Middle East respiratory syndrome in the Kingdom of Saudi Arabia: Insights from publicly available data

by

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Abstract. Since 2012, more than 1300 cases of Middle East respiratory syndrome (MERS) have been diagnosed worldwide, the vast majority of which have occurred in Saudi Arabia and over 40% of which have ended in death. In Spring 2014, a large outbreak of MERS originated in the Kingdom of Saudi Arabia – concentrated in nosocomial settings in Riyadh and Jeddah – resulting in over 300 infections.

We used publicly available data from the Saudi Ministry of Health and World Health Organization to examine the outbreak potential of *MERS-Coronavirus* and to explore possible risk factors for MERS-related mortality within the context of Saudi Arabia. We also investigated how differential case characteristics between patients reported during the Spring 2014 Saudi MERS outbreak and those reported during non-outbreak periods may provide insight into the propagation of future outbreaks.

We found that the Spring 2014 Saudi MERS outbreak was likely due to a super-spreading event, in which a small fraction of cases caused the vast majority of secondary transmissions. Though most cases infected 1 or fewer other individuals, propensity for super-spreading suggests that the outbreak potential of *MERS-Coronavirus* is significant and that future outbreaks of similar size are expected to occur. Furthermore, we found that early administration of supportive care may be essential to survival once an individual is infected with *MERS-Coronavirus*; this is especially true for the elderly, who are at increased risk of death. Thus, surveillance – especially among the elderly, who are at increased risk for MERS-related death – is key to reducing fatality. Surveillance is also integral to detecting zoonotic introduction (i.e. host-to-human transmission) events that may trigger future outbreaks if left uncontained. Finally, we found that female and non-comorbid individuals were preferentially infected during the Spring 2014 outbreak, which may lend insight into the enabling conditions that are necessary for MERS outbreaks to emerge and propagate.
Further exploration of the mechanisms that result in the zoonotic introduction of MERS-Coronavirus into the human population – as well as the emergence and propagation of MERS outbreaks – is crucial.

As demonstrated by the steady stream of sporadic cases that have been reported since the Spring 2014 outbreak, MERS has already gained a firm foothold in the Kingdom of Saudi Arabia. Given that Saudi Arabia is a universal religious travel destination, localized outbreaks may have massive global implications. Because of this, we conclude with the recommendation that the Saudi government should immediately prioritize systematic outbreak planning, preparedness, and prevention. Developing an early warning system (EWS) for MERS in Saudi Arabia using engineering systems modeling methods – namely, system dynamics – may help achieve these ends. If successfully within the context of *MERS-Coronavirus* in Saudi Arabia, such a modeling framework may also be generalized to other zoonotic pathogens with similar emergent properties and global ramifications.

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I. Background. In September 2012, ProMED announced the discovery of a novel human coronavirus (1). Later name Middle East Respiratory Syndrome Coronavirus (*MERS-Coronavirus),* the virus was isolated from a 60-year-old patient in the Kingdom of Saudi Arabia who presented with acute renal failure and pneumonia in June 2012 (1, 2). Two more cases, one of whom had traveled to Saudi Arabia in August 2012, were announced soon thereafter in the United Kingdom (3, 4).

Many characteristics of MERS closely resemble those of severe acute respiratory syndrome (SARS), including the predominance of respiratory symptoms and high case fatality rate (2, 5). However, MERS progresses to respiratory failure much faster than SARS (24); moreover, unlike *SARS-Coronavirus*, *MERS-Coronavirus* frequently presents with gastrointestinal and renal symptoms (5 – 8).

MERS-Coronavirus also seems to be more pervasive than *SARS-Coronavirus*; since 2012, more than 1300 cases of MERS have been diagnosed worldwide. To date, cases of MERS have been exported to the United Kingdom, France, Germany, Greece, and most recently, South Korea – among others (3, 4, 9 – 12). However, all known index cases have been either directly or indirectly linked to countries in the Arabian Peninsula – the majority from the Kingdom of Saudi Arabia (13).

In Spring 2014, a large outbreak originated in the Kingdom of Saudi Arabia – concentrated in nosocomial settings in Riyadh and Jeddah – resulting in over 300 infections. Although apparent instances of sustained secondary transmission did occur in family clusters (14, 15) and healthcare facilities (8, 11, 15, 16) prior to early 2014, *MERS-Coronavirus* was until this time regarded as a primarily zoonotic pathogen with limited potential for human-to-human transmission.

The precise zoonotic origins of *MERS-Coronavirus* remain unknown, but bats and camels are likely intermediary hosts (17). Related coronaviruses have been found in different bat families including *Vespertillionidae*, *Molosidae*, *Nyteridae*, and *Emballonuridae* (18). Furthermore, *MERS-Coronavirus* has been isolated in camels from Saudi Arabia, Oman, Qatar, Jordan, and Kenya (19 – 23), and evidence suggests that humans can acquire *MERS-Coronavirus* directly from dromedary camels (24).

Despite these advances, it still remains unclear whether zoonotic or human-to-human transmissions are the main drivers of MERS (17). Furthermore, many of the epidemiological questions raised about MERS in the early days of its discovery still remain – including risk factors for mortality and true outbreak potential, as well as characteristic differences between cases that occur during non-outbreak periods (i.e. sporadic transmission) and outbreak periods (i.e. non-sporadic transmission).

Prior to the Spring 2014 outbreak, several modeling studies estimated the basic reproduction number of *MERS-Coronavirus* to be near or below the critical outbreak threshold of $R_0 > 1$ (4, 25 – 27). As a result, the Spring 2014 outbreak was largely unexpected. However, most of these estimates accounted for neither the large numbers of asymptomatic or mild cases that have been known to occur as a result of *MERS-Coronavirus* infection, nor the impact of appropriate infection control and public health response on transmissibility. In this sense, the conventional definition of the basic reproductive number – namely, the *average* number of secondary infections caused by a given case – does not capture the context-dependent nature of disease transmissibility. As suggested in a study that focused on modeling the reproductive number for the Spring 2014 outbreak, there is likely substantial situational heterogeneity of MERS transmissibility (28). For instance, the reproductive number in healthcare settings is likely to be higher than those observed in community and household settings due to the increased likelihood of super-spreading events – a theory that deserves rigorous investigation in the context of the Spring 2014 outbreak.

In addition to limited understanding regarding the outbreak potential of *MERS-Coronavirus*, characteristic differences between sporadic and non-sporadic cases – as well as mortality risk factors – are not yet well understood either. MERS seems to exhibit substantial mortality among patients who are older and those who have comorbidities (6, 29). However, analysis using case data through 2015 is necessary to assess the robustness of this conclusion given that diagnoses in 2012 and 2013 were general skewed towards older, more comorbid patients. Moreover, as is common among other coronaviruses, it is possible that sporadic, zoonotic transmission might cause more severe illness than non-sporadic, human-to-human transmission (3). Like the aforementioned demographic risk factors, this hypothesis warrants further testing now that more complete patient information regarding contact with animals and animal products exists. Furthermore, comparison of descriptive characteristics between cases that occurred due to human-to-human transmission during the Spring 2014 outbreak and cases that have occurred sporadically (i.e. during non-outbreak periods) may help us better understand the enabling conditions necessary for MERS outbreaks to emerge.

Scope. Clearly, the outbreak potential of *MERS-Coronavirus* and risk factors for MERS-related mortality have not yet been thoroughly studied; furthermore, case characteristics that may provide insight into the propagation of MERS outbreaks have yet to be identified. In this thesis, we attempt to address these topics using publicly available data. Following an account of the available data in Chapter II, we conduct a large *N* descriptive study in Chapter III to assess characteristic differences between Saudi MERS cases that occurred during the Spring 2014 outbreak and sporadic cases that were reported prior to it or have been reported since. We then use a series of mortality analyses in Chapter IV to explore how risk factors for death from MERS in Saudi Arabia have changed over time. In Chapter V, investigate the probable role of super-spreading during the Spring 2014 outbreak and possible implications regarding the outbreak potential of *MERS-Coronavirus* in the future. After providing a summary of our findings, we conclude with policy recommendations for the Saudi Ministry of Health and avenues for future collaboration with the Saudi government.

