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A Scenario-Based Evaluation of the Middle East Respiratory Syndrome Coronavirus and the Hajj

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Between April 2012 and June 2014, 820 laboratory-confirmed cases of the Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported in the Arabian Peninsula, Europe, North Africa, Southeast Asia, the Middle East, and the United States. The observed epidemiology is different to SARS, which showed a classic epidemic curve and was over in eight months. The much longer persistence of MERS-CoV in the population, with a lower reproductive number, some evidence of human-to-human transmission but an otherwise sporadic pattern, is difficult to explain. Using available epidemiological data, we implemented mathematical models to explore the transmission dynamics of MERS-CoV in the context of mass gatherings such as the Hajj pilgrimage, and found a discrepancy between the observed and expected epidemiology. The fact that no epidemic occurred in returning Hajj pilgrims in either 2012 or 2013 contradicts the long persistence of the virus in human populations. The explanations for this discrepancy include an ongoing, repeated nonhuman/sporadic source, a large proportion of undetected or unreported human-to-human cases, or a combination of the two. Furthermore, MERS-CoV is occurring in a region that is a major global transport hub and hosts significant mass gatherings, making it imperative to understand the source and means of the yet unexplained and puzzling ongoing persistence of the virus in the human population.

KEY WORDS: Epidemiology; Hajj; mass gatherings; MERS-CoV; models

1. INTRODUCTION

A string of apparently sporadic, severe acute respiratory infections (SARIs) occurring in the Arabian Peninsula since April 2012 has been attributed to a novel human coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV).(1) noncomemmercial From April 2012 to June 26, 2014, 820 laboratory-confirmed cases of MERS-CoV were identified in the Arabian Peninsula, and spread to over a dozen countries, including 286 deaths.(2) A significant increase in reported cases was recently observed; the number of reported cases in April 2014 alone exceeded the total number of cases that had been reported in the two years prior. All reported cases originated in the Arabian Peninsula or can be epidemiologically linked to an index case via an infected traveler from the region; however, the reason for prolonged persistence of infection in human populations despite a low reproductive number (R)(3) remains unknown. The epidemiology of MERS-CoV, with a slow, sporadic pattern and prolonged persistence, contrasts sharply to SARS, which had a higher estimated R value and

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yet peaked in a classic epidemic pattern and was over within eight months.(4) Local transmission of MERS-CoV has been reported in various familial and hospital settings, but appears limited and variable, suggesting that the infectivity of the virus is low.(2,5,6) The fact that new infections continue to occur over two years after emergence points to an ongoing source of new infections that is not yet elucidated.

This epidemiology of MERS-CoV can be explained by several scenarios or a combination of these scenarios, including: multiple introductions to humans from a nonhuman source (such as an animal, environmental, or other source) resulting in unsustained human-to-human transmission; a genetically evolving pathogen with increasing transmissibility; a sustained low-level human-to-human transmission with occasional super-spreading events; or a significant degree of unreported cases, including the possibility of asymptomatic or mild cases undetected by syndromic surveillance for SARI.

As of June 2014, no clear animal source of transmission between animals and humans has been identified, nor is there a consistent history of animal contact among cases. However, phylogenetic analysis has identified a close relationship between MERS-CoV in humans and various bat species.(7–10) Additionally, MERS-CoV and MERS-CoV-like antibodies have been identified in dromedary camels,(11–23) suggesting that MERS-CoV is widespread, and previously infected various camel populations (including countries where human cases have yet to be reported). The studies have also revealed that MERS-CoV has been in circulation since at least 2003,(16) much longer than previously estimated based on the most common ancestor for the MERS-CoV strains found in humans.(24) A recent study by Memish *et al.*(25) analyzed the virus in an infected camel and infected caretaker of the camel, and the findings suggested cross-species transmission, though it is unknown if the camel infected the human, or the other way around. Infected camels may therefore represent a direct source to humans, or the virus may have crossed from camels to alternative zoonotic hosts or environmental sources responsible for the recent transmission to humans. Additional evidence supporting camels as a host animal was provided by a recent study that sequenced complete MERS-CoV isolates from five camels in Saudi Arabia, which were shown to be identical to published sequences of human isolates.(23) Multiple introductions from zoonotic sources to humans, resulting in limited clusters of cases, is one explanation of the observed epidemiology, although it is unknown how many jumps to humans have occurred, or what the mode of transmission is between the animals and humans.(26)

