in Saudi Arabia? What patient level factors contribute to mortality rate (age, gender, nationality)?

To answer these questions, we will look at region specific mortality rates and compare them to search for significant differences. We will also factor in hospitals by sector of healthcare providers to look for discrepancies in health outcomes of patients treated by different providers.

Chapter 2 – Literature Review

Many studies have emerged since the beginning of MERS-CoV outbreak trying to describe the epidemiology and explain the behavior of this novel virus. We have explored studies that share a common interest in investigating the epidemiology and mortality rate is Saudi Arabia. Special focus was made on studies that report healthcare-facility related outbreaks whether in or outside Saudi Arabia. In addition, we are interested in understanding the strategy that South Korea followed to control the spread of the virus. Finally, we are shedding some light on the scientific base of the analysis method that we will be using for our research.

Overall Mortality Rates

MERS-CoV is a cause of concern due to its relatively high mortality. The global mortality rate for reported cases was estimated by the WHO to be around 36%[3]. However, mortality rates vary across different countries. The very first known outbreak of MERS-CoV was discovered retrospectively in Jordan in April, 2012, after the detection of the first case of MERS in Saudi Arabia. It involved 13 infections with 2 fatalities[4]. The number of infections escalated to 35 with 14 deaths (40% mortality) by October 2015[5]. Furthermore, an analysis of the second largest MERS-CoV outbreak in South Korea revealed that 186 individuals were infected and 38 of those died[6]. The outbreak in South Korea resulted in a mortality rate of approximately 20%.

The vast majority of infections are observed within the Arabian Peninsula. By October 2015, KSA ranked the highest with 1255 cases and 539 deaths (42.9% mortality), United Arab Emirate came second with 81 cases and 11 deaths (13.6%

mortality), and Qatar in the third place with 13 cases and 5 deaths (38.5% mortality). The rest of countries in the region had 11 cases and 6 deaths collectively[5].

The observation of varying mortality rates for different countries led to the suspicion of association between geographic location of MERS-CoV infected cases and mortality. This association could be influenced by different circulating viral strains, healthcare standards, and/or infection control policies. Therefore, different regions in Saudi Arabia might manifest different mortality rates.

Hospital Outbreaks

The transmission of MERS-CoV is characterized by being highly active within healthcare sittings compared to community transmission[7]. Hospital outbreaks of MERS infections were observed throughout the last three years in many countries. Several factors might contribute to this phenomenon, such as lack of proper preparedness plans and isolation units in healthcare facilities, overcrowding of emergency departments, the exposed individuals have more comorbidities, prolonged contact with healthcare workers, and/or frequent testing and intense screening.

In April 2012, the first known hospital-associated outbreak occurred in an intensive care unit (ICU) of a major hospital in the city of Zarqa, Jordan. A retrospective investigation was performed by the Jordanian Ministry of Health to unveil the cause of dissemination of lower respiratory tract infections to 11 cases with 2 fatalities. They could not identify a known cause of the infection initially, but after the discovery of the first case of MERS-CoV infection in KSA and the involvement of the U.S. Center for Disease Control and Prevention (CDC) in the outbreak investigation in Jordan, they discovered that MERS-CoV was the infectious agent that caused this outbreak [8]. Two cases were referred to other hospitals to receive treatment, but no infection outbreaks were observed in the recipient hospitals. This was believed to be due to compliance to infection control protocols. There were several reports of lack of compliance to infection control in the focal hospital, in addition to the absence of isolation rooms with negative air pressure and ICU patients being separated only by cloth draped [8].

One of the major hospital-associated outbreaks of MERS-CoV infection occurred in South Korea in May 2015. A man traveled to multiple countries in the Arabian Peninsula and after traveling back to South Korea he started to develop symptoms and was treated in a hospital. During his stay in the hospital, the infection was transmitted to 36 individuals. Afterwards, the primary case was transferred to another hospital and transmitted the virus to an additional 89 individuals[9]. Although South Korea in known to have one of the most advanced health care and public health systems[9], several factors were recognized by the World Health Organization (WHO) to contribute to the widespread of the virus[6]. First, the public's and health care workers' knowledge about new emerging infections, including MERS, was defective. Second, gaps in infection control practices for within-hospital transmission. Third, crowded emergency departments and having more than one patient admitted to the same hospital room allowed for prolonged short-distance contact. Fourth, the structure of health care system permits patients to freely choose their provider known as "doctor or hospital shopping". Finally, visiting family and friends admitted in hospitals is a common local tradition that influenced secondary transmission of infection.

A study investigated 65 cases of MERS-CoV infections in Abu Dhabi, United Arab Emirates, and recognized that 27 cases (42%) were healthcare-associated. Among those, 19 were healthcare workers (70%), 6 were hospital inpatients (22%), and 2 were visitors (7%)[10]. These cases formed three clusters within healthcare facilities. The first cluster occurred in July 2013, when an index case was admitted to a hospital with undiagnosed respiratory symptoms and transferred to a second hospital with an ambulance two days later, where he was diagnosed with MERS and developed acute illness and died. Screening of potential healthcare contacts revealed 4 positive transmissions, 1 was a nurse that accompanied the index case in the ambulance, and 3 were involved in the initial assessment of the case in the second hospital prior to diagnosis. All 4 cases of healthcare workers reported prolonged contact with the index case without taking the appropriate precautions. The second cluster occurred in March-April 2014 and involved secondary transmission to 2 healthcare workers and a hospital patient and a tertiary transmission to another hospital patient. The third cluster happened in March-April 2014 when an index case transmitted the virus to 15 individuals within the hospital. Ten acquired the infection in the emergency department, 1 was a health warker that provided care for the index patient in ICU, and 4 were health workers that had no contact with the index patient but acquired the infection through tertiary contact with infected co-workers.