II. Description of Publicly Available Data Sources. Patient and outcome data were collected through July 10, 2015 from the Saudi Ministry of Health daily MERS reports and curated into a machine-readable line-list (1, 2). Daily reports, which included all confirmed cases of MERS that had been reported to the Saudi Ministry of Health, were available in both Arabic and English. Ms. Majumder curated reports in English, and the Arabic-speaking public health data curation team at HealthMap curated reports in Arabic. The Arabic and English daily reports were validated against each other, and in the event of discrepancy, data from the original-language Arabic reports were used preferentially. When available, data were also validated against MERS Disease Outbreak News reports from the World Health Organization, which were also curated by Ms. Majumder (3).

The analyses reported in this thesis were limited only to cases with complete case histories and outcomes ($N = 719$); cases with missing information were excluded ($N = 322$).

Exploratory Data Analysis. 45% of the 719 cases in our data set ended in death, which closely approximates the July 10, 2015 Saudi Ministry of Health all-time estimate of 44% (4). Consistent with previous findings published by the World Health Organization, age was normally distributed around 51 years (SD: 18.8), 66% of cases were male, and 56% had pre-existing comorbidities of some kind (3). Given constancy of these statistics against both Saudi Ministry of Health and World Health Organization metadata, our sample is likely representative of all Saudi cases that have been reported to date and a reliable proxy for gold-standard hospital data.

Among the 110 cases for which comorbidity status details were publicly available, diabetes, kidney disease, and cardiovascular illness were commonly cited. Only 9% of the 719 cases in our data set reported contact with relevant animals (e.g. camels) or animal products (e.g. camel milk or meat); meanwhile, 39% reported contact with other MERS cases. 14% were healthcare workers and 30% were nosocomial; in addition to hospital-acquired infections that were specifically noted in the Saudi Ministry of Health MERS reports, cases were also categorized as nosocomial if their original date of hospital admission preceded date of symptom onset. 20% of cases in the data set were either mild or asymptomatic, while the remaining 80% experienced standard or severe symptoms; 33% were in critical condition at time of reporting.

Data Limitations. Our use of publicly available data poses unique challenges; though such data enable timely execution of preliminary epidemiological research for novel and emerging pathogens, case information is stringently restricted to protect patient privacy. Because of this, follow-up analyses should be conducted pending availability of additional case and covariate data from the Saudi Ministry of Health.

III. Comparing outbreak and non-outbreak cases of MERS in Saudi Arabia. More than a year since its end, it still remains unclear why the Spring 2014 Saudi MERS outbreak occurred or whether cases that were diagnosed during the outbreak were somehow different from cases that had been reported prior or have been reported since. It is possible that the enabling conditions associated with the emergence and propagation of the Spring 2014 are due to considerable month-to-month variability of several critical case characteristics (Figure 1). In this first-ever large *N* descriptive epidemiology study of Middle East respiratory syndrome, we use both univariate and multivariate statistical methods to compare outbreak (i.e. non-sporadic) and non-outbreak (i.e. sporadic) Saudi MERS cases.

Methods. Using the data set described in Chapter II, cases were first sorted by binary descriptive characteristics and time periods (Table 1.1), i.e. pre-outbreak, outbreak, and post-outbreak – where the outbreak period was defined as April 2014 to May 2014 (1). Four sets of chi-square analyses were then conducted to compare available descriptive case characteristics between time periods, namely: pre-outbreak vs. outbreak; pre-outbreak vs. post-outbreak; outbreak vs. post-outbreak; and outbreak vs. non-outbreak. After running these univariate analyses, multivariate logistic regression was conducted on the characteristics that were statistically significant. The significant characteristics served as covariates and whether or not a given case occurred during the Spring 2014 outbreak served as the outcome.

Results. **Univariate Chi-Square Analyses.** Several statistically significant trends emerged from the univariate chi-square analyses (Table 1.2).

Among the 719 cases in our data set, the fatality rate associated with *MERS-Coronavirus* infection was significantly less among cases that occurred during the Spring 2014 outbreak (*CFR* = 38%) than those that occurred prior to it (*CFR* = 63%). Though the fatality rate has increased in the months since (*CFR* = 46%), it still remains notably lower than during the pre-outbreak period ($p = .003$); moreover, the fatality rate during the post-outbreak months thus far has not differed significantly from the Spring 2014 outbreak months ($p = .058$).

In addition to these differences in fatality, an unexpectedly large number of women were diagnosed with MERS during the Spring 2014 outbreak when compared against non-outbreak months ($p < .001$). Younger individuals – specifically, those under the mean age of 51 – were also disproportionately represented among cases reported during the Spring 2014 outbreak when compared against both pre-outbreak ($p = .007$) and post-outbreak months ($p < .001$). Similarly, a much larger number of non-comorbid individuals were diagnosed with MERS during the Spring 2014 outbreak than during non-outbreak months ($p < .001$).

Mild and asymptomatic cases represented a much larger fraction of diagnoses during the Spring 2014 outbreak than during non-outbreak months ($p < .001$). Furthermore, a significantly smaller proportion of reported cases have been mild or asymptomatic in post-outbreak months than in pre-outbreak months ($p < .001$). Correspondingly, a much smaller number of critical MERS cases were reported during the Spring 2014 outbreak than during non-outbreak months ($p = .036$). This relationship is particularly strong when comparing outbreak and post-outbreak cases ($p = .002$).

Far fewer cases reported contact with animals or relevant animal products (e.g. camel milk) during the Spring 2014 outbreak than during non-outbreak months ($p < .001$). However,

nosocomial transmission and MERS incidence in healthcare workers did not vary significantly among time periods, nor did transmission among individuals who had contact with known MERS cases.

Multivariate Logistic Regression. Of the 7 descriptive characteristics that demonstrated statistically significant univariate differences between outbreak and non-outbreak cases, 4 remained significant after adjusting for all 7 covariates: sex, symptomatic case status, animal contact, and comorbidity status (Table 1.3). Directionality of relationships also remained unchanged for these 4 covariates. Age, critical case status, and final outcome (i.e. deceased vs. recovered) were no longer significant after adjusting for all model covariates.

Discussion. Of the 10 binary descriptive characteristics considered, the majority varied appreciably from one month to the next (Figure 1.1). This variability is well captured in the univariate chi-square analyses, which show that – when considered independently – the majority of the 10 descriptive characteristics differed substantially among the three time periods.

Based off of the univariate chi-square analyses alone, it seems that the cases reported during the Spring 2014 outbreak were notably different from those reported during non-outbreak months in that they were generally younger, healthier, and less severe. The lower case fatality rate associated with the Spring 2014 outbreak is likely due to a combination of these factors; death due to MERS – as well as severe illness due to *MERS-Coronavirus* – is likely more common among cases with pre-existing conditions – conditions that happen to occur more often in older individuals. Moreover, given that women were disproportionately represented during the Spring 2014 outbreak, it is also possible that men are more susceptible to severe illness and death. Indeed, upon closer inspection via multivariate analysis, it becomes evident that the difference in age and case fatality rate between outbreak and non-outbreak months is no longer significant once other factors – such as sex and comorbidity status – are taken into account.

For reasons that remain unknown, an unexpectedly large fraction of female and non-comorbid cases were reported during the Spring 2014 outbreak. As we try to determine the exact mechanism by which the outbreak occurred and why, these findings should be kept in mind. The enabling conditions that propagated the outbreak may have infected female and non-comorbid individuals preferentially.

Despite the fact that the Spring 2014 outbreak has thus far been hypothesized as largely nosocomial in nature (1, 2), we found that – when compared against non-outbreak months – there was no marked increase in nosocomial transmission or healthcare worker infections. This is not to say that the nosocomial setting does not aid the transmission of *MERS-Coronavirus*; indeed, a number of small hospital outbreaks of MERS occurred in Saudi Arabia prior to 2014 (3 – 6).