Human-to-human transmission of MERS-CoV has been confirmed in familial and nosocomial clusters, but has so far been limited to close household and occupational contact and hospital settings.(27–30) Mild and asymptomatic cases have been identified in contacts of confirmed cases;(28) however, a large number of undetected asymptomatic or mild cases have not been found during contact tracing among health-care workers or close contacts of MERS-CoV patients at German,(31) U.K.,(32) or KSA hospitals,(1) nor in a serologic survey conducted on blood donors and abattoir workers in the infected region in 2012.(33) Furthermore, an epidemic pattern of a rising number of cases, similar to that of SARS,(4) would be expected early for a disease with a reproductive number (R) >1 (average number of infections arising from one infected case), which has strikingly not occurred with MERS-CoV, which instead has shown an ongoing, sporadic pattern. Fig. 1(a) shows the striking differences in the epidemiology of SARS and MERS-CoV when cases are plotted from the date of emergence.(34) Fig. 1(b) illustrates the temporal pattern of all reported cases for MERS-CoV, showing a peak of infections associated with a nosocomial outbreak in Al-Ahsa in May–June 2013, more than a year after the emergence of the virus, and a significant increase in the number of reported cases since March 2014. The pattern in the Al-Ahsa outbreak, which resulted in 26 cases, shows an epidemic curve that on the surface was interpreted as a classic human-to-human, rapid-onset, short time-frame nosocomial outbreak,(35) and could possibly represent an evolving epidemiology. Yet, inexplicably, multiple different clades of the virus were identified in that one outbreak, and 3 of 13 transmissions could not be explained by human-to-human transmission, and instead appear to be independent transmission events, all within a very short time period.(36) Similar conclusions were reached by Memish *et al.*(37) in a study conducted to identify common exposure and transmission patterns of all cases of MERS-CoV reported from the Hafr Al-Batin outbreak. The results indicated multiple sources of transmission, and the authors suggested camels as the most likely source. Evidence for multiple transmission sources is further supported by Briese *et al.*,(23) who found that viral particles from individual camels contained more genetic variation than MERS-CoV isolates from humans. Under the assumption that camels are the