In Saudi Arabia, multiple hospital-associated outbreaks of MERS-CoV transmission occurred across different regions of the country. One of the first detected outbreaks was in the eastern region, which included four healthcare facilities and resulted in 23 confirmed cases and 11 probable cases [11]. During April 2013, three patients were admitted to hospital A with respiratory symptoms, one was admitted to the medical ward, the second was admitted to the ICU, and the third was admitted to the medical ward with a history of long-term hemodialysis in the same hospital. During the stay of these patients in the hospital, MERS-CoV infection was confirmed in nine additional cases and probable in 8 cases who underwent hemodialysis in this hospital. Therefore, strict infection control measures were implemented in the hemodialysis unit to prevent further transmission, but 8 days after the implementation of these measure, disease developed in additional six cases and one of them was a confirmed case of MERS-CoV and the rest were probable. In the ICU, confirmed transmission to two additional patients was observed and control measures similar to that in hemodialysis unit were taken with no further transmission. In the medical ward, transmission occurred in two cases that occupied rooms adjacent to known cases. One confirmed case occurred among health workers in hospital A. One of the patients that acquired the infection in hospital A received hemodialysis in hospital C and transmitted the infection to two additional cases. Eight confirmed cases were transferred from hospital A to hospital D and transmission was recorded to two additional patients and a physician.

In March 2014, sudden increase in the number of reported MERS-CoV cases in Jeddah caused international concern [7]. Several hypotheses were thought to be behind this, either individually or combined. These hypotheses were mutation in viral genome facilitating transmission, seasonal pattern not previously identified, intense screening and case detection, change in animal-human contact leading to increased primary transmission, sustained viral circulation in the community, and healthcare-related transmission. Assistance of the CDC was requested to investigate the outbreak, which lead to the identification of 255 confirmed cases. Healthcare workers constructed 78 cases (30.6%). Investigators were able to contact 130 symptomatic non-healthcare workers to assess source of transmission. Of those, they were able to recognize infection sources in 112 cases during 14-day period prior to disease onset and they were as the following: three cases had no secondary exposure (2.7%), 37 cases were admitted to a hospital (33.9%), 68 cases visited a healthcare facility as patients (62.4%), 22 had contact with a confirmed MERS-CoV case (20.2%), and four cases had contact with people with severe respiratory illness of unknown cause (3.7%). Renal dialysis was the most common cause of visiting healthcare facilities prior to onset of MERS. Healthcare-related transmission is believed to be the main source of infection in Jeddah outbreak.

A cluster of 38 MERS-CoV cases in Taif was linked to four healthcare facilities [12]. Although no epidemiologic link between hospitals was found, viral genomic sequencing was identical in six patients sampled from all hospital suggesting a linked transmission. However, non-identical sequences were detected within a single facility, a finding supporting multiple sources of infection.

South Korea Response to MERS

As of May 2015, the largest outbreak outside the Middle East of MERS-CoV occurred in South Korea [13] and persisted for two months with 186 confirmed MERS-CoV cases and 36 deaths [14]. More than 16,000 people have been exposed to patients with MERS and 98 hospitals all over the country were involved in treating MERS-CoV patients either as outpatients in clinics or inpatients admitted to hospital rooms [13]. 39 health care personnel were infected (8 physicians and 15 nurses) and 15 hospitals paused their regular medical services and were placed under governmental control for isolation purposes and outbreak containment [13]. In July 2015, World Health Organization and South Korean government declared that MERS-CoV outbreak has ended [13].

As the majority of MERS-CoV cases in South Korea were hospital-associated, efforts to contain the outbreak and prevent further transmission of the virus focused on healthcare infection prevention and control [14]. Operation of isolation units within hospitals, MERS patient treatment, control and follow-up of contacts, enforcing personal protective equipment, extensive cleaning and disinfection, in addition to other precautions were major factors in controlling the outbreak in South Korea.

Early in the outbreak, the Korea Centers for Disease Control and Prevention disseminated their guidelines in response to the outbreak, which were based on the CDC and WHO guidelines[13]. However, healthcare workers struggled to comply with these documents as they were too general and detailed instructions were needed. As a result, scientific structures in infectious diseases and infection control released a detailed guideline on MERS-CoV infection control, but the application was complicated as hospitals had varying environments. Infection control nurses (ICNs) played a major role in limiting the outbreak as they helped establishing individual hospital's protocols for infection control. They also trained health workers on using personal protective equipment and accessing isolation rooms with negative pressure. Detailed descriptions on dealing with MERS-CoV patients were designed by ICNs for each hospital. Furthermore, nationwide guidelines were created by the MERS-CoV Infection Prevention and Control Guideline Development Committee [14].

A joint collaboration between different associations and teams lead to control and enclose the outbreak by ensuring that compliance to the governmental guidelines is taking place on the ground. More than 300 visits were made to hospitals treating MERS-CoV patients. The aim was to increase the awareness about infection control protocols.

Compliance difficulties in hospitals were reported to the government in order to provide appropriate resources and ease these difficulties [13].

MERS-CoV Infection Control Protocols in Healthcare Settings

In June 2015, The Saudi Ministry of Health issued their updated guidelines on infection control and prevention of MERS-CoV [15]. This was based on previous guideline issued on June 26 and December 8, 2014 in addition to WHO and CDC guidelines, which were all reviewed by the scientific advisory board. The updated case definition was modified so that suspected cases would include patients without fever. Moreover, the criterion of “acute febrile, non-localizing illness with leukopenia and thrombocytopenia” was adjusted to be unexplained by other clinical or epidemiological means. Due to extensive screening and testing of patients, a case definition for pediatric patients was added to prevent avoidable testing.

KSA’s case definition of MERS-CoV consists of three categories; suspected cases which are individuals who need to be tested; probable cases and confirmed cases. Adult suspected cases include those with (I) acute respiratory illness with clinical and/or radiological, evidence of pulmonary parenchymal disease (pneumonia or Acute Respiratory Distress Syndrome); (II) healthcare associated pneumonia patients diagnosed based on clinical and radiological findings who are hospitalized; (III) upper or lower respiratory illness occurring within 2 weeks of exposure to a confirmed or probable case of MERS-CoV infection; (IV) unexplained acute febrile (≥38°C) illness, and body aches, headache, diarrhea, or nausea/vomiting, with or without respiratory symptoms, and leukopenia (WBC<3.5x109/L) and thrombocytopenia (platelets<150x109/L)[15].

Pediatric suspected cases include those who meet the above case definition and have either a history of exposure to a confirmed or suspected MERS-CoV in the 14 days prior to onset of symptoms and/or a history of contact with camels or camel products in the 14 days prior to onset of symptoms. In addition, children are suspected cases when they have unexplained severe pneumonia [15]. Probable cases meet the criteria of suspected cases and have inconclusive laboratory results for MERS-CoV and other possible pathogens, are close contacts of a laboratory-confirmed MERS-CoV case, or work in a hospital where MERS-CoV cases are cared for or have had recent contact with camels or camel products [15]. Confirmed cases meet the criteria for suspected cases and have a confirmed lab result for MERS infection [15].

