

Modeling the spread of Middle East respiratory syndrome coronavirus in Saudi Arabia

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Abstract

Middle East respiratory syndrome coronavirus has been persistent in the Middle East region since 2012. Abundant scientific evidence showed that dromedary camels are the primary host of the virus. Majority of human cases (i.e., 75% or 88%) are due to human-to-human transmission, while the others are due to camel-to-human transmission. Mathematical modeling of Middle East respiratory syndrome coronavirus camel-to-camel transmission was lacking. Using the plug-and-play likelihood-based inference framework, we fitted a susceptible-exposed-infectious-recovered-susceptible model of camels to the reported human cases with a constant proportion of human cases from camels (i.e., either 25% or 12%). We considered two scenarios: (i) the transmission rate among camels is time-varying with a constant spill-over rate from camels to human or (ii) the spill-over rate is time-varying with a constant transmission rate among camels. Our estimated loss-of-immunity rate and prevalence of Middle East respiratory syndrome coronavirus infections among camels largely matched with previous serological or virological studies, shedding light on this issue. We recommended including dromedary camels in animal surveillance and control of Middle East respiratory syndrome coronavirus in Saudi Arabia which could help reduce their sporadic introductions to humans.

Keywords

Mathematical modeling, iterated filtering, Middle East respiratory syndrome

I Introduction

Since the first human case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, identified in Jeddah, Saudi Arabia in September 2012, 2040 laboratory-confirmed cases, including 712 deaths, have been reported in 27 countries as of 12 July 2017.¹ The virus circulated in the Arabian Peninsula, particularly in Saudi Arabia. In May 2015, the Republic of Korea reported the largest outbreak outside the Middle East region.

Many external factors could possibly impact the transmission of MERS-CoV among camels and human. In particular, Hajj and Umrah are two annual religious festivals that attract more than 10 million pilgrims from 184 countries to Saudi Arabia. Hajj is considered a major pilgrimage and involves mass gathering that lasts for six days during the 12th month of the Islamic calendar each year, whereas Umrah, a minor pilgrimage which could be highly individualized, is made mostly during Ramadan, a period of 29 to 30 days during the 9th month of the Islamic calendar.² Several studies have demonstrated that these mass gatherings, which attracted pilgrims worldwide, were potential for transmission of infectious diseases.³ Lessler et al.⁴ estimated the potential incidence of MERS-CoV among pilgrims attending Hajj in Saudi Arabia in 2014 to be 6.2, 11.7, and 47.6 pilgrims under the expected, high, and very high incidence scenarios, respectively. Furthermore, Poletto et al.⁵ suggested that population movement and human mixing, which were common in Hajj and Umrah, played an important role in MERS-CoV transmission. Besides population movement and human mixing during religious events, camel

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racing, closing and reopening of camel markets, as well as climatic factors could impact on the transmission of MERS-CoV among camels, spill-over from camels to human and among human.

Reproduction number (\mathcal{R}_0), defined as the average number of cases generated by a typical case, quantifies the intensity of transmission.⁶ Past research showed substantial variations on the estimate of reproduction number on MERS-CoV epidemic, depending on a number of factors: the specific location (i.e., Middle East region or Republic of Korea), the time period considered, mode of transmission, and the choice of mathematical modeling techniques.^{5,7–11}

Chowell et al.⁹ developed a dynamic transmission model that distinguished between the different routes of MERS-CoV transmission. They found that zoonotic transmission was much more effective than human-to-human transmission, with their \mathcal{R}_0 being 0.84 and 0.36, respectively. Breban et al.¹¹ used Bayesian analysis to estimate the pandemic risk of MERS-CoV. \mathcal{R}_0 generated for human-to-human transmission under the most pessimistic scenario and the most optimistic scenario were 0.69 and 0.60, respectively. Their study also highlighted the importance of reducing the rate of zoonotic introductions to the human populations. Poletto et al.⁵ used a novel maximum likelihood approach to jointly estimate \mathcal{R}_0 and the rate of sporadic introduction of MERS-CoV in the Middle East region. They found that \mathcal{R}_0 was 0.50 and the rate of sporadic introduction was 0.28 case per day. More recently, Poletto et al.¹⁰ used a stochastic modeling approach combined with the analysis of imported cases out of the Middle East region. Their model, which assumed partial information on transmission scenario, was a much better fit than the model that assumed complete information on transmission. Their combined modeling approach was able to show that about 75% of the MERS-CoV cases were human-to-human transmission. In other words, primary human cases that are acquired via camels or camel-related products, accounted for 25% of all human cases. Cauchemez et al.¹² developed a comprehensive statistical framework to analyze the transmission patterns of MERS-CoV among human in Saudi Arabia between January 2013 and July 2014. They found that the proportion of human cases from the reservoir was 12% (95% CI: 9%, 15%), and they also noted that the ratio could be 17% (95% CI: 13%, 20%) if only restricted to passive surveillance cases only.¹² Kucharski and Althaus⁷ modeled on MERS-CoV transmission in South Korea. Their study showed substantial over-dispersion in transmission, which indicated there was a potential for superspreading of MERS-CoV. Superspreading cases are primary cases which infect disproportionately more secondary contacts than other primary cases of the same disease. Hsieh⁸ studied the South Korean MERS-CoV outbreak using a Richard's model and found that the turning point, which is the peak timing of an epidemic, took place at 23 to 24 days after the onset of the index case. The estimated \mathcal{R}_0 ranged between 7.0 and 19.3. All of these modeling studies on MERS-CoV had primarily focused on human cases.