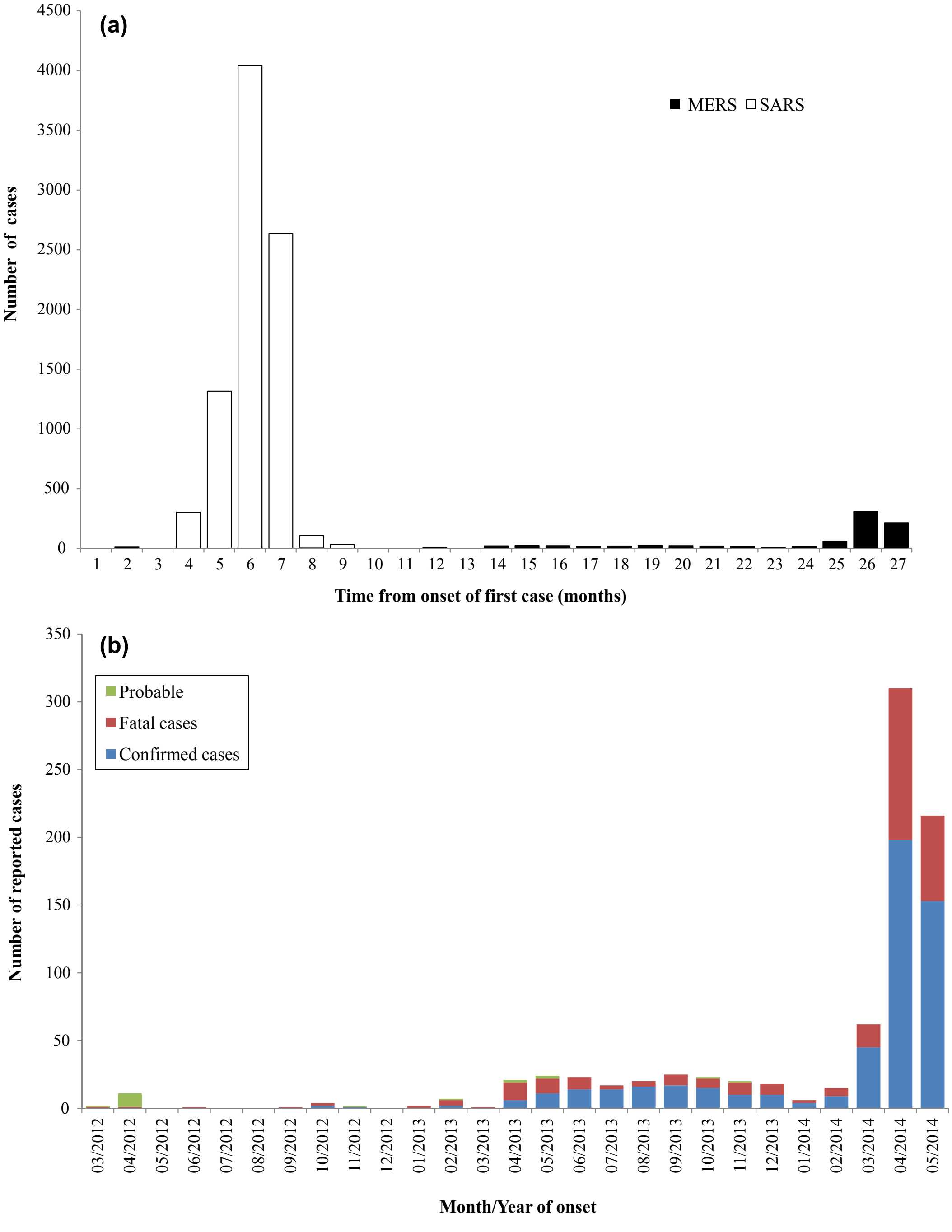

Fig. 1. (a) Comparison of the epidemiology of SARS and MERS-CoV illustrated by epidemic curves from the date of the first case. (b) Epidemic curve summarizing temporal pattern of cases of MERS-CoV, March 2012–June 2014 by month of onset.(2)

source of the virus to humans, only certain genotypes may be able to infect humans, offering a possible explanation as to why human cases are less common.

The sustained pattern of geographically and temporally sporadic cases over the last 25 months for an infection with an apparently low reproductive number, such as this, contradicts the expected behavior of a novel infectious disease capable of human-to-human transmission. Given evidence of human-to-human transmission, the aim of this study is to compare the observed and the expected epidemiology of MERS-CoV in the context of a significant mass gathering such as the Hajj. The Hajj occurs in approximately October each year, based on the Islamic lunar calendar, during which over 3 million pilgrims congregate in Mecca. During both the 2012 and 2013 Hajj, new MERS-CoV cases were identified in Saudi Arabia. Of specific interest is the fact that no confirmed MERS-CoV infections in Hajj pilgrims were reported either year, despite extreme close contact environments and attempts at surveillance of symptomatic pilgrims.(38–40) Similarly, no infections have been reported in pilgrims returning from the Umrah pilgrimages, which occurred in July–August 2012 and 2013.(2)

2. METHODS

Using probabilistic mathematical models, we explore the possible basis of the observed epidemiology of MERS-CoV. Our analysis was conducted in three stages. In the first stage, we test the hypothesis that the virus was sustained in the population between two successively reported cases solely through human-to-human transmission. In the second and third stages of our analysis, we evaluate various transmission patterns in a close contact setting, representative of a social contact network at the Hajj, to compare the observed and expected epidemiology. The methods are described in detail below. Results from the models are compared against the known status of the outbreak. Epidemiological data to inform the models were obtained from official news reports from the WHO, ProMED-Mail, and rapid journal publications.