Rapid recognition and filtration of cases is important to prevent infection spread in emergency departments, dialysis units, and outpatient clinics. Any patient with acute respiratory illness (ARI) should be advised to wear a surgical mask and be separated from other patients. Clinical and epidemiologic evaluation should be initiated as soon as possible with the support of laboratory testing. For all MERS-CoV infected patients, whether suspected, probable, or confirmed, who are not critically ill, standard, contact, and droplet precautions are advised. For critically ill patients, standard, contact, and airborne precautions are advised due to the high probability of involvement of aerosol-generating procedures. Standard, contact, and airborne precautions are recommended for all patients regardless of severity of illness whenever aerosol-generating procedures are involved in the management [15].

Patients who are not critically ill should be placed in single rooms in a separated area. High-efficiency particulate arrestance (HEPA) air filters can be used, if available.

These patients should be placed in a negative air-pressure room if aerosol-generating procedures are to be used [15].

On the other hand, critically ill patients should always be placed in infection isolation rooms with negative air-pressure due to the high probability of using aerosol-generating procedures. If negative pressure rooms are not available, these patients should be placed in properly ventilated single rooms with HEPA air filters placed at the bedside on maximum power. In case single room cannot be provided, group patients with similar diagnoses in shared rooms. Patient movement outside isolation rooms or designated areas should be avoided unless medically required. The use of portable diagnostic and radiographic machines is recommended. When transporting, patients are required to wear surgical face masks, special routes should be used to minimize exposure, recipient department should be notified with patient diagnosis and required precautions prior to patient arrival, healthcare workers involved in transporting patients must use the appropriate personal protective equipment (PPE) and commit to hand hygiene [15].

Upon entry to patient room or care area, healthcare workers should wear the PPEs that include gown, surgical mask, eye protection, gloves. If airborne precautions are applied to a patient, everyone entering the patient’s room should wear an N-95 mask that is fit tested and seal checked and those who fail the fit testing should use alternative respirators. All PPEs should be removed when exiting at the doorway or the anteroom, except for N-95 masks that should be removed after leaving the room and closing the door [15].

Hand hygiene should be maintained at all times, especially before and after contacting patients and their surroundings and after removing PPEs. It is preferred to use disposable or dedicated medical equipment (eg., stethoscopes, blood pressure cuffs, and thermometers), but if they have to be shared, they must be cleaned and disinfected after each use [15].

Patient Characteristics and MERS-CoV Mortality

A study examined MERS-CoV cases in KSA between 2012 and July 2015 [16]. The number of cases reported in that period was 939 and 66% of those were male, 33% were more than 60 years old, and 3.2% were less than 20 years old. Healthcare workers had the highest proportion of females compared to other sources of infection. Riyadh, Jeddah, and Eastern regions had the highest proportions of cases in descending order. Primary cases and secondary cases that acquired infection as hospital inpatients were older than those who were household contacts of known cases or acquired the disease as healthcare workers [16].

Source of infection was recognized in 788 patients. Of those, 329 were primary cases and 459 were secondary contacts of known MERS-CoV cases. Of those contacts, 114 cases were household contacts, 174 were hospital inpatients, and 171 were healthcare workers. Healthcare workers had the highest proportion of asymptomatic cases followed by household contacts[16]. Comorbid health problems were reported for 421 patients with 351 patients had at least one comorbidity. Older patients (>60 years old) and secondary inpatient contacts had high proportions of comorbidities [16].

Data displayed overall increase in mortality rate in higher age groups. Unadjusted analysis by logistic regression showed positive association between mortality and acquiring disease as a hospital inpatient, hypertension, renal disease, cardiac disease, and cancer. Adjusted analysis showed independent association with mortality for age >80 years, cardiac disease, and cancer. Healthcare workers and household contacts had the lower mortality rates compared to primary cases [16].

Chapter 3 – Manuscript

Abstract

Background: Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) has caused persistent outbreaks in the Kingdom of Saudi Arabia (KSA) since 2012. Of special concern has been the virus's transmission within healthcare facilities, affecting hospital patients, visitors, and healthcare workers. The objective of this study is to describe differences in the mortality rates of MERS patients among different regions and healthcare providers in KSA from 2012 to 2015 and to examine the relationship between patient mortality and predictors of interest using Generalized Estimating Equations accounting for clustering effect and correlation of outcome within hospital.

Methods: Data from the KSA Ministry of Health (MoH) were collected through the national MERS-CoV surveillance system. All confirmed, symptomatic MERS-CoV cases in KSA from September 2012 to December 2015 were included. We performed Chi-square tests for the association of outcome with all predictors, and we used cross-sectional multi-level analysis to generalize estimating equations (GEE). Cases were analyzed as observations within hospitals and hospitals were grouped into regions.

Results: A total of 1,283 cases of MERS-CoV infection were reported with an overall mortality rate of 43%. The probability of death for symptomatic MERS patients in Ministry of Health (MoH) hospitals (adjusted for age, gender, nationality, and infection source) was 39% in the Central division, 19% in the Eastern division, and 16% in the Western division. National Guard (NG) hospitals showed lower odds of death compared to MoH hospitals in the Central and Eastern divisions. Military hospitals showed higher odds of death compared to MoH hospitals only in the Western division.

Conclusion: Discrepancies were observed in the probability of death for MERS-CoV patients across different divisions and healthcare provider sectors in KSA. Patient age and source of infection are strong predictors of mortality in all regions. Inconsistent case reporting from some regions led to the inability to estimate probabilities and odds of mortality for those regions. Observed results reflect variability in standards of care across healthcare providers in KSA. Improving infection control protocols in hospitals could limit the transmission of MERS-CoV and improve the survival of patients.

Introduction

The first reported case of MERS-CoV infection occurred in Jeddah, Kingdom of Saudi Arabia (KSA) in June 2012 [1]. Since then, cases have been observed in different parts of the world and most especially KSA. As of April 2016, there have been 1,698 cases, with 609 deaths in 26 countries (≅36% mortality)[3].

The transmission of MERS-CoV is characterized by its prominence in healthcare facilities. Hospital-associated outbreaks involving inpatients, visitors, and healthcare workers have occurred in several countries. Often linked to the poor practice of infection prevention and control, variability in healthcare standards could result in varying mortality rates.