In a review article by Zumla et al.,¹³ it was pointed out that camel-to-human transmission could be due to indirect exposure, e.g., patients might be exposed to MERS-CoV virus via consumption of unpasteurized camel milk, a practice which is not uncommon in Saudi Arabia. In a sero-prevalence study of MERS-CoV by Muller et al.,¹⁴ the percentages of MERS-CoV-antibody positive in the general population, camel shepherds, and slaughterhouse workers were found to be 0.15%, 2.3%, and 3.6%, respectively. Sero-positive rates exceeding 74%, which indicates previous infections, were found among camels in Saudi Arabia and its neighboring countries. The virus isolation rate was also high among camels, exceeding 7% but they vary across localities and are higher among juvenile camels.^{15–20} Re-infections of MERS-CoV among camels were also identified.^{21,22}

In this work, we fit the weekly primary human cases of MERS-CoV with a susceptible-exposed-infectious-recovered-susceptible (SEIRS) model for the dromedary camel population, with a constant proportion of primary human cases from camels (i.e., either 25% or 12%). We considered two scenarios: (i) the transmission rate among camels is time-varying while the spill-over rate is constant; (ii) the spill-over rate is time-varying while the transmission rate is constant. Our aim is to find out whether simple epidemic models with largely biologically plausible parameters can simulate the epidemics of MERS-CoV among camels. If yes, our objectives are to answer the followings: (i) How prevalent is the MERS-CoV infection among camels? (ii) How fast does the immunity decay among camels? (iii) Do these estimates match with those of earlier serological and virological studies?

2 Methods

2.1 Data

We obtained weekly MERS-CoV cases from the EMPRES-i Global Animal Disease Information System.²³ Monthly percentages of MERS-CoV-infected camels from May 2014 to April 2015 in Saudi Arabia are obtained from Sabir et al.²⁴

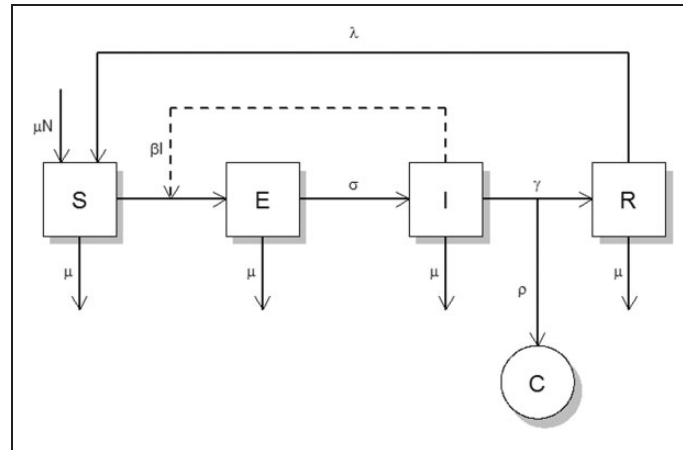


Figure 1. SEIRS model structure.

2.2 Mathematical Modeling

Our mathematical model is an SEIRS framework for camel-to-camel transmission. The model structure is depicted in Figure 1. Here, S, E, I, and R represent the numbers of susceptible, exposed, infectious, and recovered, and C represents the weekly laboratory-based human confirmations. The total population size of dromedary camels, $N = S + E + I + R$, is assumed to be constant at 270,000^{25,26} and the study period went from 1 January 2014 to 31 May 2016.

The maximum lifespan of dromedary camels in captivity could reach 28.4 years.²⁷ A number of studies showed that calves that are younger than two years old with primary infections were more likely play a stronger epidemiological role in MERS-CoV transmission compared to older camels that are two to four years old. This is because infected calves have frequent viral shedding and demonstrate a lower rate of seroconversion than older camels.^{28–33} Furthermore, a more recent study by Sabir et al.²⁴ found that the evolution of MERS-CoV has led to diverse lineages; they suggested that dromedary camels hosted this recombination event. Thus, we suspect the duration of immunity protection induced by MERS-CoV infection could last for many years. The infectious period for camels was in days,³⁰ and we assume a latent period of two days and an infectious period of four days.