Instead, it is possible that the Ministry of Health experienced breakdowns in data collection during the Spring 2014 outbreak, which may be introducing bias into our analyses. The unusually large number of cases that occurred between April and May 2014 likely placed strain on surveillance-related resources, which may be evidenced by the marked decrease in cases that reported animal contact during this time period paired with the lack of notable increase in transmissions among patients with known contacts. Because *MERS-Coronavirus* is a zoonotic pathogen with the capacity for human-to-human infection, an outbreak is only

likely to occur when one of these two modes of transmission is up regulated – neither of which is apparent from the patient information available in our data set.

This fact – in addition to the large percentage of mild and asymptomatic cases that were reported during the Spring 2014 outbreak – suggests that case-finding efforts were prioritized over patient data collection and dissemination. However, it is also possible that the increased prevalence of sub-clinical (i.e. mild or asymptomatic) cases was due to over-sampling of the "worried well", which is frequently observed during outbreaks of novel respiratory pathogens. As was well documented during the 2003 Hong Kong epidemic of the related *SARS-Coronavirus*, mild cases that would have otherwise been mistaken as the common cold or seasonal flu were diagnosed as SARS due to heightened awareness and care seeking among the general population (7). A similar phenomenon may have occurred during the Spring 2014 outbreak of MERS in Saudi Arabia, providing an alternative or supplementary hypothesis to improved surveillance.

In either event, there has been a considerable drop off in the reporting of mild and asymptomatic cases in the months since the outbreak. Assuming that improved surveillance contributed – at least in part – to the increased reporting of a mild and asymptomatic cases during the outbreak, this could indicate that discovery of less severe cases may no longer be of import to the Saudi Ministry of Health. This may be the result of the July 2014 World Health Organization MERS probable case definition revision, which requires the presence of respiratory symptoms (8).

However, on account of how little is known about MERS epidemiology to date, discovery of mild and asymptomatic cases is imperative and may provide insight into population-level prevalence of the disease. If *MERS-Coronavirus* circulates at low-levels in the population at all times, this may explain the emergence of outbreaks in the absence of known zoonotic introductions. Furthermore, active case-finding efforts may provide further insight into the true fatality rate and mortality risk factors associated with *MERS-Coronavirus*.

IV. Mortality risk factors of MERS cases in Saudi Arabia. Middle East respiratory syndrome has been fatal in more than 40% of cases that have been reported since its discovery in 2012. Despite this, risk factors associated with mortality remain largely unknown. Only a handful of small *N* studies have explored this topic to date (1 – 3). Here, we conduct a large *N* mortality risk factor analysis among Saudi MERS cases and compare risk factors between outbreak and non-outbreak cases.

Methods. Using the data set described in Chapter II, risk factors for mortality were evaluated using univariate and multivariate logistic regression models for 3 time periods: outbreak months, non-outbreak months, and all months. The outbreak period was defined as April 2014 to May 2014 (Figure 2.1). Covariates included sex, age, critical case status, healthcare worker status, known contact with other MERS cases, nosocomial case status, known contact with relevant animals or animal products, and comorbidity status. Symptomatic case status was included to control for the presence of mild and asymptomatic cases in the data set, none of which ended in death. Time from onset-to-death and onset-to-discharge was also analyzed for all time periods.

Results. **All Cases.** Of the 719 cases in our data set, 324 died – resulting in a case fatality rate (CFR) of 45%. The median time from onset-to-death was 9 days [Range: 0, 188], and the median time from onset-to-discharge was 15 days [Range: 0, 94] (Figure 2.2).

Univariate logistic regression models for each risk factor showed that all but nosocomial case status ($p = .956$) and contact with animals ($p = .470$) were significantly associated with mortality. After adjusting for all 9 variables in a multivariate logistic regression model, male sex no longer remained statistically significant (Table 2.1). The model estimated that the odds of dying were nearly 2 times higher for nosocomial cases relative to non-nosocomial cases (95%CI: 1.10 – 3.18) and more than 2.5 times higher for cases that were in critical condition at time of reporting relative to non-critical cases (95%CI: 1.81 – 3.96); furthermore, for every one-year increase in age, odds of dying increased by 4% (95%CI: 1.02 – 1.05). Meanwhile, healthcare workers were 75% less likely to die than non-healthcare workers (95%CI: .11 – .54), and individuals that had known contact with other MERS cases were 38% less likely to die than individuals that did not have known contact (95%CI: .40 – .96).

Outbreak Cases. 38% of the 294 cases that were reported during outbreak months died. The median of time from onset-to-death was 11 [0, 104], and the median of time from onset-to-discharge was 18 [4, 94] (Figure 2.3).

Univariate logistic regression models for each risk factor showed that age (i.e. $\geq$ vs. $<$ 51 years old), symptomatic case status, critical case status, healthcare worker status, known contact with other MERS cases, and comorbidity status were significantly associated with mortality (all $p < .001$). After adjusting for all 9 variables in a multivariate logistic regression model, only age remained statistically significant (Table 2.2). The model estimated that, for every one-year increase in age, odds of dying increased by 5% (95%CI: 1.02 – 1.07).

Non-Outbreak Cases. Of the 425 cases that occurred during non-outbreak months, 213 died (CFR = 50%). The median of time from onset-to-death was 8 [0, 188], and the median of time from onset-to-discharge was 12 [0, 88] (Figure 2.4).

Univariate logistic regression models for each risk factor showed that all but sex ($p = .121$), nosocomial case status ($p = .951$), and contact with animals ($p = .957$) were

significantly associated with mortality. After adjusting for all 9 variables in a multivariate logistic regression model, male sex no longer remained statistically significant (Table 2.3). The model estimated that the odds of dying were 3.74 times higher for cases that were in critical condition at time of reporting relative to non-critical cases (95%CI: 2.30 – 6.10) and nearly 2.5 times higher for nosocomial cases relative to non-nosocomial cases (95%CI: 1.24 – 4.65); moreover, for every one-year increase in age, odds of dying increased by 3% (95%CI: 1.02 – 1.05). Conversely, healthcare workers were 82% less likely to die than non-healthcare workers (95%CI: .07 – .47).

Discussion. Although all-time (June 2012 – June 2015) fatality from *MERS-Coronavirus* is higher among men (CFR = 49%) than among women (CFR = 38%), we found that this relationship is no longer significant after adjusting for other covariates. Likewise, it seems that the impact of pre-existing comorbidities on MERS mortality is non-significant after other factors are taken into account – despite the fact that the CFR among all comorbid cases in our data set (62%) is higher than the CFR among non-comorbid cases (24%).

It is possible that sex and comorbidity status were not significant in any of our multivariate logistic regressions because age adequately captures both. Among all 719 cases in our data set, non-comorbid cases were on average 19 years younger than comorbid cases (mean = 40 and 59, respectively). Similarly, male cases were on average 4 years older than female cases (mean 52 and 48, respectively).

Given that age was a significant covariate in all three multivariate regression models, it may be the most important risk factor for MERS mortality in the Saudi population. Meanwhile, critical case status, healthcare worker status, and nosocomial case status were significant for the "all months" and "non-outbreak months" time period; known contact with other MERS cases was significant only for the "all months" time period. This finding suggests that there may be risk factors for mortality from MERS may be context-dependent (e.g. outbreak vs. non-outbreak) and thus fluctuate over time. However, it is also worth noting that the protective nature of having contact with other MERS cases may have emerged when analyzing the whole data set because the smaller subsets (i.e. outbreak and non-outbreak time periods) were more prone to censoring.

When considering all 719 cases in our data set, those that were critical at time of reporting were more likely to end in death, which indicates that early care seeking may improve rates of survival. Nosocomial cases that were not healthcare workers were also more likely to end in death; this is perhaps because such individuals – even after adjusting for comorbidities – are uniquely immunosuppressed due to bombardment with a whole host of hospital-borne pathogens, including but not limited to *MERS-Coronavirus*. It is possible that being a healthcare worker is protective against death due to occupation-specific knowledge that allows for self-administration of early supportive care. Healthcare workers – as well as individuals that have known contact with other MERS cases – may also be more likely to seek care early, i.e. immediately after exposure.

