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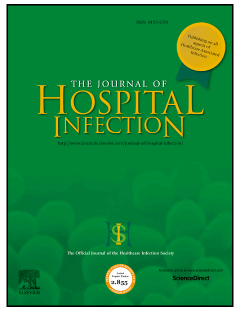

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High reproduction number of Middle East respiratory syndrome coronavirus in nosocomial outbreaks: Mathematical modelling in Saudi Arabia and South Korea

Short title: High reproduction numbers of MERS-CoV

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Keywords: nosocomial infection; basic reproduction number; epidemiology; Middle East respiratory syndrome coronavirus; mathematical modelling; South Korea

Summary

Background: Effective countermeasures against emerging infectious diseases require an understanding of transmission rate and basic reproduction number (R_0). The R_0 for severe acute respiratory syndrome (SARS) is generally considered to be >1, whereas that for Middle East respiratory syndrome (MERS) is considered to be <1. However, this does not explain the large-scale outbreaks of MERS that occurred in Kingdom of Saudi Arabia (KSA) and South Korean hospitals.

Aim: To estimate R_0 in nosocomial outbreaks of MERS.

Methods: R_0 was estimated using the incidence decay with an exponential adjustment model. The KSA and Korean outbreaks were compared using a line listing of MERS cases compiled using publicly available sources. Serial intervals to estimate R_0 were assumed to be 6–8 days. Study parameters (R_0 and countermeasures [*d*]) were estimated by fitting a model to the cumulative incidence epidemic curves using Matlab.

Findings: The estimated R_0 in Korea was 3.9 in the best-fit model, with a serial interval of 6 days. The first outbreak cluster in a Pyeongtaek hospital had an R_0 of 4.04, and the largest outbreak cluster in a Samsung hospital had an R_0 of 5.0. Assuming a 6-day serial interval, the KSA outbreaks in Jeddah and Riyadh had R_0 values of 3.9 and 1.9, respectively.

Conclusion: The R_0 for the nosocomial MERS outbreaks in KSA and South Korea was estimated to be in the range of 2–5, which is significantly higher than the previous estimate of <1. Therefore, more comprehensive countermeasures are needed to address these infections.

Introduction

The emergence of infectious diseases associated with Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and Ebola has created unprecedented public health challenges. These challenges are complicated by the lack of basic epidemiological data, which makes it difficult to predict epidemics. Thus, it is important to quantify actual outbreaks as novel infectious diseases emerge. Disease severity and rate of transmission can be predicted by mathematical models using the basic reproduction number (R_0).[1] For example, R_0 has been extensively used to assess pathogen transmissibility, outbreak severity, and epidemiological control.[2-4]

In previous studies, the R_0 for MERS has ranged from 0.42 to 0.92,[5-8] which suggests that the MERS coronavirus (MERS-CoV) has limited transmissibility. However, these studies typically considered community-acquired MERS infections. In this context, nosocomial infections can exhibit different reproduction numbers, as the transmission routes for community-acquired and nosocomial infections often differ.[9] Recent studies have also examined large healthcare-associated outbreaks of MERS-CoV infection in Jeddah and Riyadh within the Kingdom of Saudi Arabia (KSA). One study reported higher healthcare-acquired R_0 values than those from community-acquired infections when using the incidence decay with exponential adjustment (IDEA) model, which yielded values of 3.5–6.7 in Jeddah and 2.0–2.8 in Riyadh.[10] The IDEA model is simple because it does not consider the population-level immune status, which makes it especially useful for modelling emerging infectious diseases in resource-limited settings.

The MERS outbreak in South Korea was associated with hospital-acquired infections. At that time, the Korea Centre for Disease Control and Prevention (KCDC) assumed that the outbreak had an $R_0<1$. Thus, the initial countermeasures were not sufficiently aggressive to prevent the spread of MERS-CoV infection to other hospitals. Therefore, we used the IDEA model to evaluate and compare the MERS R_0 values from the outbreaks in both the KSA and South Korean hospitals.

Methods

Data source

The KSA data were obtained using a line listing of MERS-CoV cases that was maintained by Andrew Rambaut (updated on 19 August 2015). The line listing was created using data from the KSA Ministry of Health and World Health Organization reports (WHO).[10] Since only 44% of the cases in the KSA listing included the onset date, hospitalization dates or reported dates were used instead. The Korean data were obtained from the KCDC. Among the 186 MERS cases, 178 had confirmed onset dates. The eight cases with unknown dates of onset were assigned dates based on those of laboratory confirmations. All cases in the KSA and Korea were confirmed based on laboratory findings. Study parameters (R_0 and countermeasures [d]) were estimated by fitting a model to the cumulative incidence epidemic curves using Matlab software (Mathworks, Natick, MA, USA).