We focused on weekly human cases in Saudi Arabia from 1 January 2014 to 31 May 2016. In our model (Figure 1), ρ is the spill-over rate between camel cases and primary human cases. We assume that the primary human cases are 1/4 of all human cases in any week, and we consider this ratio to be 12% as shown in the Supplementary Materials. Thus we convert the reported weekly overall human cases to primary human cases by multiplying 1/4 and round all numbers up to the next integer. Thus, we assume each MERS-CoV camel case leads to roughly 4ρ human cases (i.e., both primary and secondary cases). The assumption of 1/4 is due to the observation that 25% of human cases are likely primary cases. A minor change on this primary case ratio (e.g., from 1/4 \rightarrow 1/2) will change the estimate from $\rho \rightarrow \tilde{\rho}$, but this will keep their product roughly constant, i.e., $4\rho = 2\tilde{\rho}$. Also, it will have a minor impact on the overall fitting and other parameter estimates. However, if the primary case ratio is too small, (e.g., 1/4 \rightarrow 1/10), the estimated primary human cases will become 1 for almost every week due to data transformation, thus we will lose the temporal pattern in the original data. In that case, we need to seriously consider modeling for the human-to-human transmission. In our data, the primary case ratio is not too small, the temporal patterns are largely kept. Human-to-human transmission is limited to close contacts within a hospital ward or a household setting,³⁴ all of which justify our simple transformation.

The model is as follows

$$\begin{aligned}
 \dot{S} &= \mu N + \lambda R - \beta(t)SI - \mu S \\
 \dot{E} &= \beta(t)SI - \sigma E - \mu E \\
 \dot{I} &= \sigma E - \gamma I - \mu I \\
 \dot{R} &= \gamma I - \lambda R - \mu R
 \end{aligned} \tag{1}$$

where $\beta(t)$ is the transmission rate, μ are the natural death and birth rates, N is the population size of camels, and σ and γ are rates at which infected camels change status from exposed to infectious or from infectious to recovered. Finally, λ is the rate at which recovered camels lose immunity protection due to multiple factors, such as evolution of the virus,^{24,35} natural loss-of-immunity,^{24,35} imports of susceptible juvenile camels, and exports or consumption of recovered adult camels.³⁶ Susceptible camels could also be exported and consumed for meat. We assumed that the replenishment of susceptible camels to be immediate, i.e., the export and consumption of susceptible camels will cancel out with the import of them, and these terms will not appear in the model equations. We also assumed that there is no export or consumption of infectious camels, which is acceptable if the prevalence is less than 10% during the study period.

Thus, the model simulated weekly number of primary human cases due to spill-over are

$$Z_i = \int_{\text{week } i} \rho \gamma I dt \quad (2)$$

where I is the number of MERS-CoV camel cases at any time. We denoted C_i as the observed number of primary human cases in i th week, and we assume it follows Negative-Binomial (NB) distribution (R version 2.15.2).

$$C_i \sim \text{NB}(\text{mean} = Z_i, \text{variance} = Z_i(1 + \tau Z_i)) \quad (3)$$

where τ is an over-dispersion parameter which will be estimated. When $\tau = 0$, the NB distribution is reduced to Poisson distribution.

The log likelihood function is

$$l(\theta) = \sum_{i=1}^n \log f(C_i | C_{1:i-1}, \theta) \quad (4)$$

where θ is the set of unknown parameters and $f(C_i | C_{1:i-1}, \theta)$ are the conditional densities for C_i given $C_{1:i-1}$, which will be numerically calculated via Sequential Monte Carlo.³⁷

We use Partially Observed Markov Process (POMP) iterated filtering method^{38–42} within a plug-and-play likelihood-based inference framework³⁷ to generate the maximum likelihood estimates for θ (R Package ‘pomp’ is available in literature⁴³). A tool for maximum likelihood inference on partially observed dynamical system is the iterated filtering algorithm. For parameter space exploration, stochastic perturbations to the unknown parameters are introduced. Sequential Monte Carlo, i.e., the particle filter, is applied to the extended model and this will result in selection of parameter values that are more consistent with the data. If these procedures are well constructed, then iterated filtering with successively diminished perturbations will result in the convergence of the maximum likelihood estimate. This approach is non-trivial. It is described in more detail in the Supplementary Materials, technical documentation of R package⁴³ and Wikipedia.⁴⁴ Infectious disease modeling studies such as Ebola, cholera, malaria, influenza, pertussis, HIV, measles, and polio virus have used this method.⁴⁴ The merits of this package are fivefold: (i) Only model simulation is required to compute the likelihood, with only a few lines of C programming codes that describes the model equations. (ii) It can be implemented in the R software package which is freely available, and where C programming codes can be executed. (iii) Hidden state variables are calculated and are available in the output. (iv) One can assume a parameter to be time-dependent (such as a cubic-spline function of time) and then estimate the flexibility. Flexibility is reflected by the number of nodes, or degrees of freedom, in a time-dependent cubic spline function. If the number of nodes is very large, then the parameters represented by the spline function could change very rapidly over time, or vice versa. This is an advancement compared to previous models where constant parameters (or a particular function, such as an exponential function) were frequently assumed. (v) The POMP package can be run on high performance workstation in a parallel or a serial manner, which makes large-scale modeling selection feasible. POMP is described in more detail in Supplementary Material S1.