Long-term low-level exposure to *MERS-Coronavirus* may also stimulate antibody generation in healthcare workers and individuals that have known contact with other MERS cases before symptom onset. A similar mechanism may also be at play for individuals that have had contact with relevant animals and animal products. Among all 719 cases in the data set, animal contact was protective but not statistically significant; this may be in part because

only 9% of cases reported such contact, which poses a practical challenge for multivariate risk factor analysis (see Table 2.2).

Despite the potentially protective properties of low-level exposure from animals infected with *MERS-Coronavirus*, there exists evidence that host-to-human acquisition of coronaviruses from zoonotic sources (i.e. spillover) is more likely to cause death than human-to-human transmission among humans (4). Moreover, given the inverse relationship between lethality and transmissibility of most viral pathogens, it is likely that individuals infected with *MERS-Coronavirus* via host-to-human transmission are less likely to infect others than those who are infected by human-to-human transmission. This is at least in part driven by the nosocomial context in which human-to-human transmissions of *MERS-Coronavius* occur most frequently; given the inherently immune-compromised population and closed-quarters, it is possible for a single case to infect many others in the absence of appropriate prevention measures in such settings. With this in mind, further investigation of the relationship between relevant animal contact and mortality due to infection – as well as *MERS-Coronavirus* transmissibility – should be prioritized.

V. Super-spreading and the Spring 2014 Saudi Arabian MERS outbreak. Sporadic, host-to-human transmissions comprised the bulk of MERS cases until the Spring 2014 Saudi MERS outbreak. Because these data were used to determine the basic reproductive number associated with MERS-Coronavirus, most initial estimates were sub-critical ($R_0 < 1$) – suggesting that a large outbreak of MERS would be unlikely (1 – 5). These estimates were called into question during the Spring 2014 outbreak, which caused over 300 known infections in a span of only 8 weeks. Here, we show that – despite the magnitude of this outbreak – it is possible that most reported cases infected very few other individuals; instead, the outbreak may have been propagated by a super-spreading event, in which a small fraction of cases caused a large number of secondary infections.

Methods. Using the data set described in Chapter II, we first determined the number of new cases (i.e. infectious agents, N) that were generated during serial interval $t = 1$ through 9 (Figure 3.1). A start-date of April 1, 2014 and an interval length of 7 days were utilized (6, 7). Next, we calculated the mean number of secondary infections caused per infectious agent – or serial-interval-specific reproductive number, R_{SI} – for each interval using the following formula: $R_{SI}(t) = N(t) \div N(t-1)$

We then used simulation to determine feasible distributions of secondary infections for each serial interval. In the simulations, new cases at serial interval t (e.g. 13 cases at $t = 1$) acted as the infectious agents responsible for cases generated during the subsequent serial interval (e.g. 24 secondary infections between $t = 1$ and $t = 2$) (Figure 3.1). 100 trial distributions were simulated for each serial interval using the GRG non-linear optimization algorithm, and for any given serial interval, we required the simulated distributions to fulfill the following criteria: infectious agent and secondary infection counts that matched existing outbreak data (Figure 3.1); a mean number of secondary infections per infectious agent that was equivalent to the calculated $R_{SI}(t)$ (Figure 3.2); and, if possible, the 80/20 rule of transmission heterogeneity, which states that 20% of cases that occur during interval t generally infection 80% of cases that occur in the subsequent interval (8).

Results. Based off of the 294 MERS cases in our data set that occurred during the model-constrained outbreak period (i.e. April 1, 2014 – June 3, 2014), peak incidence occurred at $t = 3$ ($N = 62$) and $t = 4$ ($N = 63$) (Figure 3.1). The simulated distributions suggest that during these first 4 intervals, 4 infectious agents caused ≥9 secondary infections – one of which was an index case at $t = 0$ (Figure 3.3). Because of this, our calculated value of R_{SI} was very high at $t = 1$, but decreased dramatically over the following serial intervals and eventually became sub-critical by $t = 5$ (Figure 3.2) after the outbreak peaked (Figure 3.1). We also found that it was possible to simulate an 80/20 (heavy-tailed) distribution of secondary infections after pre-conditioning on the mean number of secondary infections per infectious agent to $R_{SI}(t)$ for all serial intervals (Figure 3.3). Among these simulated distributions, 179 (61%) of cases caused 0 secondary infections, and 237 (81%) cause 1 or fewer.

Discussion. Our simulated distributions demonstrate that most cases during the Spring 2014 outbreak likely infected 1 or fewer other individuals, which is consistent with previous sub-critical estimates of R_0 (1 – 5) among sporadic cases. Thus, our work validates the hypothesis that this outbreak may have been driven by a super-spreading event, in which a very small number of cases have been responsible for the vast majority of secondary infections. Because

of this heterogeneity, a given outbreak of MERS may have an early-outbreak R_{SI} that is greater than 1, which may help explain why studies that have attempted to quantify transmissibility during outbreaks have yielded larger estimates of the reproductive number.

Transmissibility itself is context-dependent – a reality that is not well captured by the conventional definition of the basic reproductive number. A more nuanced understanding of transmissibility that considers both infection and contraction heterogeneity is critical. Heterogeneity in the number of secondary infections a given case causes is often due to situational factors like the environment in which the infections are occurring (8). Like a number of smaller outbreaks that preceded it, the Spring 2014 outbreak appears to be driven by nosocomial transmissions (6, 9 – 12), indicating that inadequate infection control in the hospital setting may facilitate super-spreading events of *MERS-Coronavirus*.

Moreover, a recent study found that *MERS-Coronavirus* demonstrates substantial propensity for super-spreading – especially when driven by nosocomial transmission (13). As a result, significant outbreak potential exists and outbreaks of over 150 cases are not unexpected, despite the fact that most cases will likely infect 1 or fewer others (13). This phenomenon was well documented during the 2015 South Korean MERS outbreak, which infected nearly 200 individuals and was driven largely by nosocomial infections (14). Determining the role of a super-spreading event during this outbreak was relatively straightforward; the data necessary to define transmission chains were publicly available via the South Korean Ministry of Health and Welfare (14).

In the absence of transmission chain data, simulation allows us to test the hypothesis that the Spring 2014 Saudi Arabian MERS outbreak may have also been propagated by a super-spreading event. However, other viable hypotheses exist; for instance, it is possible that many of the cases that occurred during the outbreak were actually caused by sub-clinical individuals who were never diagnosed or reported, thus resulting in multiple unseen chains of transmission and eliminating the need for a super-spreading event. If transmission chain data had been collected and made available by the Saudi Ministry of Health during the Spring 2014 outbreak, conclusions similar to those we have reached here may have been drawn in a more responsive and decisive manner. Without such ground truth, alternative hypotheses remain plausible and should be investigated further.

VI. Conclusion. Though the Spring 2014 Saudi MERS outbreak was the first of its scale, it is not likely to be the last. While most cases appear to only infect 1 or fewer other individuals, context-dependent super-spreading events have the potential to propagate outbreaks in settings where infection prevention or control measures are inadequate and initial introduction from either an exportation event (e.g. 2015 South Korean MERS outbreak) or zoonotic source (e.g. Spring 2014 Saudi MERS outbreak) is possible.

Within the context of Saudi Arabia and other endemic countries, further research should be conducted to assess the influence of sporadic, zoonotic transmission (i.e. host-to-human transmission) on lethality and transmissibility. However, within the context of Saudi Arabia, our finding that known contact with other MERS cases (i.e. human-to-human transmission) is protective against MERS-related death supports the hypothesis that *MERS-Coronavirus* – like other coronaviruses – is less lethal and more transmissible when infection occurs non-sporadically (i.e. human-to-human transmission). Irrespective of transmission mode, early care seeking appears to be key to survival. Thus, surveillance – especially among the elderly, who are at notably increased risk for death – is key to reducing fatality and detecting spillover events in Saudi Arabia. This is also imperative to capturing sub-clinical cases during non-outbreak periods, when awareness among the general public is limited and care seeking by the "worried well" is less likely to occur. Identification of such cases may also help us better understand the true prevalence of *MERS-Coronavirus* among the Saudi population. Because it is possible that sporadic mild and asymptomatic cases can transmit *MERS-Coronavirus*, such individuals – especially if they comprise a significant percentage of the overall Saudi population – may act as high-frequency index patients that are capable of triggering future outbreaks if left uncontained.