As KSA has seen the greatest number of cases with multiple hospital-associated outbreaks, the belief that hospitals are the source of infection results in patients refusing care in those with MERS-CoV outbreaks [2]. We examined mortality rates across KSA hospitals treating MERS-CoV patients to provide policymakers with information to guide intervention. We asked these questions: Are there significant differences in MERS-CoV mortality among KSA regions? Are there significant differences in MERS-CoV mortality between sectors of KSA healthcare providers? What patient factors contribute to MERS-CoV mortality rates (e.g., age, gender, nationality)?

Methods

Data from the KSA Ministry of Health (MoH) were collected through the national MERS-CoV surveillance system. All confirmed, symptomatic MERS-CoV cases in KSA from September 2012 to December 2015 were included. This study did not meet the criteria for human subjects research and thus was not subject to review by the Emory IRB.

Study Variables

Key independent variables were the hospital name; region of hospital; and sector of healthcare provider. Control variables were age group, gender, nationality, and the probable source of infection. The outcome variable was whether the patient died or survived. All variables were categorical. The region variable was originally divided into the MoH's classification, which includes 18 regions: Al-Bahah, Al-Hassa, Al-Jawf, Al-Qunfutha, Aseer, Bisha, Eastern, Hafar-Al-Batin, Jeddah, Madinah, Makkah, Najran, Northern, Qaseem, Qurayat, Riyadh, Tabouk, and Taif. As many regions had only a few cases, it was recoded and grouped by division, each encompassing several regions. The five divisions were Central (Qaseem and Riyadh), Eastern (Al-Hassa, Eastern, and Hafar-Al-Batin), Northern (Al-Jawf, Northern, Qurayat, and Tabouk), Southern (Al-Bahah, Aseer, Bisha, and Najran), and Western (Al-Qunfutha, Jeddah, Madinah, Makkah, and Taif).

In the original dataset, the sector variable encompassed all healthcare provider categories involved in treating MERS-CoV patients: ARAMCO (a hospital that provides healthcare for the employees of the Saudi oil company), King Faisal Specialized Hospital and Research Center (KFSHRC), Ministry of Education (MoE), Ministry of Health (MoH), Ministry of Interior (MoI), Military, National Guard (NG), Private, and the Royal Commission (RC). We combined the government-owned but independently-operated healthcare facilities of ARAMCO, KFSHRC, MoE, MoI, and RC under the category "Others," as they treated few MERS patients. The age group variable was coded in four groups: < 30 years of age; from 30 to 49 years of age; from 50 to 69; and > 70 years of age. Although many nationalities were listed, we combined all non-Saudi nationalities. The source of infection variable referred to the known route of transmission through which the patient acquired the disease. Primary cases were those who presented with disease but with no link to a known MERS-CoV case [16]. Secondary cases were those with a confirmed epidemiologic link to a known case, either household contacts that acquired disease in the community, hospital contacts that acquired disease in healthcare facilities, or healthcare workers. Some sources of infection were labeled unclassified in the original dataset because the evidence was inconclusive.

Statistical Analyses

In our descriptive analyses, we performed Chi-square tests for the association of outcome with all predictors, and we used cross-sectional multi-level analysis to generalize estimating equations (GEE). All analyses were performed using SAS™. Cases were analyzed as observations within hospitals and hospitals were grouped into regions, which produced a multi-level analysis allowing for the consideration of patient-related and hospital-related risk factors to study mortality. We considered hospitals to be the independent units for analysis.

GEE – developed by Liang and Zeger (Biometrika 1986) – was the most appropriate analytic tool to address this research question because it supported the assumption that the outcome of patients within the same hospital was correlated. In addition, it took into account the clustering effect of patients in regions. We adopted a compound symmetry correlation structure; all correlations within a hospital were assumed equal.

Results

Descriptive Statistics

Regions with the largest proportion of MERS-CoV patients treated in their hospitals were Riyadh with 616 patients (48%) and Jeddah with 284 patients (22%). MoH hospitals were involved in the treatment of 752 patients (59%), while military hospitals treated 170 (13%) and NG hospitals treated 146 patients (11%). A small proportion (n=92) sought care in private hospitals (7%).

The mean age of MERS-CoV patients was 50.54 years (SD=18.8). Predominantly male (64.4%) and Saudi (68%), primary cases represented 29%, while 46.2% were secondary contacts. Of those, healthcare workers constituted 19%, household contacts 15%, and hospital inpatients 13%. Twenty-five percent were unclassified.

The vast majority of individuals with MERS-CoV infection (88%) developed symptoms. The peak period of transmission occurred in 2014 with 661 cases (52%). Of all patients, 551 died; a case-fatality rate of 43%.

Table 1: Descriptive Analysis of Predictors of Mortality for Middle Eastern Respiratory Syndrome, Kingdom of Saudi Arabia, 2012 – 2015: (n=1283)

Variable	Levels	N (%)	Mean (SD)	Missing
Region[*]	Al Bahah	1 (0.08)		0
	Al Hassa	75 (5.85)		
	Al Jawf	14 (1.09)		
	AlQunfutha	4 (0.31)		
	Aseer	11 (0.86)		
	Bisha	2 (0.16)		
	Eastern	63 (4.91)		
	Hafar Al Batin	14 (1.09)		
	Jeddah	284 (22.14)		
	Madinah	55 (4.29)		
	Makkah	38 (2.96)		
	Najran	22 (1.71)		
	Northern	3 (0.23)		
	Qaseem	17 (1.33)		
	Qurayat	2 (0.16)		
	Riyadh	616 (48.01)		
	Tabouk	15 (1.17)		

	Taif	47 (3.66)		
Sector[$]	ARAMCO	20 (1.56)		0
	KFSHRC	51 (3.98)		
	MOE	36 (2.81)		
	MOH	752 (58.61)		
	MOI	12 (0.94)		
	Military	170 (13.25)		
	NG	146 (11.38)		
	Private	92 (7.17)		
	RC	4 (0.31)		
Age			50.54 (18.80)	0
Gender	Male	826 (64.38)		0
	Female	457 (32.62)		
Nationality	Saudi	872 (67.97)		0
	Non-Saudi	411 (32.03)		
Source of Infection	Primary	374 (29.15)		0
	Secondary case hospital acquired	163 (12.70)		
	Secondary case healthcare worker	240 (18.71)		
	Secondary case household contact	190 (14.81)		
	Unclassified	316 (24.63)		
Symptoms	Symptomatic	1130 (88.07)		0
	Asymptomatic	153 (11.93)		
Year	2012	5 (0.39)		0
	2013	159 (12.39)		
	2014	661 (51.52)		
	2015	458 (35.70)		
Outcome	Deceased	551 (42.95)		0
	Survived	732 (57.05)		

[*]Region refers to location of the hospital in which MERS patient was treated.
[$]Sector of healthcare providers; ARAMCO: Saudi Oil Company Hospital; KFSHRC: King Faisal Specialized Hospital and Research Center; MOE: Ministry of Education; MOH: Ministry of Health; MOI: Ministry of Interior; Military: Military Hospitals; NG: National Guard; RC: Royal Commission.