Bayesian information criterion (BIC)⁴⁵ is used for assessing the performance of different models

$$BIC = -2l(\hat{\theta}) + N_p \ln N_d \quad (5)$$

where N_d denotes the number of data points and N_p denotes the number of free parameters. We use BIC rather than Akaike Information Criterion because the former generally penalizes free parameters more strongly.

We studied the following modeling scenarios: (i) we assumed only transmission rate is time-dependent and the flexibility is determined by BIC; (ii) we assumed only transmission rate is time-dependent without restriction on the flexibility; and (iii) we assumed only the spill-over rate is time-dependent and the flexibility is determined by BIC.

3 Results

Figure 2 shows the spatio-temporal patterns of MERS-CoV overall human cases in Saudi Arabia and worldwide, monthly percentages of MERS-CoV infectious camels in Saudi Arabia,²⁴ noting Hajj and Ramadan periods. The top panel shows the distribution of confirmed cases of MERS-CoV infection worldwide, which are mostly concentrated in the Middle East, followed by the Republic of Korea, and have spread to 27 countries. The bottom panel shows the temporal patterns of MERS-CoV human cases and percentages of MERS-CoV camels cases.

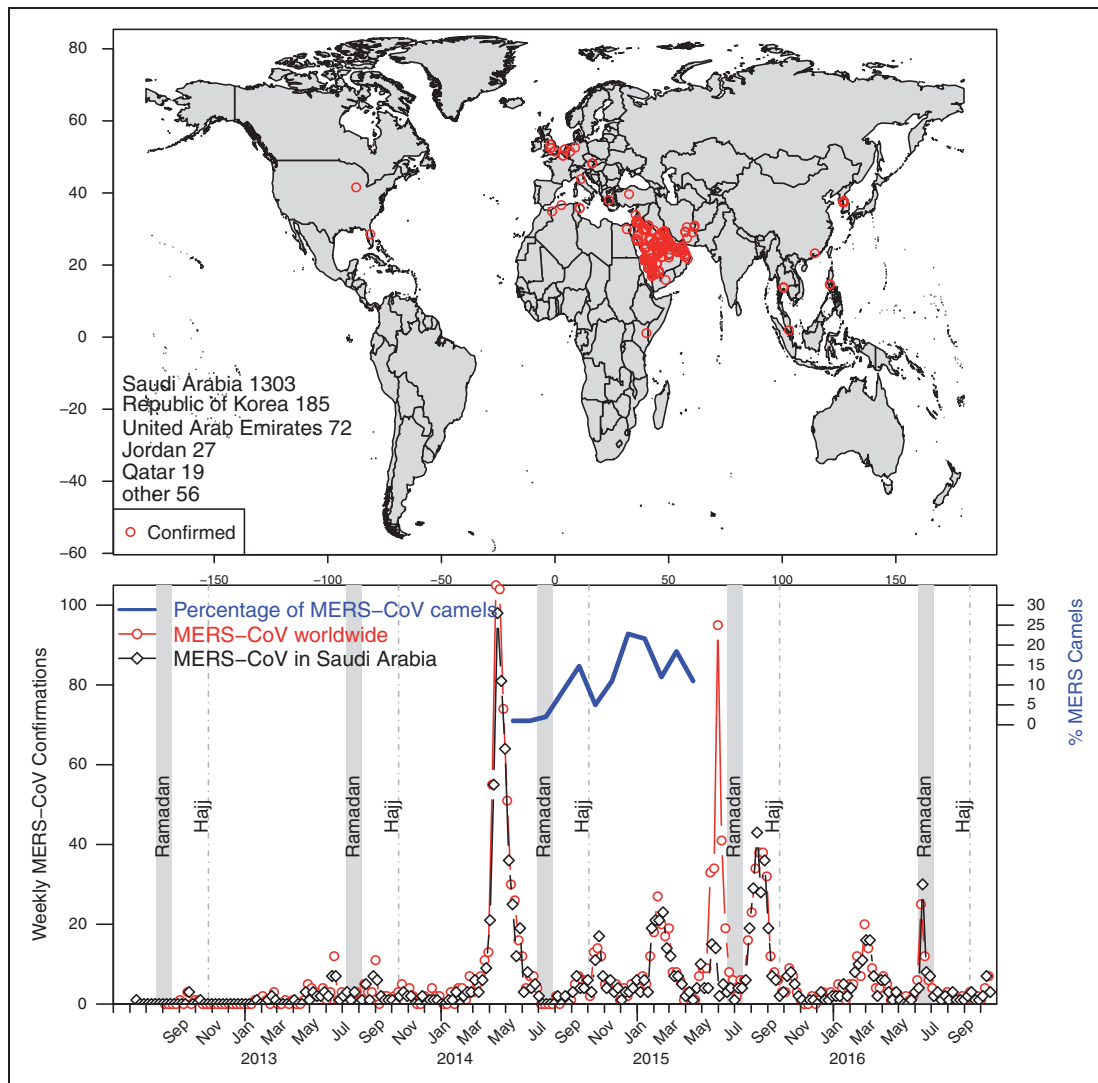


Figure 2. Spatio-temporal patterns of MERS-CoV human cases and percentage of MERS-CoV camels. The top panel summarizes the cumulative global cases from September 2012 to May 2016. The bottom panel shows the weekly confirmed cases of MERS-CoV human cases worldwide (red lines with circles) and in Saudi Arabia only (black lines with diamonds). Bold black curve shows monthly percentage of MERS-CoV infectious camels during May 2014 to April 2015. There were three waves in the MERS-CoV camels which were followed by three waves in the weekly human MERS-CoV cases. We also showed the period of religious events, Hajj (light grey vertical dash line) and Ramadan (shaded bars). The map was made with R programming language, and the country borders were downloaded from Sandvik B., World Borders Dataset, <http://thematicmapping.org> (2009).

Major MERS-CoV waves peaked in May 2014, February 2015, June 2015 (South Korea), August 2015, and March 2016. Most of them occurred mainly in Saudi Arabia, except that the third wave occurred mainly in the Republic of Korea. The percentage of MERS-CoV infectious camels showed three waves in a year (May 2014 to April 2015) which were followed by three waves in the weekly human MERS-CoV confirmations. This phenomenon suggests that the waves in the human cases could be driven by the epidemic waves of infections among camels.