In addition to the necessary introduction of *MERS-Coronavirus* into a given population (e.g. spillover or exportation event) and the possible role of sub-clinical cases in endemic countries, our finding that female and non-comorbid individuals were preferentially infected during the Spring 2014 outbreak may lend further insight into the enabling conditions that are necessary for MERS outbreaks to emerge and propagate. To prevent future outbreaks, further exploration of this mechanism is essential.

Future Work. Without question, *MERS-Coronavirus* is a significant public health concern – not only for the Kingdom of Saudi Arabia, but also worldwide. As demonstrated by a steady stream of sporadic cases since the Spring 2014 outbreak, MERS has already gained a firm foothold in the Kingdom of Saudi Arabia. Given that Saudi Arabia is a universal religious travel destination, localized outbreaks may have massive global implications. Though large-scale outbreaks have not yet been associated with the Hajj (1 – 3), pilgrims have contracted MERS while performing Umrah – suggesting that sustained transmission in large congregations may be possible (4). This unique, potentially high-impact risk – alongside documented propensity for super-spreading and likelihood of survival that is largely contingent on early supportive care seeking – suggests that systematic outbreak planning, preparedness, and prevention should be immediately prioritized by the Saudi government.

Developing an early warning system (EWS) for MERS in Saudi Arabia using engineering systems modeling methods – namely, system dynamics – may help achieve these ends. Though the systemic mechanisms remain unclear, notable seasonal fluctuations in new case reports exist; namely, compared to winter and fall months of the same year, spring and summer months tend to experience an uptick in cases. Because human-to-human

transmissions and super-spreading events of *MERS-Coronavirus* are feasible, being able to predict the size of these upticks may help us predict large outbreaks.

One hypothesis that could be explored using a system dynamics approach is where or not camel-birthing season influences the magnitude of seasonal trends in human MERS cases. More specifically, because dromedary camels are usually more susceptible to *MERS-Coronavirus* as juveniles (5), taking care of these animals may result in seasonal spillover into humans. Furthermore, seasonal prevalence of *MERS-Coronavirus* among juvenile dromedary camels would likely govern the number of camel-to-human spillover events – and the larger this number, the more likely we are to witness a human-to-human outbreak soon thereafter.

However, this is just one of many system-level research topics that may provide valuable insight into MERS in Saudi Arabia. Others include the impact of a large expatriate labor force on population-level immunity due to constant low-level exposure among native communities; how sex-segregation, ritual ablution, and other cultural norms create heterogeneity in individual risk for both contracting and transmitting the disease; and perhaps most importantly, the broader relationship between nosocomial, community, and zoonotic domains of transmission.

Indeed, a three-pronged (e.g. nosocomial, community, and zoonotic) system dynamics model of MERS in Saudi Arabia with an underlying network structure that effectively captures representative human-human and camel-to-human interactions could likely address many of these system-level questions. Publicly available case data, expert opinion on socioeconomic and cultural practices, and the findings presented in this thesis in addition to newly-acquired government hospital data from the Saudi Ministry of Health could be used to build and parameterize such a model in the near future. The model could then be tested using a large array of simulated initial conditions (e.g. pilgrim population, camel populations, etc.) to probabilistically deduce potential trigger scenarios for large-scale MERS outbreaks – and in this same way, it could be used as a prototype early warning system as well.

Provisional Dissertation Topic. Withstanding approval from my committee, the proposed framework – which includes both system dynamics and network methods for modeling an emerging infectious disease – could act as the central contribution of my doctoral dissertation. If so, the work would be made generalizable to a multitude of zoonotic pathogens. The frequency of emergent, zoonotic disease outbreaks – MERS and otherwise – are expected to increase in the years ahead. Bourgeoning urbanization paired with population growth and often-inevitable ecological disruption will likely make our ever-globalizing world more vulnerable to zoonotic spillover and accelerated rates of human-to-human transmission. Given the richness of the available data, recent collaborative partnerships with members of the Saudi Ministry of Health, and existing familiarity with the literature, MERS would be an ideal candidate to act as a test case for the proposed emerging infectious disease modeling framework.

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VIII. Tables.

Table 1.1. MERS cases reported by the Kingdom of Saudi Arabia, sorted by descriptive characteristics and time periods.

	Jun '12 – Mar '14	Apr – May 2014	Jun '14 – Jun '15	
	Pre-Spring 2014 Outbreak, N	*Spring 2014 Outbreak, N*	*Post-Spring 2014 Outbreak, N*	***Total, N***
Deceased	70	111	170	324
Recovered	42	183	143	395
Male	73	165	236	474
Female	39	129	77	245
Nosocomial	41	80	95	216
Non-nosocomial	71	214	218	503
Healthcare worker	22	42	39	103
Non-HCW	90	252	274	616
Contact with case	38	109	136	283
No known contact	74	185	177	436
Comorbid	68	99	235	402
Non-comorbid	44	195	78	317
Symptomatic	86	184	307	577
Asymptomatic	26	110	6	142
Critical condition	26	83	127	236
Non-critical	86	211	186	483
Animal contact	11	2	54	67
No known contact	101	292	259	652
≥51 years old	64	122	177	363
<51 years old	48	172	136	356
Total Cases, N	**112**	**294**	**313**	**719**

Table 1.2. Chi-square and p-values (with Yates' correction) comparing descriptive characteristics among cases reported during pre-outbreak, post-outbreak, outbreak, and non-outbreak months by the Kingdom of Saudi Arabia.

	Pre-Outbreak vs. Outbreak	*Pre-Outbreak vs. Post-Outbreak*	*Outbreak vs. Post-Outbreak*	*Outbreak vs. Non-Outbreak*
Deceased vs. Recovered				
χ^2	19.111	8.666	3.600	10.235
p-value	<0.001	0.003	0.058	0.001
Male vs. Female				
χ^2	2.382	3.842	24.275	20.543
p-value	0.123	0.050	<0.001	<0.001
Nosocomial vs. Non-nosocomial				
χ^2	2.988	1.210	0.584	1.675
p-value	0.084	0.271	0.445	0.196
Healthcare worker vs. Non-HCW				
χ^2	1.373	2.902	0.293	0.001
p-value	0.241	0.088	0.588	0.975
Case contact vs. no known contact				
χ^2	0.225	2.712	2.302	0.932
p-value	0.635	0.100	0.129	0.334
Comorbid vs. Non-comorbid				
χ^2	23.388	7.630	103.362	98.257
p-value	<0.001	0.006	<0.001	<0.001
Symptomatic vs. Asymptomatic or mild				
χ^2	6.718	50.720	121.295	96.055
p-value	0.010	<0.001	<0.001	<0.001
Critical condition vs. Non-critical				
χ^2	0.800	10.050	9.670	4.411
p-value	0.371	0.002	0.002	0.036
Animal contact vs. No known contact				
χ^2	19.016	2.966	47.757	42.209
p-value	<0.001	0.085	<0.001	<0.001
≥51 years old vs. <51 years old				
χ^2	7.380	0.012	13.148	15.479
p-value	0.007	0.913	<0.001	<0.001

Table 1.3. Multivariate logistic regression model comparing descriptive characteristics between outbreak and non-outbreak cases.

Variable	**Odds ratio**	**95%CI**	***p***
Male	0.638	0.446 – 0.913	0.014
≥ 51 years old	1.335	0.878 – 2.029	0.176
Symptomatic status	0.200	0.118 – 0.341	<0.001
Critical condition	1.577	1.055 – 2.357	0.026
Animal contact	0.053	0.013 – 0.224	<0.001
Comorbid	0.256	0.167 – 0.389	<0.001
Deceased	1.463	0.949 – 2.256	0.085

Table 2.1. Multivariate logistic regression model assessing mortality risk factors among all cases reported from June 2012 and June 2015 ($N = 719$).