2.1. Stage 1: Computing Bounds for Unreported Cases

The first analysis *quantifies the minimum number of cases* that must have occurred in the Arabian Peninsula if spread was achieved via human-to-human transmission during the 89-day period between the June 6 and September 3, 2012, cases, which represents the longest gap between two successively confirmed infected cases. This process could also be applied to the periods between other reported MERS-CoV infections. In this analysis, we assume that the source node is responsible for the infection of the target node, and evaluate the *minimum number of persons* that must have been infected in order to connect the two known reported cases for a range of serial intervals. To compute a lower bound, we assume that there is a chain of infected individuals, each transmitting the infection to a *single person* that connects the two cases. Because the objective is to quantify a *lower bound* on the number of missing cases during the 89-day period, we ignore other sources of transmission and the probability of transmission to contacts that do not connect confirmed cases. A recognized limitation of this study is the assumption that the two reported cases are connected. We do acknowledge that MERS-CoV may have infected humans through multiple introductions from a sporadic source, in which case the lower bound in the analysis is effectively zero. Our analysis simply addresses one possible explanatory scenario for the fact that MERS-CoV cases are still being reported in Saudi Arabia. The lack of reported infections elsewhere during that time, the increasing evidence of human-to-human transmission in multiple clusters, the absence of clear evidence of zoonotic transmission in most human cases nor consistent history of animal contact, and an increasing number of asymptomatic and mild cases revealed in the region supports the reasoning for this simple analysis.

2.2. Stage 2: Disease Transmission Model

In the second analysis, a probabilistic transmission model was applied to a hypothetical contact network representative of group social interactions during the Hajj to *estimate the probability that no secondary cases occurred* during this mass gathering (which appears to be the case based on available information).(38,39,41) The model used to quantify the probability of transmission in a contact network is summarized as follows. Given a contact network composed of a single infected individual s and C susceptible contacts, the infected individual s poses a risk of infection to all susceptible contacts. For the simple contact network evaluated, the relationship between p and expected R_0 is $R_0 = NHp$, where H is the exposure period during the Hajj, N is daily number of contacts, and p is the probability of transmission per contact. If p is the probability of infection per contact (per day) during the Hajj, the likelihood of an infected individual s not infecting any group member can be modeled as a binomial experiment $B(n,p)$, where $n = C*H$. We compute the probability of $k = 0$ successes, or the probability of no secondary infections resulting from a single infected individual s, which depends on p, C, and H. We therefore consider a range of transmission probabilities and group

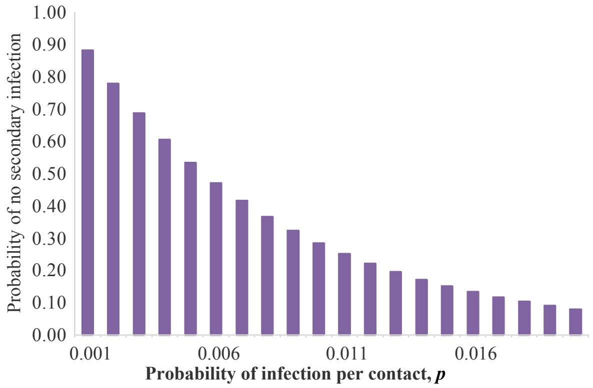

Fig. 2. Sensitivity analysis for probability of no secondary infection relative to probability of infection per contact. Analysis is based on 25 daily contacts.

sizes in the analysis presented. The results are presented in Figs. 2 and 3.