The transmission rate, β , can be affected by climatic factors, as well as closing and reopening of markets during general holidays or religious festivals. Thus, we used a cubic spline to model the transmission rate. We uniformly distributed n_β nodes over the time period, where n_β is to be estimated. The cubic spline function was a smooth function that passed through the n_β nodes. We compared models with different number of nodes and found the best model which attained the smallest BIC. We fixed the following parameters within biologically reasonable ranges: the lifespan of camels at 14 to 20 years, the latent period at 2 days, and the infectious period at 4 days. The results are shown in Figure 3. Figure 3(a) shows the case of the life span μ^{-1} of 14 years, while Figure 3(b) shows that of 20 years. The inset panels on the left show the profile of the model BIC as a function of n_β . In both cases, the smallest BIC was attained when n_β is 10. Therefore, in the main panels, we display the model fitting results with n_β is 10. The inset panels on the right show the profile of Maximum Log-likelihood (MLL) as a function of the spill-over rate ρ . In both simulations, the models were able to capture the four major epidemic waves out of six waves during the period. We found that the duration of immunity is about 1 year in both cases, or more specifically, 0.86 year (Figure 3(a)) and 1.14 year (Figure 3(b)). We found that the spill-over rate was about 0.00053 (95% confidence interval (CI): 0.00042, 0.0028) and 0.00065 (95% CI: 0.00044, 0.00268), respectively, which corresponded to the prevalence of MERS-CoV infection among camels to be as high as 9%. This largely matched with the observed prevalence of 11%.²⁴ A smaller spill-over rate implies a higher prevalence. Through computing the models' profile MLL as a function of λ^{-1} , we estimated the 95% CI of the duration of immunity to be (0.34 year, 5.82 years) (Figure 3(a)) and (0.35 year, 7.09 years) (Figure 3(b)). The estimated mean \mathcal{R}_0^{camels} were 2.71 and 3.34.

The above results used standard model selection approaches to achieve the optimal flexibility in the transmission rate. Recall that the transmission rate could be affected by climatic factors and camels-related activities, thus the real flexibility in the transmission rate could be higher than our model estimate. If we choose a large n_β , such as 17 or 19, we could achieve improved fitting as shown in Figure 4. Figure 4(a) shows the fitting results with $n_\beta = 17$ and Figure 4(b) shows that of $n_\beta = 19$. In the inset panel, we show the model's profile MLL as a function of λ^{-1} . The MLL estimates of λ^{-1} are 0.62 year (95% CI: 0.27 year, 3.07 years) and