Variable	**Odds ratio**	**95%CI**	***p***
Male	1.14	.75 – 1.73	.535
Age	1.04	1.02 – 1.05	<.001
Symptomatic	*	*	*
Critical condition	2.68	1.81 – 3.96	<.001
Healthcare worker	.25	.11 – .54	<.001
Contact with case	.62	.40 – .96	.031
Nosocomial case	1.87	1.10 – 3.18	.021
Contact with animal	.56	.31 – 1.01	.054
Comorbid	1.30	.85 – 1.99	.226

*Whether or not a case was symptomatic was included in the model to control for the presence of mild and asymptomatic cases in the data set, none of which ended in death.

Table 2.2. Multivariate logistic regression model assessing mortality risk factors among cases reported during outbreak months (April – May 2014) ($N = 294$).

Variable	**Odds ratio**	**95%CI**	***p***
Male	1.02	.51 – 2.03	.966
Age	1.05	1.02 – 1.07	<.001
Symptomatic	*	*	*
Critical condition	1.43	.71 – 2.89	.318
Healthcare worker	.56	.14 – 2.31	.422
Contact with case	.71	.27 – 1.89	.491
Nosocomial case	1.37	.53 – 3.57	.515
Contact with animal	**	**	**
Comorbid	1.74	.84 – 3.62	.139

*Whether or not a case was symptomatic was included in the model to control for the presence of mild and asymptomatic cases in the data set, none of which ended in death.

**Only 2 of the 294 cases in this time period reported contact with relevant animals or animal products; of these 2, 1 recovered and 1 died, resulting in non-interpretable values for reported multivariate logistic regression statistics.

Table 2.3. Multivariate logistic regression model assessing mortality risk factors among cases reported during non-outbreak months ($N = 425$).

Variable	**Odds ratio**	**95%CI**	*p*
Male	1.26	.73 – 2.17	.403
Age	1.03	1.02 – 1.05	<.001
Symptomatic	*	*	*
Critical condition	3.74	2.30 – 6.10	<.001
Healthcare worker	.18	.07 – .47	<.001
Contact with case	.61	.36 – 1.04	.067
Nosocomial case	2.40	1.24 – 4.65	.001
Contact with animal	.53	.28 – 1.00	.050
Comorbid	1.21	.67 – 2.17	.528

*Whether or not a case was symptomatic was included in the model to control for the presence of mild and asymptomatic cases in the data set, none of which ended in death.

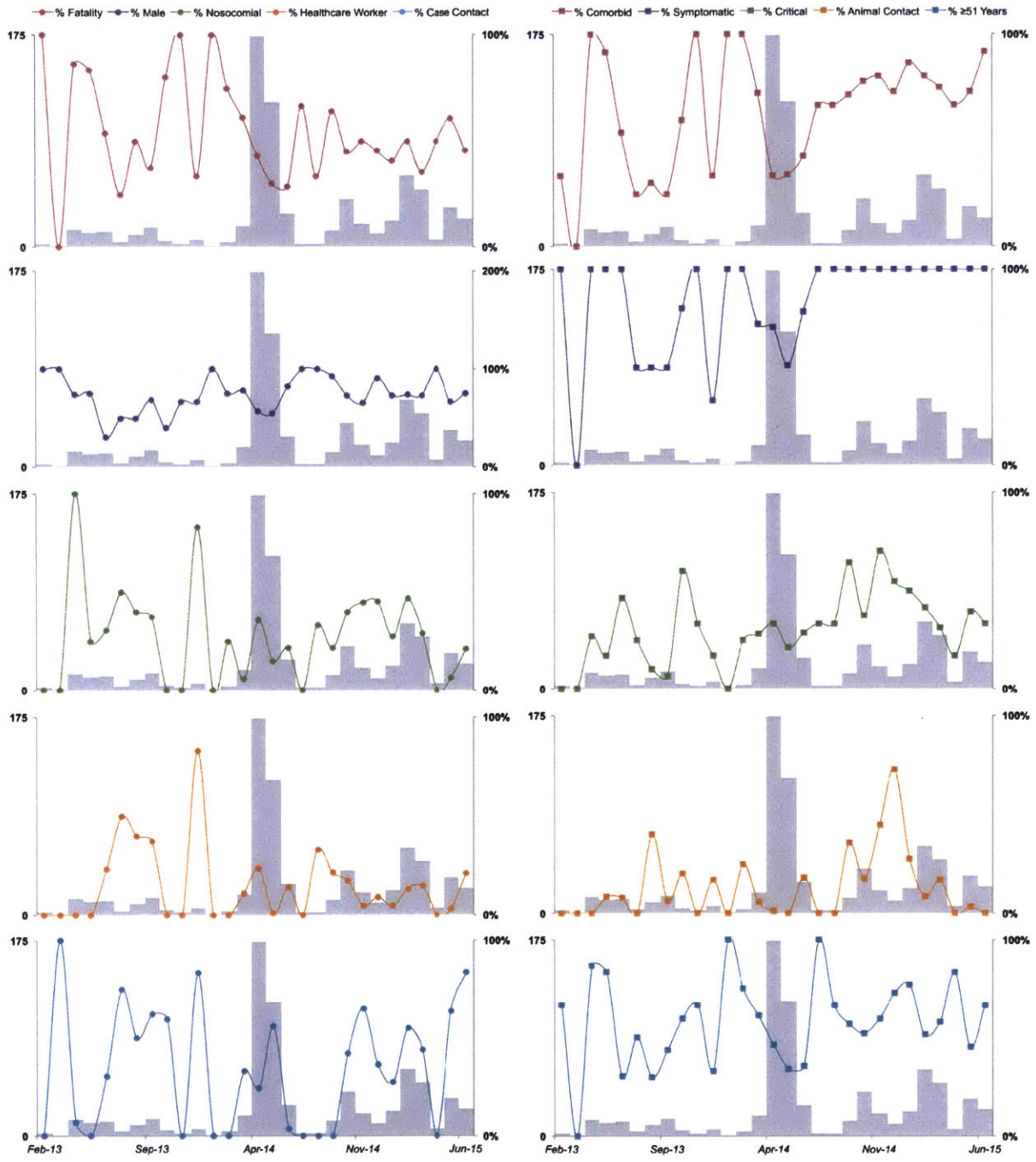
IX. Figure legends.

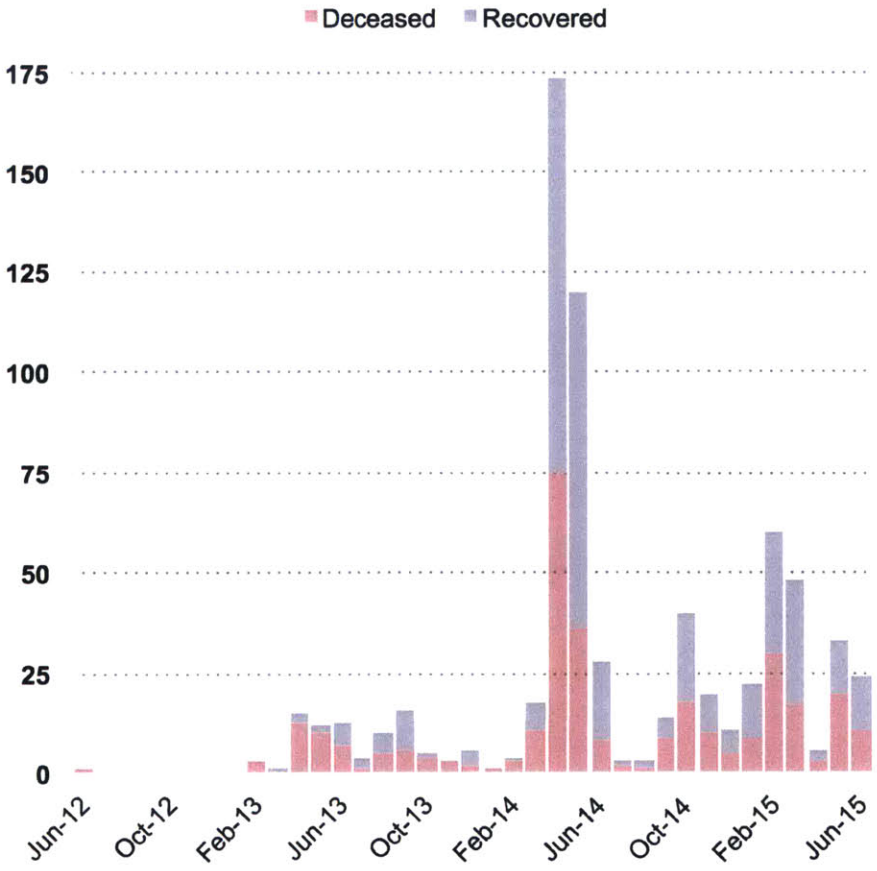
Figure 1.1. Monthly epicurves through June 2015 and presence of risk factors over time.