2.3. Stage 3: Expected Outbreak Behavioral Model

Finally, we *estimate the minimum number of reported cases* expected by pilgrims returning from the Hajj. The number of individuals expected to be in either an exposed or infected state after five days is computed using a stochastic compartmentalized susceptible-exposed-infected-removed (SEIR) simulation model. We evaluate a lower bound on the expected number of secondary cases, which represents the minimum number of cases we would expect to have been reported based on pilgrims returning from the Hajj. This estimate is a lower bound on the expected number of reported cases because we assume that only one infected individual was present in an observed group that is itself considered as an isolated social network.

3. RESULTS

3.1. Stage 1: Bounds for Unreported Cases in the Arabian Peninsula

The minimum number of persons who must have been infected in order to connect the reported cases from June 6 and September 3 are computed for three different serial intervals. The first two serial intervals correspond to the maximum and minimum published estimates of the MERS-CoV latency and infectiousness periods.(29,35) The third scenario uses the serial interval estimated from the Al-Ahsa outbreak. Using a maximum serial interval of 35 days, based on the upper bounds for the latent period and infectious period, that is, $L = 15$ days and $D = 20$ days,(4) respectively, a minimum of three cases were required to form the infection path from the June 6 to September 3 cases; *hence, only one unreported case during this 89-day period was required for the virus to have remained in circulation*. The apparently low infectivity of the virus and recent asymptomatic cases in screened contacts(2) suggests that this scenario is plausible; however, this relies on the significant assumption that the two reported cases in June and September are linked. If the lower bounds of the latent and infectious period are used, that is, $L = 2$ and $D = 1$, corresponding to a serial interval of 3, the minimum number of undetected cases increases to 28. Using the serial interval estimated from the Al-Ahsa outbreak of 7.6 days,(35) the expected number of cases required to link the June and September cases was also computed, and equal to 12. This simple analysis reveals the possibility that MERS-CoV could have been sustained in the population over a three-month period solely via human-to-human transmission under the provision that only a few cases went undetected.

3.2. Stage 2: Probability of Secondary Infections at the Hajj

The focus of the next stage of analysis is the Hajj, which takes place around October in Saudi Arabia. Laboratory-confirmed cases were identified in Riyadh, Saudi Arabia, during both the 2012 and 2013 Hajj, including a family cluster in Riyadh, Saudi Arabia, in 2012.(2) The large population size, close contact environment, and the lack of observed infections in Hajj pilgrims during (and after) the Hajj contradicts the expected behavior were the virus to be circulating. For this reason, we *quantified the likelihood that at least one individual was infectious with MERS-CoV during the Hajj, but did not result in a single secondary infection*, which would be consistent with observed data. Given the low number of reported cases and known opportunity for transmission, the MERS-CoV behaves like a disease with a very low transmission probability. Based on these observations, the analysis will only consider the range of $p < 0.02$, where p is the probability of transmission per contact.

The time period considered for analysis is five days; a minimum period of contact corresponding to the duration of the Hajj obligatory rituals and