Mortality by Predictor

Testing for significant differences in mortality proportion across geographical divisions revealed no statistically significant differences. However, sectors of healthcare providers did show statistically significant differences in mortality proportions. Of the total who died, 57% were treated in MoH hospitals, 17% in Military hospitals, and 8% in private hospitals. Examined from the perspective of patient outcomes by sector, we found that 55% of MERS-CoV patients treated in Military hospitals died, 49% died in private hospitals, and 42% died in MoH hospitals.

Age groups showed different mortality rates; this was statistically significant. The youngest age group (<30) had the lowest mortality rate (19%), while the oldest age group (>=70) had the highest (78.3%). Those between 50 to 69 years of age who died of MERS-CoV had a 41.4% mortality rate. Of those who died, 69% were male, 75% were Saudi, and 96% were symptomatic; these are statistically significant. Primary cases had the highest mortality rate (37%) followed by unclassified cases (32%). The smallest proportion was observed among healthcare workers (3%).

Table 2: Bivariate Analysis of Mortality by Predictors for Middle Eastern Respiratory Syndrome Cases, Kingdom of Saudi Arabia, 2012 – 2015: (n=1283)

Variable	Level	N (%)	Death n (%)	Mortality Rate %	P-value[#]
Outcome	Deceased	551 (42.95)			
	Survived	732 (57.05)			
Division[*]	Center	633 (49.34)	266 (48.28)	42.02	0.2283
	East	152 (11.85)	78 (14.16)	51.32	
	North	34 (2.65)	12 (2.18)	35.29	
	South	36 (2.81)	16 (2.90)	44.44	
	West	428 (33.36)	179 (32.49)	41.82	
Sector[$]	MOH	752 (58.61)	314 (56.99)	41.76	0.0037
	Military	170 (13.25)	93 (16.88)	54.71	
	NG	146 (11.38)	54 (9.80)	36.99	
	Private	92 (7.17)	45 (8.17)	48.91	
	Other	123 (9.59)	45 (8.17)	36.59	
Age	less than 30	187 (14.58)	35 (6.35)	18.72	<.0001
	30 to 49	420 (32.74)	100 (18.15)	23.81	
	50 to 69	436 (33.98)	228 (41.38)	52.29	
	70 and above	240 (18.71)	188 (34.12)	78.33	
Gender	Male	826 (64.38)	378 (68.60)	45.76	0.0061
	Female	457 (32.62)	173 (31.40)	37.86	
Nationality	Saudi	872 (67.97)	411 (74.59)	47.13	<.0001
	Non-Saudi	411 (32.03)	140 (25.41)	34.06	
Source of Infection	Primary	374 (29.15)	206 (37.39)	55.08	<.0001
	Secondary case hospital acquired	163 (12.70)	114 (20.69)	69.94	
	Secondary case healthcare worker	240 (18.71)	15 (2.72)	6.25	
	Secondary case household contact	190 (14.81)	41 (7.44)	21.58	
	Unclassified	316 (24.63)	175 (31.76)	55.38	
Symptoms	Symptomatic	1130 (88.07)	529 (96.01)	46.81	<.0001
	Asymptomatic	153 (11.93)	22 (3.99)	14.38	
Year	2012+2013	164 (12.78)	79 (14.34)	48.17	0.3384
	2014	661 (51.52)	281 (51.00)	42.51	
	2015	458 (35.70)	191 (34.66)	41.70	

[*]Central division includes Qaseem and Riyadh; Eastern division includes Al-Hassa, Eastern, and Hafar-Al-Batin; Northern division includes Al-Jawf, Northern, Qurayat, and Tabouk; Southern division includes Al-Bahah, Aseer, Bisha, and Najran; Western region includes Al-Qunfutha, Jeddah, Madinah, Makkah, and Taif.
[$]Other includes ARAMCO, KFSHRC, MOE, MOI, and RC.
[#]This refers to the p-value of Chi Square test of independence.

Unadjusted Analysis

Geographically, the Eastern Division had the greatest probability of death, estimated to be 58%. The Southern Division had the lowest (37%). By sector of healthcare provider within geographic division, we found that the probability of death for patients treated in MoH hospitals in the Northern Division was 60%, in the Western

Division was 51%, in the Eastern Division was 46%, in the Central Division was 41%, and in the Southern Division was 37%. In the Western Division, patients treated in military hospitals were 2.1 times more likely to die than those treated in MoH hospitals. In the Central Division, patients treated in NG hospitals were 0.8 times more likely to die than those treated in MoH hospitals. In the Eastern Division, patients treated in private hospitals were 3.2 times more likely to die than those treated in MoH hospitals. Across all divisions, the odds of death for patients 70 years and older was significantly greater than the odds for patients < 30 years of age. Gender was not a statistically significant factor in any division. Nationality was significant in both Eastern and Western divisions, where the odds of Saudis dying from MERS were higher than those of non-Saudis. In terms of infection source, the odds of death for patients that acquired MERS-CoV in healthcare facilities were greater than those for primary cases. Secondary cases such as healthcare workers and household contacts had lower odds of death than primary cases.