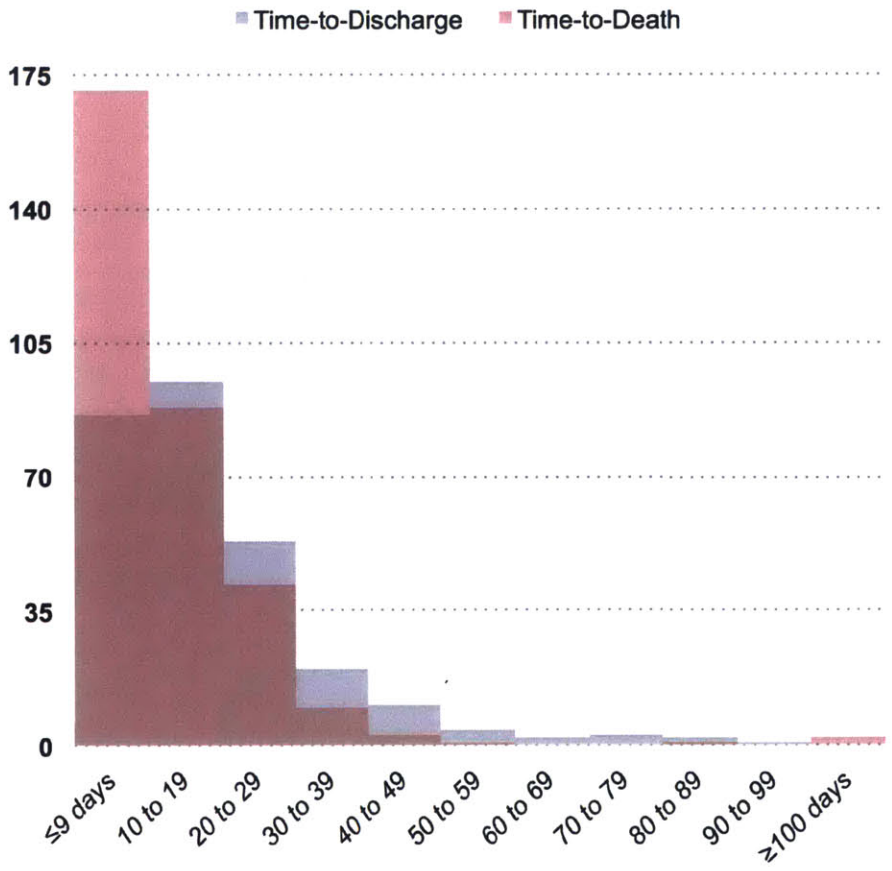
Figure 2.1. Epicurve of recovered and deceased Saudi MERS cases through June 2015.
Figure 2.2. Time from onset-to-outcome for cases reported all-time.
Figure 2.3. Time from onset-to-outcome for cases reported during outbreak months.
Figure 2.4. Time from onset-to-outcome for cases reported during non-outbreak months.

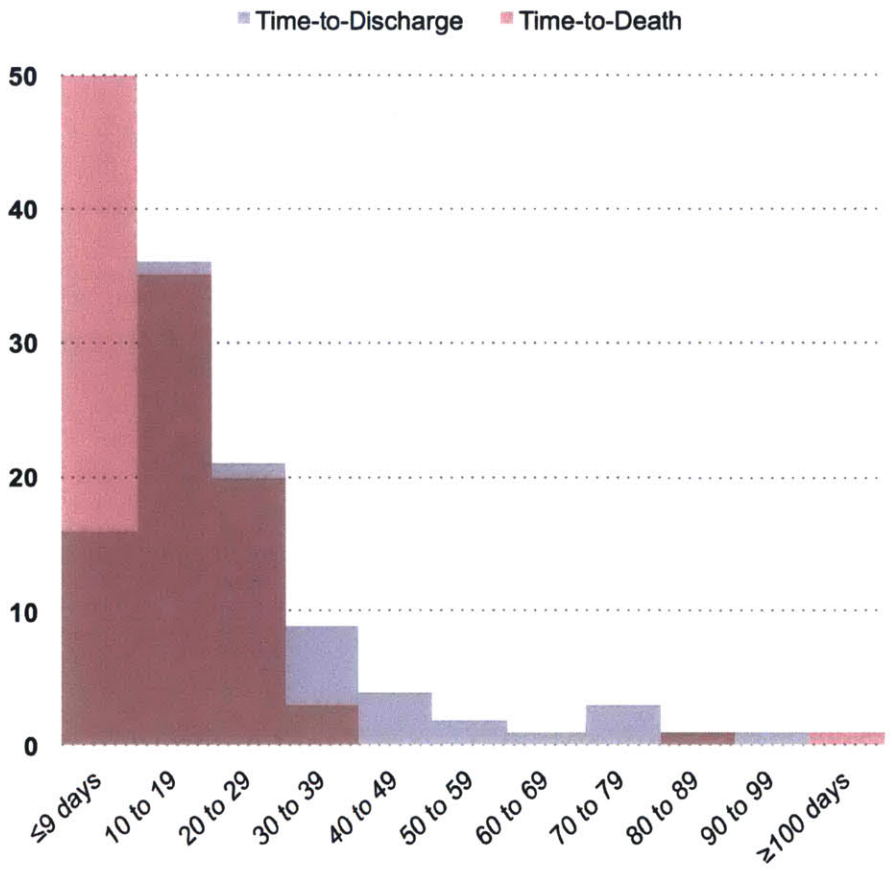
Figure 3.1. Incidence curve aggregated by serial interval. April 1, 2014 marks serial interval, $t = 0$ and June 3, 2014 marks serial interval, $t = 9$.
Figure 3.2. Serial-interval-specific reproductive number over time. Three successive values of R_{SI} were calculated and plotted for serial interval $t = 1$ through 9.
Figure 3.3. Probable distributions of secondary infections across 9 serial intervals.

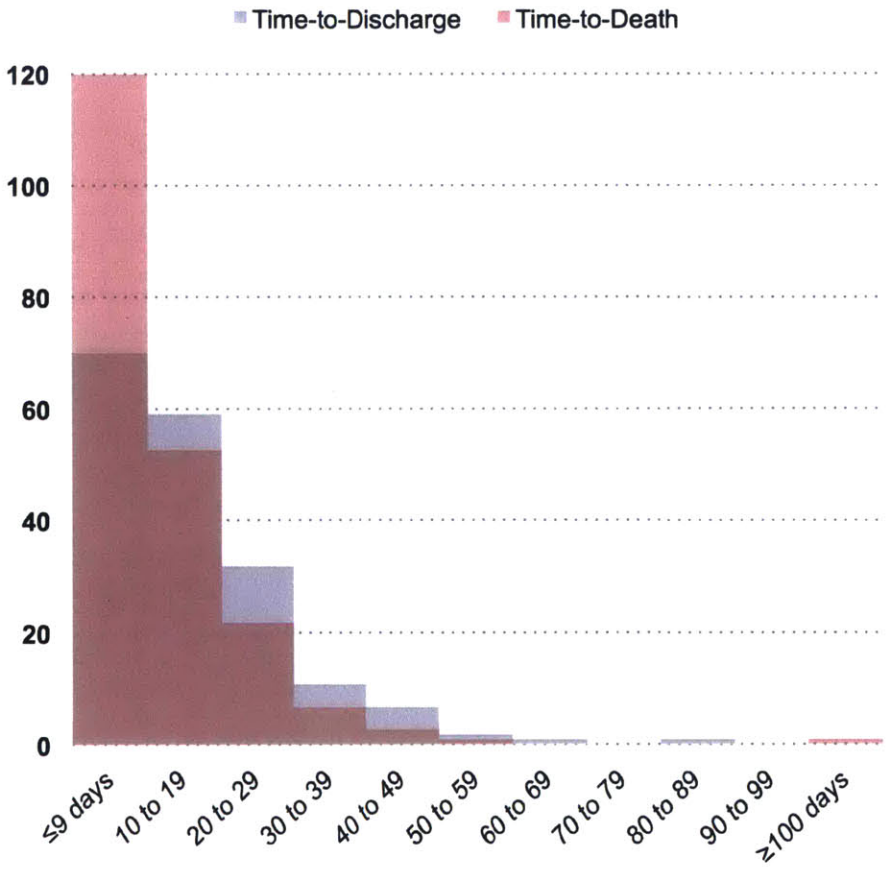
X. High-resolution figures in order of appearance.