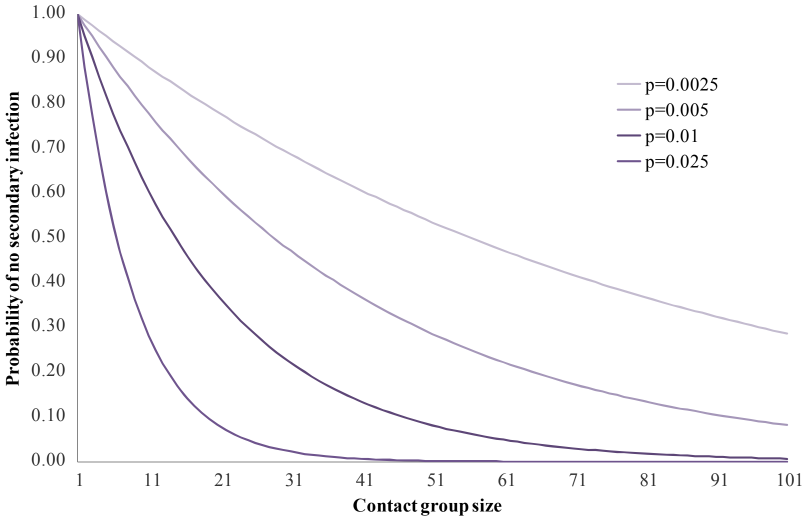

Fig. 3. Sensitivity analysis for probability of no secondary infection relative to the group size for various probabilities of infection.

travels, during which a group of individuals (e.g., an extended family or organized Hajj travel group) can be assumed to remain in close contact and regularly interact over the course of the Hajj. In this setting, we evaluate the probability that a single infected individual did not infect any group member over the entire period of the Hajj, given a range of group sizes (obtained from the range of known group sizes in the Hajj) and infection probabilities. Only one generation of infection was considered (i.e., only secondary cases from the initially infected individual were modeled) due to the short five-day duration of the Hajj and estimated incubation period of 9–12 days.

For a contact network composed of a single infected individual and multiple susceptible contacts, the infected individual poses a risk of infection to all susceptible contacts. We trace the probability of no secondary infections occurring in the contact network for a range of transmission probabilities, p, and group sizes. Fig. 2 illustrates the probability of no secondary infection occurring at the Hajj within a group of size 25 for the range $0.001 < p < 0.02$, which corresponds to $0.1 < R_0 < 2.5$. This range includes recent estimations of R_0 from two independent works, $0.42 < R_0 < 0.92$,$^{(42)}$ and $0.8 < R_0 < 1.5$.$^{(26)}$ However, the inclusion of asymptomatic and mild infections and the increasing size and transmission generations of recent clusters would underestimate these calculations. Furthermore, the actual R_0 value for MERS-CoV still remains unknown, and even estimates that have been derived from specific clusters are unlikely to translate to the Hajj setting where extremely close contact conditions exists. Therefore, the analysis presented considers a wide range of p values and group sizes.

The results illustrate that the probability of no secondary infections quickly approaches zero as the probability of infection per contact increases. Even for a small group size of 25, and probability of infection $p = 0.005$, at least one secondary infection will occur with a probability of 0.47 over the five-day period of the Hajj. For a probability of infection greater than 0.005, there is an over 50% likelihood that at least one secondary infection would occur within a group of 25. The likelihood will be even higher with larger group sizes, which are common in the setting of the Hajj.

Fig. 3 illustrates the probability of no secondary infection occurring for a range of group sizes and a discrete set of transmission probabilities between 0.0025 and 0.025. We observed that even for a probability of transmission $p = 0.005$, the *probability of no secondary infection* approaches zero as the group size increases. This trend is emphasized when the probability of transmission is higher. The results suggest that at least one secondary infection was likely to have occurred at the Hajj.

3.3. Stage 3: Expected Number of Unreported Cases at the Hajj

To complement the previous analysis, we *estimate the minimum number of cases expected* to have been detected and reported after the Hajj. Although the majority of Hajj pilgrims originate from