Table 3: Unadjusted Analysis of Generalized Estimating Equations Probability of Mortality, Odds of Mortality, and Odds Ratios by Geographic Divisions for Symptomatic Middle Easters Respiratory Syndrome Cases, Kingdom of Saudi Arabia, 2012 – 2015 (n=1130, alpha=0.05 for CI and p-value)

Division*	Variable	Level	Reference	Probability	95% CI		Odds (OR)	95% CI odds		P-value
Center	Intercept			43.95	38.76	49.27	0.78	0.63	0.97	0.0259
East	Intercept			57.58	47.70	66.89	1.36	0.91	2.02	0.1322
North	Intercept			57.33	51.70	62.77	1.34	1.07	1.69	0.0109
South	Intercept			36.86	36.83	36.89	0.58	0.58	0.58	<.0001
West	Intercept			49.05	42.79	55.34	0.96	0.75	1.24	0.7678
Center	Intercept			40.72	39.92	41.52	0.69	0.66	0.71	<.0001
	Sector	Military	MOH				1.49	1.27	1.74	<.0001
		NG					0.78	0.75	0.80	<.0001
		Private					1.46	0.61	3.52	0.4000
		Other$					1.01	0.79	1.31	0.9245
East	Intercept			45.90	45.75	46.05	0.85	0.84	0.85	<.0001
	Sector	Military	MOH				4.82	0.44	53.12	0.1993
		NG					0.40	0.27	0.61	<.0001
		Private					3.23	1.78	5.88	0.0001
		Other$					1.37	1.08	1.75	0.0108
North	Intercept			59.98	59.94	60.03	1.50	1.50	1.50	<.0001
	Sector	Private	MOH				0.25	0.25	0.25	<.0001
South	Intercept			36.86	36.82	36.91	0.58	0.58	0.59	<.0001
	Sector	Military	MOH				2.08	0.60	7.28	0.2508
West	Intercept			50.51	50.34	50.68	1.02	1.01	1.03	<.0001
	Sector	Military	MOH				2.09	1.77	2.46	<.0001
		NG					1.31	0.64	2.69	0.4642
		Private					1.19	0.74	1.90	0.4700
		Other$					0.39	0.30	0.50	<.0001
Center	Intercept			22.39	13.77	34.27	0.29	0.16	0.52	<.0001
	Age	30 to 49	less than 30				0.82	0.46	1.47	0.5120
		50 to 69					3.92	2.17	7.08	<.0001
		70 and above					10.83	5.33	22.02	<.0001
East	Intercept			46.31	12.25	84.20	0.86	0.14	5.33	0.8736
	Age	30 to 49	less than 30				0.84	0.14	4.95	0.8461
		50 to 69					1.40	0.30	6.61	0.6729
		70 and above					7.16	1.15	44.73	0.0352
North	Intercept			39.60	16.95	67.81	0.66	0.20	2.11	0.4783
	Age	30 to 49	less than 30				2.94	1.81	4.79	<.0001
		50 to 69					1.00	0.25	4.08	0.9997
		70 and above					4.13	0.67	25.59	0.1271
West	Intercept			28.18	17.46	42.11	0.29	0.16	0.52	<.0001
	Age	30 to 49	less than 30				0.82	0.46	1.47	0.5120
		50 to 69					3.92	2.17	7.08	<.0001
		70 and above					10.83	5.33	22.02	<.0001
Center	Intercept			42.16	35.80	48.78	0.73	0.56	0.95	0.0205
	Gender	Male	Female				1.13	0.93	1.37	0.2257
East	Intercept			56.93	42.78	70.04	1.32	0.75	2.34	0.3371

Division*	Variable	Level	Reference	Probability	95% CI		Odds (OR)	95% CI odds		P-value
	Gender	Male	Female				1.04	0.56	1.91	0.9082
North	Intercept			64.19	40.93	82.26	1.79	0.69	4.64	0.2287
	Gender	Male	Female				0.74	0.15	3.52	0.6997
South	Intercept			9.58	0.85	56.78	0.11	0.01	1.31	0.0805
	Gender	Male	Female				7.74	0.47	127.27	0.1520
West	Intercept			44.43	32.57	56.95	0.80	0.48	1.32	0.3837
	Gender	Male	Female				1.29	0.78	2.16	0.3230
Center	Intercept			42.92	36.14	49.99	0.75	0.57	1.00	0.0497
	Nationality	Saudi	Non-Saudi				1.06	0.80	1.41	0.6961
East	Intercept			20.87	9.09	41.03	0.26	0.10	0.70	0.0071
	Nationality	Saudi	Non-Saudi				7.33	2.60	20.67	0.0002
North	Intercept			56.14	37.96	72.80	1.28	0.61	2.68	0.5123
	Nationality	Saudi	Non-Saudi				1.05	0.30	3.60	0.9445
South	Intercept			22.45	11.70	38.75	0.29	0.13	0.63	0.0019
	Nationality	Saudi	Non-Saudi				3.26	0.92	11.48	0.0662
West	Intercept			35.30	25.20	46.91	0.55	0.34	0.88	0.0138
	Nationality	Saudi	Non-Saudi				2.40	1.25	4.60	0.0086
Center	Intercept			55.94	50.46	61.29	1.27	1.02	1.58	0.0338
	Source of infection	Secondary case hospital acquired	Primary				1.38	0.83	2.28	0.2166
		Secondary case healthcare worker					0.05	0.02	0.13	<.0001
		Secondary case household contact					0.11	0.05	0.24	<.0001
		Unclassified					0.88	0.62	1.25	0.4727
East	Intercept			57.72	42.25	71.82	1.37	0.73	2.55	0.3281
	Source of infection	Secondary case hospital acquired	Primary				10.76	2.67	43.38	0.0008
		Secondary case healthcare worker					0.09	0.03	0.31	0.0002
		Secondary case household contact					0.66	0.18	2.40	0.5307
		Unclassified					1.00	0.39	2.56	1.0000
West	Intercept			56.03	50.51	61.41	1.28	1.02	1.59	0.0323
	Source of infection	Secondary case hospital acquired	Primary				2.40	1.22	4.70	0.0111
		Secondary case healthcare worker					0.11	0.06	0.22	<.0001
		Secondary case household contact					0.58	0.24	1.38	0.2162
		Unclassified					1.20	0.70	2.04	0.5126
Center	Intercept			39.44	33.62	45.58	0.65	0.51	0.84	0.0008
	Year	2012+2013	2015				1.32	0.82	2.15	0.2578
		2014					1.35	0.79	2.33	0.2742
East	Intercept			47.68	40.01	55.46	0.91	0.67	1.25	0.5593
	Year	2012+2013	2015				2.37	1.28	4.38	0.0060
		2014					1.10	0.38	3.18	0.8551
South	Intercept			30.46	19.51	44.18	0.44	0.24	0.79	0.0062
	Year	2012+2013	2015				1.68	0.67	4.19	0.2665
		2014					2.50	0.42	14.80	0.3131
West	Intercept			37.56	24.33	52.95	0.60	0.32	1.13	0.1118
	Year	2012+2013	2015				1.40	0.58	3.39	0.4587
		2014					1.73	0.78	3.80	0.1760

*Central division includes Qaseem and Riyadh; Eastern division includes Al-Hassa, Eastern, and Hafar-Al-Batin; Northern division includes Al-Jawf, Northern, Qurayat, and Tabouk; Southern division includes Al-Bahah, Aseer, Bisha, and Najran; Western region includes Al-Qunfutha, Jeddah, Madinah, Makkah, and Taif.
$Other includes ARAMCO, KFSHRC, MOE, MOI, and RC.