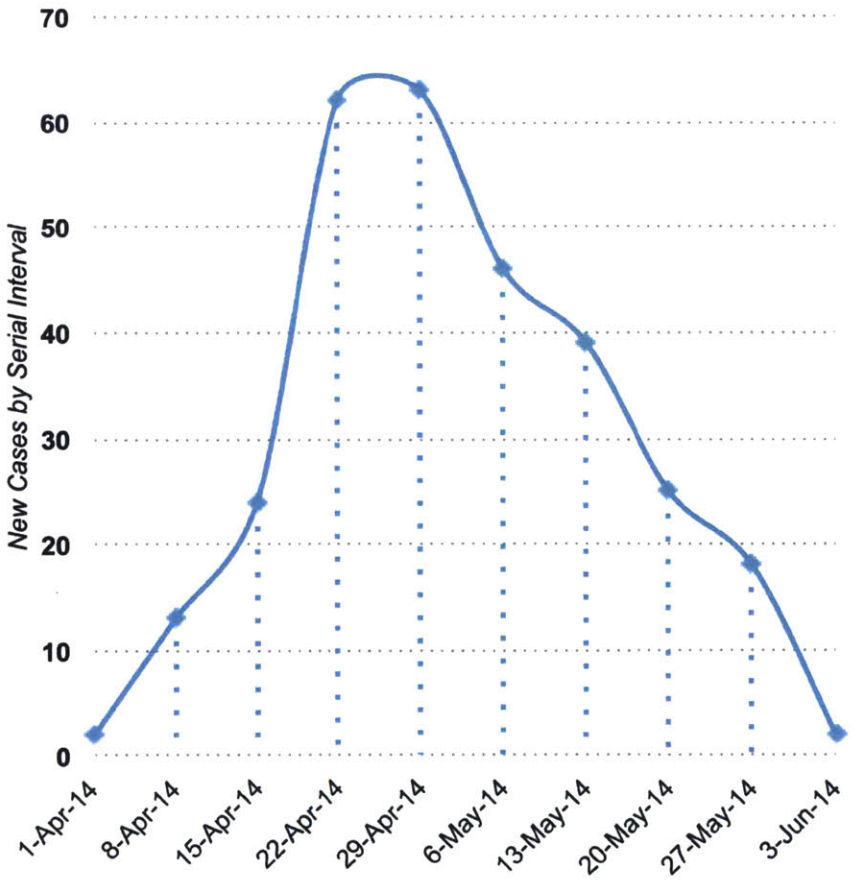

% Fatality
% Male
% Nosocomial
% Healthcare Worker
% Case Contact
% Comorbid
% Symptomatic
% Critical
% Animal Contact
% ≥51 Years
175
0
100%
200%
0%
Feb-13
Sep-13
Apr-14
Nov-14
Jun-15

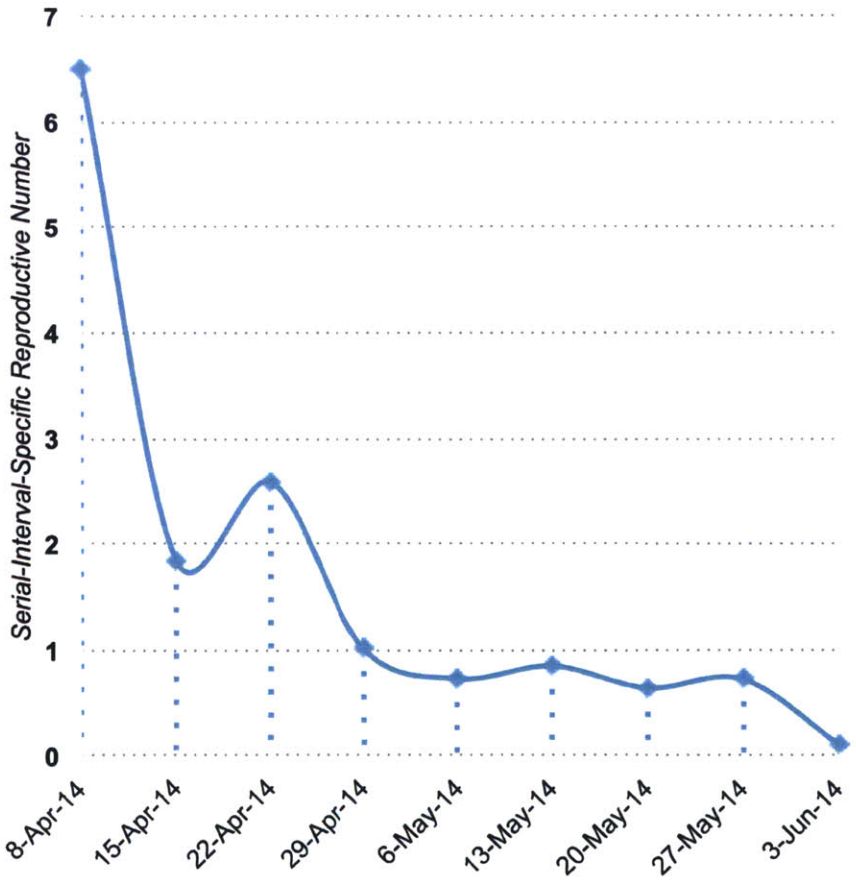

Deceased
Recovered
175
150
125
100
75
50
25
0
Jun-12
Oct-12
Feb-13
Jun-13
Oct-13
Feb-14
Jun-14
Oct-14
Feb-15
Jun-15


Time-to-Discharge
Time-to-Death
175
140
105
70
35
0
≤9 days
10 to 19
20 to 29
30 to 39
40 to 49
50 to 59
60 to 69
70 to 79
80 to 89
90 to 99
≥100 days


Time-to-Discharge
Time-to-Death
50
40
30
20
10
0
≤9 days
10 to 19
20 to 29
30 to 39
40 to 49
50 to 59
60 to 69
70 to 79
80 to 89
90 to 99
≥100 days


Time-to-Discharge
Time-to-Death
120
100
80
60
40
20
0
≤9 days
10 to 19
20 to 29
30 to 39
40 to 49
50 to 59
60 to 69
70 to 79
80 to 89
90 to 99
≥100 days


70
60
50
40
30
20
10
0
New Cases by Serial Interval
1-Apr-14
8-Apr-14
15-Apr-14
22-Apr-14
29-Apr-14
6-May-14
13-May-14
20-May-14
27-May-14
3-Jun-14


Serial-Interval-Specific Reproductive Number
7
6
5
4
3
2
1
0
8-Apr-14
15-Apr-14
22-Apr-14
29-Apr-14
6-May-14
13-May-14
20-May-14
27-May-14
3-Jun-14

Infectious Agents at t = 0
Infectious Agents at t = 1
Infectious Agents at t = 2
Infectious Agents at t = 3
Infectious Agents at t = 4
Infectious Agents at t = 5
Infectious Agents at t = 6
Infectious Agents at t = 7
Infectious Agents at t = 8
0 5 10 15 20 25 30 35 40
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Secondary Infections Caused in Subsequent Serial Interval