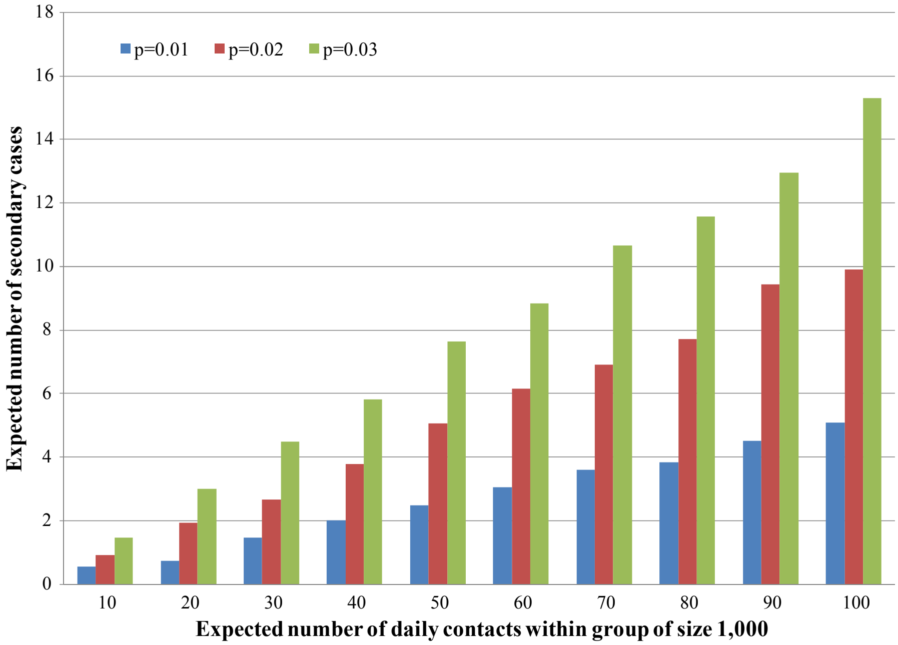

Fig. 4. Expected number of secondary infections in a group of size 1,000 for various contact rates and probability of infection. Results are based on a stochastic SEIR simulation model.

developing countries, which have less capacity for surveillance and response systems in compliance with new international health regulations(43) and in accordance with current interim surveillance recommendations for MERS-CoV,(44) we assume that cases from the Hajj would be detected through the various screening studies that have been conducted in compliance with the Saudi health recommendations among pilgrims attending the Hajj.(38) We do, however, acknowledge that Hajj pilgrims returning to low-income countries may remain undetected and unreported.

The final stage of analysis is based on the assumptions that MERS-CoV is present in one individual at the Hajj, who remains infectious during the entire five-day Hajj period. The infected individual is part of a group of pilgrims residing together over the five-day Hajj period before returning to a high-income country. During this period, the individuals in the group are each assumed to make an average number of daily contacts (which is less than the total size of the group). Group size was based on approximate tent sizes for performing Hajj rituals, frequented daily by the same pilgrims for the duration of the Hajj.

For the purposes of this study, the group is of size 1,000, the number of average daily contacts ranges between 10 and 100, and the probability of infection ranges between 0.01 and 0.03, corresponding to a wide range for R_0 in accordance with the unusual Hajj contact settings. The lower bound on the expected number of exposed or infected individuals in a group on day 5 is based on an average of 100 SEIR simulations, with one initially infected individual, and a fully susceptible group. Again, only one generation of infection is assumed, which is a minimum estimate. The results are illustrated in Fig. 4.

From the figure, it is apparent that the number of contacts and the probability of infection have a significant impact on the expected number of exposed or infected individuals. Our models illustrate that the probability of no secondary infections occurring in Hajj pilgrims was close to zero for the contact patterns likely present at the event. The expected number of secondary infections ranges between 1 and 15 for the set of contacts and infection rates evaluated. Only probabilities of infection $p < 0.01$ would correspond to the likely outcome of no secondary cases. Even for a *probability of infection* $p = 0.01$, and a *single initially infected individual* in an *isolated group* of size 1,000 (i.e., no interaction with individuals outside of the group), the expected number of cases of MERS-CoV in Hajj pilgrims ranged from 1 to 5, dependent on the average number of daily contacts.

4. DISCUSSION

Using a conservative model, we have shown that based on available data, at least some cases of MERS-CoV should have been associated with the 2012 and 2013 Hajj, even if only one infected case were present. The fact that no such cases were reported is puzzling.