Adjusted Analysis

Across a health provider sector, if we looked at a certain type of patient and calculated probability of death by geographical division, we saw differences. In MoH hospitals, non-Saudi female patients < 30 years of age who were primary cases in 2015 had a 39% probability of death in the Central Division, 19% probability in the Eastern Division, and 16% probability in the Western Division. In the Central Division, the adjusted odds of death for people treated in NG hospitals were 0.8 times the adjusted odds for those treated in MoH hospitals. The adjusted odds for military and private hospitals were not significantly different from MoH hospitals. The adjusted odds of death for secondary cases like healthcare workers and household contacts were significantly less than those for primary cases, while those of secondary case inpatients were not significantly different from primary cases.

In the Eastern Division, the adjusted odds of death for people treated in NG hospitals were 0.1 times the adjusted odds for those treated in MoH hospitals. The adjusted odds for military and private hospitals were not significantly different from the MoH hospitals. The adjusted odds of death for secondary case inpatients were 8.3 times the adjusted odds for primary cases, while the adjusted odds of death for secondary case healthcare workers and household contacts were not significantly different from those for primary cases.

In the Western Division, the adjusted odds of death for people treated in military hospitals were 2.4 times the adjusted odds for those treated in MoH hospitals. The adjusted odds for NG and private hospitals were not significantly different from those for

MoH hospitals. The adjusted odds of death for secondary case healthcare workers were 0.1 times the adjusted odds for primary cases, while the adjusted odds of death for secondary case inpatients and household contacts were not significantly different from those for primary cases.

Table 4: Adjusted Analysis of Generalized Estimating Equations Probability of Mortality, Odds of Mortality, and Odds Ratios by Geographic Divisions for Symptomatic Middle Easters Respiratory Syndrome Cases, Kingdom of Saudi Arabia, 2012 – 2015 (n=1130, alpha=0.05 for CI and p-value)

Division[*]	Variable	Level	Reference	Probability	95% CI		Odds (OR)	95% CI odds		P-value
Center	Intercept			38.84	23.02	57.44	0.64	0.30	1.35	0.2378
	Sector	Military	MOH				0.97	0.69	1.36	0.8701
		NG					0.79	0.71	0.89	<.0001
		Private					1.74	0.54	5.55	0.3510
		Other[$]					0.71	0.51	0.99	0.0440
	Age	30 to 49	less than 30				0.75	0.36	1.54	0.4307
		50 to 69					2.24	1.01	4.95	0.0460
		70 and above					5.94	2.88	12.24	<.0001
	Gender	Male	Female				1.08	0.81	1.45	0.5828
	Nationality	Saudi	Non-Saudi				0.89	0.68	1.16	0.3915
	Source of Infection	Secondary case hospital acquired	Primary				1.04	0.63	1.72	0.8824
		Secondary case healthcare worker					0.08	0.03	0.24	<.0001
		Secondary case household contact					0.14	0.05	0.34	<.0001
		Unclassified					0.80	0.55	1.15	0.2314
	Year	2012+2013	2015				1.44	0.84	2.47	0.1854
		2014					1.33	0.74	2.39	0.3344
East	Intercept			18.64	5.04	49.69	0.23	0.05	0.99	0.0481
	Sector	Military	MOH				1.64	0.08	34.80	0.7515
		NG					0.11	0.03	0.35	0.0002
		Private					1.26	0.18	9.05	0.8155
		Other[$]					0.26	0.08	0.85	0.0263
	Age	30 to 49	less than 30				0.44	0.07	2.58	0.3621
		50 to 69					0.62	0.19	2.03	0.4301
		70 and above					2.31	0.32	16.55	0.4030
	Gender	Male	Female				1.22	0.59	2.53	0.5843
	Nationality	Saudi	Non-Saudi				5.95	1.67	21.16	0.0059
	Source of Infection	Secondary case hospital acquired	Primary				8.34	2.77	25.10	0.0002
		Secondary case healthcare worker					0.27	0.04	1.99	0.1986
		Secondary case household contact					0.32	0.04	2.53	0.2779
		Unclassified					0.92	0.29	2.87	0.8818
	Year	2012+2013	2015				5.26	1.61	17.25	0.0061
		2014					1.63	0.40	6.58	0.4943
West	Intercept			16.41	5.18	41.36	0.20	0.05	0.71	0.0126
	Sector	Military	MOH				2.37	1.79	3.15	<.0001
		NG					1.79	0.71	4.53	0.2182
		Private					1.16	0.65	2.07	0.6257
		Other[$]					0.46	0.31	0.67	<.0001
	Age	30 to 49	less than 30				1.00	0.44	2.28	0.9998
		50 to 69					2.78	1.25	6.19	0.0125
		70 and above					5.93	2.30	15.30	0.0002

Division*	Variable	Level	Reference	Probability	95% CI	Odds (OR)	95% CI odds		P-value
	Gender	Male	Female			1.18	0.65	2.13	0.5876
	Nationality	Saudi	Non-Saudi			1.03	0.65	1.63	0.9089
	Source of Infection	Secondary case hospital acquired	Primary			1.62	0.89	2.96	0.1167
		Secondary case healthcare worker				0.14	0.07	0.28	<.0001
		Secondary case household contact				0.52	0.22	1.24	0.1411
		Unclassified				1.02	0.62	1.68	0.9457
	Year	2012+2013	2015			3.18	1.05	9.62	0.0400
		2014				3.31	1.85	5.92	<.0001

*Central division includes Qaseem and Riyadh; Eastern division includes Al-Hassa, Eastern, and Hafar-Al-Batin; Northern division includes Al-Jawf, Northern, Qurayat, and Tabouk; Southern division includes Al-Bahah, Aseer, Bisha, and Najran; Western region includes Al-Qunfutha, Jeddah, Madinah, Makkah, and Taif.
$Other includes ARAMCO, KFSHRC, MOE, MOI, and RC.