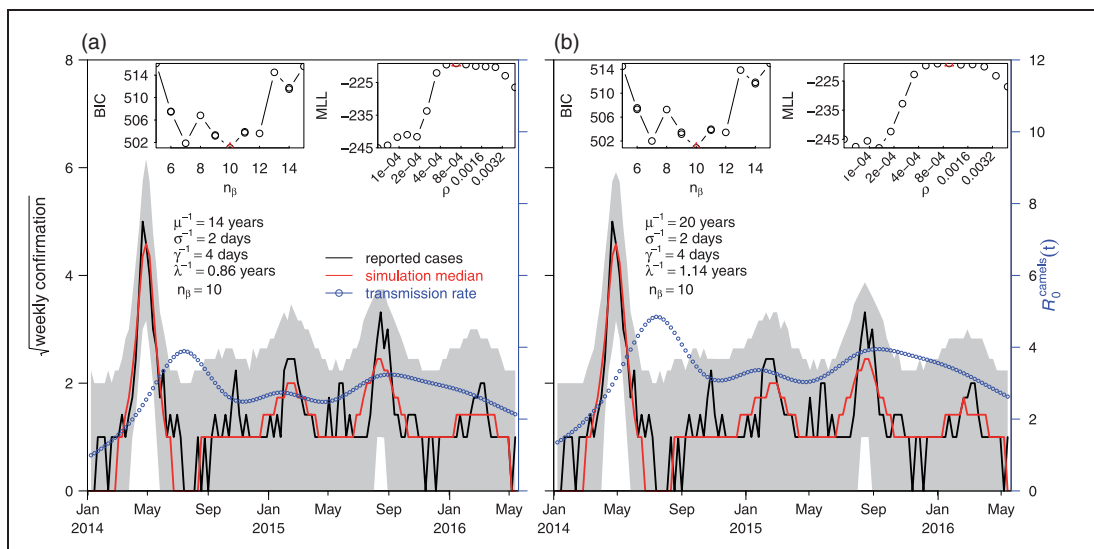


Figure 3. Model simulations versus observed MERS-CoV spill-over cases. Thin black curve represents reported spill-over cases, bold red curve represents model generated median of 1000 simulations, shaded regions represent the 95% range of simulations, and blue curve (with circles) represents the transmission rate (in units of \mathcal{R}_0). Inset panels on the left show the profile of BIC as a function of the number of nodes in the transmission rate. Inset panels on the right show the profile of MLL as a function of the spill-over rate ρ , while fixing $n_\beta = 10$.

0.44 year (95% CI: 0.08 year, 3.23 years). Again, we found that the duration of immunity protection was short. More importantly, the estimated maximum prevalence of MERS-CoV among camels was about 15% which is consistent with a previous study.²⁴ The estimated spill-over rates were about 0.00039 and 0.00033 respectively, which were lower than those as shown in Figure 3. The estimated mean \mathcal{R}_0^{camels} were 3.31 and 2.71.

So far, we have limited knowledge about the spill-over rate ρ , and we have assumed it to be constant. It was possible that both transmission rate and spill-over rate could vary over time. However, if we assume both to be flexible and then modeled them as cubic spline functions, the model would be too complex. Alternatively, we could

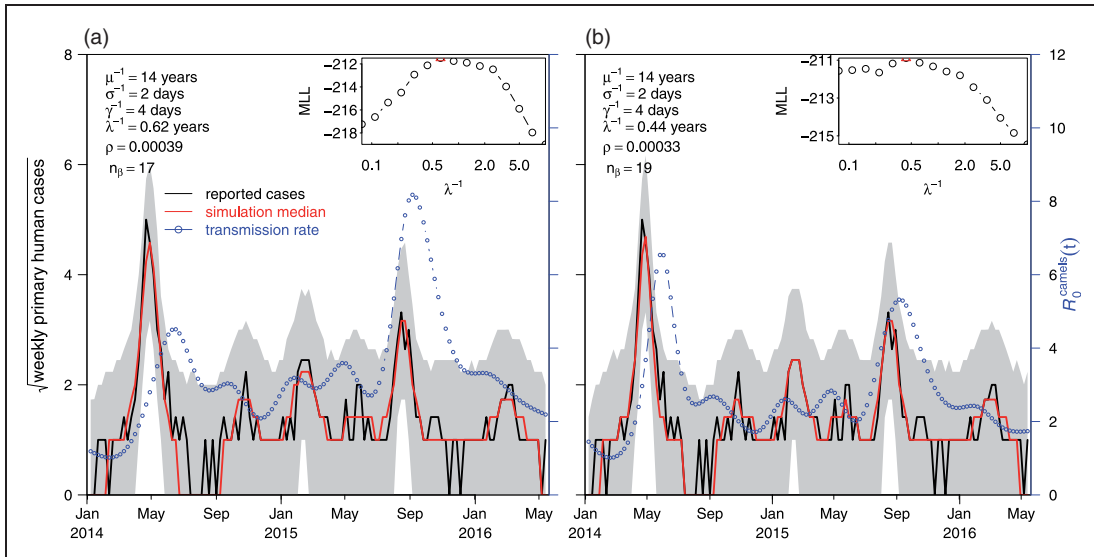


Figure 4. Model simulations versus observed MERS-CoV spill-over cases. Thin black curve represents reported spill-over cases, bold red curve represents model generated median of 1000 simulations, shaded regions represent the 95% range of simulations, and blue curve (with circles) represents the transmission rate (in units of \mathcal{R}_0). Inset panels show the profile of maximum log likelihood as a function of the duration of immunity protection.