A wide range of parameters were considered in the analysis due to the lack of available estimates on the actual transmission probability of the virus, resulting in a wide range of possible undetected cases. Furthermore, our analysis is conservative, as it used only a single index case and one generation of cases, and restricted Hajj contacts for the five days of the obligatory rituals and travel between Mecca, Mina, Arafah, and Medina. It is likely that more than one case may have been present, and that pilgrims stayed longer in Saudi Arabia, remaining in close contact with travel groups and other pilgrims, such as while visiting mosques. With the risk of transmission and subsequent importation continuing during this period, our results would underestimate the risk of transmission.

The key question remaining is: What is the source of ongoing infection that has sustained MERS-CoV for over 25 months in the human population and yet not resulted in an epidemic or even a few cases during either the 2012 or 2013 Hajj? The observed pattern of infections could be explained by several scenarios. One scenario is a predominance of sporadic human cases resulting from direct exposure to a nonhuman source (with speculation being camels) with minimal potential for human-to-human transmission. While camels have been confirmed hosts of the virus, the mode of transmission from camels to humans remains unknown. Genetic sequencing of numerous MERS-CoV isolates suggests multiple introductions to humans from a zoonotic source; however, unrecognized sustained human-to-human transmission cannot be ruled out.(36,37) At this point, no consistent pattern of zoonotic exposure has been found in human cases of MERS-CoV, although ongoing testing of plausible zoonotic and environmental sources for infection will help in identifying any source of sporadic, ongoing infection.

Another explanation is sustained human-to-human transmission, masked by unreported, mild, or undetected infections. Undetected mild cases have been posited as a factor in the apparent decrease in the case fatality rate over time in a model estimating a 940 (95%CI 290–2,200) symptomatic cases with 62% undetected.(3) However, the results from our first analysis expose the possibility that only a few undetected cases could have allowed MERS-CoV to be sustained in the population over a three-month period solely via human-to-human transmission. While there is some evidence of human-to-human transmission, subclinical or mild infection has only been documented in those associated with family clusters, and only detected during extensive contact tracing, which does not support the presence of large numbers of undetected cases. Furthermore, large-scale nasopharyngeal sampling of Hajj pilgrims(38) and a serological survey of blood donors and abattoir workers(33) failed to identify nasal carriage or serological evidence of widespread infections in the population. Diagnostic serology and contact investigation of close contacts is important to determine asymptomatic or mild infection. The need for further serological surveys or other surveillance in affected areas to determine whether a large burden of disease has gone undetected is also necessary. Finally, it is possible that we are experiencing an early-stage epidemic caused by a still evolving virus that is adapting over time to become more transmissible; however, preliminary reports of genetic sequencing suggest that this does not appear to be the case.(45)

There are currently a number of uncertainties around the MERS-CoV. The occurrence of a significant mass gathering such as the 2012 and 2013 Hajj and 2012 and 2013 Umrah in the midst of the emergence of this new disease without any obvious epidemic raises questions about the epidemiology of this disease. With an unknown transmission pattern, it is possible that the MERS-CoV could result in superspreading events, substantially altering the current epidemiology, as occurred with SARS.

In summary, MERS-CoV is a major public health concern because it is not fully understood, yet persists in a region of the world where significant mass gatherings occur, and which is a major global transport hub.(46) Our study explores a variety of possible scenarios to explain the epidemiology of MERS, and highlights the confounding nature of this virus. The combination of a sporadic source(s) and some human-to-human transmission best fits the available facts; however, most cases lack a clear history of zoonotic exposure. The number of sporadic introductions into the population and extent to which sustained human-to-human transmission persists in the population remains uncertain. Our study raises further questions about the unusual and yet unexplained epidemiology of MERS-CoV, which is very different from any other emerging infection in recent history, and should be further explored as a matter of public health urgency.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

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