Discussion

Discrepancies were observed in the probability of death for MERS-CoV patients across different divisions and healthcare provider sectors in KSA. Patient age and source of infection are strong predictors of mortality in all regions. Gender and nationality are not significant predictors of mortality, when we adjusted for the previous predictors. These discrepancies could be attributed to variations in standard of care for MERS-CoV patients among different healthcare providers.

The results we found for age and for infection source support what has been reported in previous studies [16], even though these studies controlled for comorbid diseases. This could mean that patient age is independently associated with mortality and/or incomplete data on comorbidities has led to the underestimation of their association with mortality.

This study's results diverged from previous studies' on the effects of gender on mortality [17]. A recent study on the predictors of severity and mortality of MERS-CoV patients reported that patients of male sex had significantly higher odd of death, while our results show that gender is not a significant predictor of mortality. This could be due to different proportions of females in healthcare workers compared to primary cases. Adjustment for correlation may also play a part in mitigating the effects of gender on mortality.

Limitations

Sparse data on MERS-CoV patients in regions of some divisions (like North and South) limited our ability to estimate the probability and odds of death for patients treated in hospitals located in those regions. This might be explained by limitations in the detection and/or reporting of cases in those regions or the likelihood that patients from those divisions travel to other parts of the country to seek medical care.

Data on multiple variables thought to be predictors of mortality in MERS-CoV patients, such as comorbid diseases and history of camel contact, are either lacking or deficient in the dataset we received from the MoH. We refrained from assuming that an absence of data for these variables among certain patients meant that there was no information or that these variables were not applicable, preferring to drop them from our analysis. Moreover, we were unable to assess interactions between variables due to insufficient data, which prevented the estimation process.

Strengths

The multi-level GEE approach is unprecedented in the literature. It provides a better understanding of the mechanics of mortality at the patient, hospital, and region levels. When considering this approach, outcome correlation between patients treated within the same hospital is required. This feature makes estimates produced through GEE analysis more valid than those generated from simple or multivariate logistic regression.

Chapter 4 – Conclusion and Recommendations

Several factors play a role in the mortality of MERS-CoV patients, but gaps in outbreak surveillance and case reporting limit a full understanding of these. To improve data availability and integrity, the strict compliance of healthcare providers to case reporting should be enforced. Extensive data should be collected from MERS-CoV patients and their potential contacts. Efforts to fill the gaps in previously collected data will enhance future research.

The performance of different sectors of healthcare providers warrants better monitoring to manage this disease. Standards of care should be unified and assessed on the basis of strong evidence linked to improving the survival of patients. The MoH should set, supervise, and assure MERS-CoV standards of care across all types of healthcare providers, and these should be equally maintained.

Infection control and prevention has proven to be a meaningful factor in limiting MERS-CoV outbreaks in KSA. Lack of compliance to the protocols issued by the scientific advisory board should be reported. This could also improve the survival of hospital patients, as they have significantly high odds of mortality.

Future research should use innovative methods of data analysis in order to achieve valid estimates of disease mortality and a better understanding of the outbreak. Special focus should be placed on the role of hospitals and healthcare providers, in addition to animal contact and comorbidities.

References

1. Mackay, I.M. and K.E. Arden, *MERS coronavirus: diagnostics, epidemiology and transmission.* Virol J, 2015. **12**(1): p. 222.
2. Drosten, C., et al., *Transmission of MERS-coronavirus in household contacts.* N Engl J Med, 2014. **371**(9): p. 828-35.
3. WHO. *Middle East respiratory syndrome coronavirus (MERS-CoV)*. Fact Sheets 2015.
4. Lucey, D.R., *Editorial commentary: still learning from the earliest known MERS outbreak, Zarqa, Jordan, April 2012.* Clin Infect Dis, 2014. **59**(9): p. 1234-6.
5. ECDC, *Severe respiratory disease associated with Middle East respiratory syndrome coronavirus, 21st update*, in *Rapid Risk Assessment*. 2015, European Centre for Disease Prevention and Control.
6. Lee, S.I., *Costly Lessons From the 2015 Middle East Respiratory Syndrome Coronavirus Outbreak in Korea.* J Prev Med Public Health, 2015. **48**(6): p. 274-6.
7. Oboho, I.K., et al., *2014 MERS-CoV outbreak in Jeddah--a link to health care facilities.* N Engl J Med, 2015. **372**(9): p. 846-54.
8. Al-Abdallat, M.M., et al., *Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description.* Clin Infect Dis, 2014. **59**(9): p. 1225-33.
9. Kim, Y., et al., *The Characteristics of Middle Eastern Respiratory Syndrome Coronavirus Transmission Dynamics in South Korea.* Osong Public Health Res Perspect, 2016. **7**(1): p. 49-55.
10. Hunter, J.C., et al., *Transmission of Middle East Respiratory Syndrome Coronavirus Infections in Healthcare Settings, Abu Dhabi.* Emerg Infect Dis, 2016. **22**(4): p. 647-56.
11. Assiri, A., et al., *Hospital outbreak of Middle East respiratory syndrome coronavirus.* N Engl J Med, 2013. **369**(5): p. 407-16.
12. Assiri, A., et al., *Multifacility Outbreak of Middle East Respiratory Syndrome in Taif, Saudi Arabia.* Emerg Infect Dis, 2016. **22**(1): p. 32-40.
13. Choi, J.S. and K.M. Kim, *Crisis prevention and management by infection control nurses during the Middle East respiratory coronavirus outbreak in Korea.* Am J Infect Control, 2016. **44**(4): p. 480-1.
14. Kim, J.Y., et al., *Middle East Respiratory Syndrome Infection Control and Prevention Guideline for Healthcare Facilities.* Infect Chemother, 2015. **47**(4): p. 278-302.
15. Ministry of Health, *Infection Prevention and Control Guidelines for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection*. 2015.
16. Alsahafi, A.J. and A.C. Cheng, *The epidemiology of Middle East respiratory syndrome coronavirus in the Kingdom of Saudi Arabia, 2012-2015.* Int J Infect Dis, 2016. **45**: p. 1-4.
17. Banik, G.R., et al., *Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia.* Virol Sin, 2016.