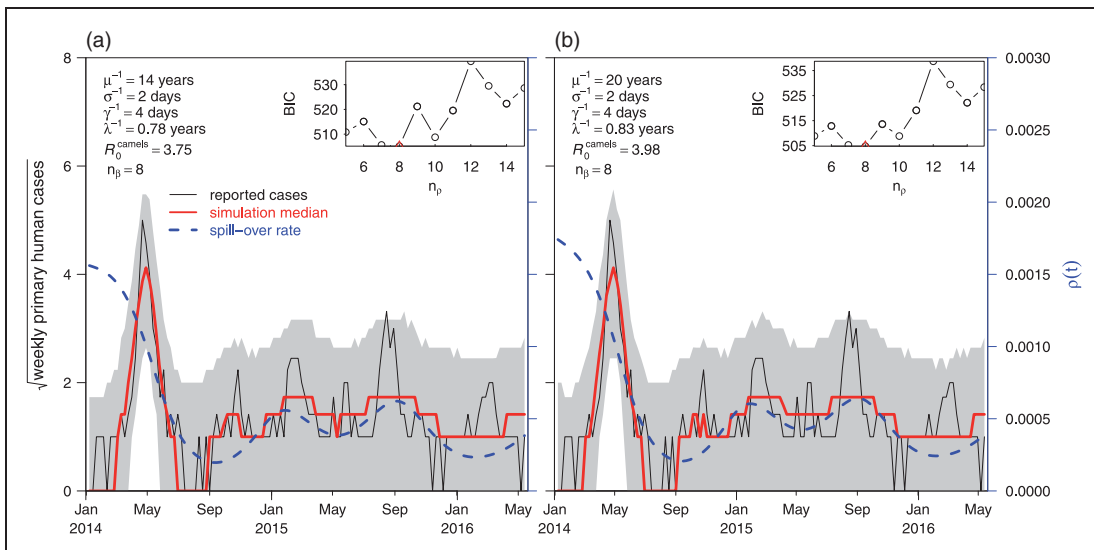


Figure 5. Model simulations versus observed MERS-CoV spill-over cases. Thin black curve represents reported spill-over cases, bold red curve represents model generated median of 1000 simulations, shaded regions represent the 95% range of simulations, and dashed blue curve represents the spill-over rate. Inset panels show the profile of BIC as a function of the number of nodes in the spill-over rate.

Table 1. Summary of parameter settings and estimates in Figures 3 to 5.

Parameter	Figure 3(a)	Figure 3(b)	Figure 4(a)	Figure 4(b)	Figure 5(a)	Figure 5(b)
μ^{-1} (years)	14	20	14	14	14	20
λ^{-1} (years)	0.86	1.14	0.62	0.44	0.78	0.83
n_β	10	10	17	19	8	8
$\langle \beta \rangle$	247.01	305.05	301.95	247.65	342.55	363.63
$\mathcal{R}_0^{\text{camels}}$	2.707	3.343	3.309	2.714	3.754	3.985
$\langle \rho \rangle$	0.000531	0.000653	0.000387	0.000331	0.000542	0.000576
T	0.003375	0.003784	0.002881	0.004018	0.007507	0.007338
$S.0$	0.79508	0.593464	0.971608	0.980595	0.196026	0.184083
$E.0$	0.003552	0.002307	0.001719	0.001047	0.000521	0.000499
$I.0$	0.003552	0.002307	0.001719	0.001047	0.000521	0.000499
$R.0$	0.197815	0.401921	0.024954	0.017312	0.802933	0.814919
MLL	-219.18	-219.1	-211.49	-210.89	-226.06	-225.89
BIC	501.03	500.86	514.57	523	505.14	504.81

BIC: Bayesian information criterion.

Note: The mean basic reproductive number is defined as $\mathcal{R}_0 = \langle \beta \rangle / \gamma$, where $\langle \cdot \rangle$ is the time average. $S.0$, $E.0$, $I.0$, and $R.0$ are initial conditions. In Figures 3 and 4, ρ is assumed constant and $\beta(t)$ is time-dependent, whereas these are reverse in Figure 5. Camel population size $N = 270,000$. $\sigma^{-1} = 2$ days. $\gamma^{-1} = 4$ days.

assume the transmission rate to be constant and then allowed the spill-over rate to vary. We repeated the fitting as shown in Figure 3, but assumed constant β and time-varying ρ . We showed the results in Figure 5. The BIC is worsened by 4.13, and the difference is marginally significant. The estimated λ^{-1} is still short, and the results were consistent. The prevalence of MERS-CoV among camels is now lower than 0.04. Thus we rejected this scenario. In reality, the observed patterns in the spill-over cases could be due to variations of other factors, and the estimated spill-over rate was about 0.00053 and 0.00056, which were comparable to that in Figure 3. The estimated $\mathcal{R}_0^{\text{camels}}$ were 3.67 and 3.88 (Table 1).

4 Discussion and Conclusions

We used a mechanistic model and likelihood-based inference framework to investigate the transmission pattern of MERS-CoV among dromedary camels in Saudi Arabia from 1 January 2014 to 31 May 2016. To our knowledge, our methodology in studying MERS-CoV is novel. Previous mathematical modeling studies on MERS-CoV had primarily focused on human-to-human transmission.^{5,7-12} Our work was largely motivated by the serological findings in Sabir et al.²⁴ which showed that there were high and fluctuating prevalence of MERS-CoV among camels. We noted that the fluctuation of the MERS-CoV camels matched with the waves in the weekly human confirmation, although this comparison was done for only one year (May 2014 to April 2015).²⁴ For the best-fitting model, the changes in transmission rate compared to the other models were not very dramatic. We considered three modeling scenarios. We found short immunity duration or high replenishment rate of camels. This is in-line with previous serologically studies. For instance, Meyer et al.³⁵ found that serum from 6 of 11 calves had completely lost their neutralizing activity after 56 months. We also found high prevalence of MERS-CoV infections among camels which matches with the results from previous virological studies. Finally, $\mathcal{R}_0^{\text{camels}} \approx 3$ or 4 is biologically reasonable and in-line with that of severe acute respiratory syndrome, which also belonged to the same virus family as MERS-CoV.

Many external factors could impact the transmission of MERS-CoV among camels, from camels to human, and among humans. The transmission rate of MERS-CoV could vary over time, so did the spill-over rate from camels to human, and transmission rate among human. In this work, we attempt to address the transmission of MERS-CoV among camels and also from camels to human (spill-over). In the future, we could include human-to-human transmission into our framework. The reason we did not include this part in current work is due to lack of detailed data. Since the \mathcal{R}_0 among human is substantially less than 1, the transmission among human was limited in hospital setting and in household transmission, we believe that the transmission among camels played the key role to form the observed temporal pattern in human cases.

In the main text, we assume that the infection from reservoir was 1/4 because this number was used in WHO reports.³⁴ In the Supplementary Material S2, we show the results when this ratio is 12%.¹² Our main conclusions

largely hold. In particular, we observed high rate of loss-of-immunity (and replenishment of susceptible pools), low spill-over rate (i.e., high prevalence among camels) and reasonable \mathcal{R}_0^{camels} .

We proposed a one-host (camel) model in the main text. In the Supplementary Materials, we extended it into a two-host (i.e., camels and human) model and presented some preliminary findings. These results have led to similar conclusions as in a crude one-host model. We considered possible impact of climatic factors (air temperature and absolute humidity) and showed preliminary analyses in the Supplementary Materials. There were no evident correlation between MERS-CoV outbreaks and the timing of Hajj.

We compared the monthly prevalence of MERS-CoV infections among camels with weekly human cases for a year in Figure 1. The waves in camel cases were followed by the waves in human, which implies that camel cases have led to human cases. Longer surveillance among camels and phylogenetic work are needed to further clarify this issue. Nevertheless, our results will motivate modeling work on the transmission of MERS-CoV among camels. In the Supplementary Materials, we illustrated how a simple two-host model could be realized. Our modeling work could be improved if data on primary and secondary human cases are available. Our framework could be extended to incorporate two time series. We assumed constant camel population size, which could be varying indeed. We expected that our fitting could still be robust if the population size changed mildly during a year or over the study period. The changes in the population size in a susceptible pool can be translated into changes in the transmission rate.⁴⁶ It is challenging but worth trying to model the estimated transmission rate using actual factors such as climate, closing and reopening of markets, holidays, or evolution of the virus and come up with a mechanistic model of these driving forces.

The major strengths of our study are that we had used a simple epidemic model to study the prevalence of MERS-CoV among camels, and that our estimates are biologically reasonable. However, our study was still subject to limitations. First, since current animal health surveillance did not routinely report MERS-CoV cases among dromedary camels, we could only assume that primary human cases were at a ratio to camel cases (i.e., constant or time-varying spill-over rate). These assumptions were appropriate when cases were predominantly zoonotic and that the propensity for MERS-CoV to cross species boundaries did not change over time. In the future, more detailed epidemiological information on human cases could improve the accuracy of estimating weekly primary cases. Animal surveillance and control of MERS-CoV in Saudi Arabia should also target dromedary camels. This could help reduce sporadic introductions to humans. Effective measures to identify, diagnose, and isolate infected dromedary camels were much needed. Preventive measures should be undertaken at the animal/human interface to reduce zoonotic transmission of MERS-CoV.

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Supplementary material

Supplementary material is available for this article online.

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