The data were narrowed down to only the hospital infection cases. Cases with unknown transmissions were considered to be hospital infections if a) the patient was in contact with a healthcare worker and/or hospitalized patients, or b) the patient was a healthcare worker. Cases were excluded if they could not be verified as hospital infections (e.g., zoonotic transmission, family contact, or community infection).

Model

We used the IDEA model to estimate the R_0 as reported previously,[11] together with publicly available data. The IDEA model is based on the concept that the number of incident cases (I) in an epidemic generation (t) that can be counted as:

$$I(t) = {R_0}^t. \tag{1}$$

When an outbreak occurs, epidemic control measures can be implemented, which can, in turn, change the R_0. Therefore, the relationship between I and R_0 with countermeasures (d) is defined as follows:

$$I(t) = \left[\frac{R_0}{(1+d)^t}\right]^t. \tag{2}$$

The R_0 and d parameters are estimated by fitting I from model (2) to the observed cumulative incidence data of MERS using the least-squares data-fitting method. Since the IDEA model is parameterized using epidemic generation time, in the present study, incidence case counts were aggregated at serial intervals of 6, 7, and 8 days.[10]

We considered two large outbreaks in each country studied: the outbreaks in Riyadh and Jeddah for the KSA, and those in Pyeongtaek St. Mary's Hospital, and Samsung Seoul Hospital for South Korea. The term *resnorm* is defined as the norm of the residual, which is the squared 2-norm of the residual; it measures the difference between observed data and the fitted value provided by a model. However, since residuals can be positive or negative, a sum of residuals is not a good measure of overall error in the fit. Therefore, a better measure of error is the sum of the squared residuals (E), which is calculated as follows:

$$\mathrm{E} = \sum_i (F(x, x\mathrm{data}_i) - y\mathrm{data}_i)^2. \quad (3)$$

The given input data (xdata), the observed output data, (ydata), and F(x, xdata) are the functions we wanted to fit, where xdata was an epidemic generation, ydata was the observed cumulative incidence data, and F(x, xdata) was equation (2).

Since the generation times and the estimated values differ according to serial interval times, the resnorm changes accordingly. Therefore, to compare the resnorm with the serial interval time, the relative resnorm was defined as follows:

$$\mathrm{E} = \sum_i \frac{(F(x, x\mathrm{data}_i) - y\mathrm{data}_i)^2}{y\mathrm{data}_i}. \quad (4)$$

The IDEA model was fitted to the cumulative South Korean MERS-CoV case data from the onset date of the first case to the onset date of the last case. The outbreak start date was defined as 11 May 2015 because that was the symptom onset date for Patient Zero, who was the index case and caused the outbreak in the Pyeongtaek hospital. MERS patient no. 14 caused the outbreak at the Samsung hospital, and his symptom onset date was 21 May 2015. The last case of the MERS outbreak in South Korea was observed on 4 July 2015. The KSA MERS outbreak model was fitted using the cumulative incidence data from 28 March 2014 to 2 June 2014 in Jeddah and from 20 March 2014 to 29 May 2014 in Riyadh.

Ethical Considerations

All data used in these analyses were de-identified publicly available data obtained from the WHO, the KSA Ministry of Health website, or KCDC datasets. As such, these data were deemed to be exempt from institutional review board assessment.

Results

The KSA outbreaks were relatively large, with 180 cases (over the course of 67 days) in Jeddah and 142 cases (over the course of 71 days) in Riyadh. The Korean outbreaks involved 186 cases (over the course of 55 days), including 36 cases (over the course of 23 days) in the Pyeongtaek hospital, and 91 cases (over the course of 45 days) in the Samsung hospital. Most Korean cases (180) were hospital acquired, with the exception of four cases acquired by household transmission and two cases with unknown modes of transmission. In the KSA, only two cases involved confirmed zoonotic transmission, while a large number of unknown transmissions (Jeddah: 99 cases; Riyadh: 69 cases) and hospital exposures (Jeddah: 80 cases; Riyadh: 70 cases) were observed (Table I).

The IDEA model was fitted to the daily KSA and Korea MERS-CoV case data according to the onset date. Figure 1 displays the cumulative MERS-CoV case data for the 2014 KSA and the 2015 South Korea MERS outbreaks. Patient Zero's symptom-onset date was 11 May 2015; however, he was admitted to the Pyeongtaek hospital on 15 May 2015. Therefore, the outbreak was assumed to start on 15 May 2015 via a simulation of the Pyeongtaek hospital outbreak. The outbreak start date for the Samsung hospital was determined to be 25 May 2015, following the same logic (Figure 1).

Figure 2 shows the results of the 2014 KSA outbreak. Squares (□), circles (○), and asterisks (*) represent data aggregation of the number of cases by serial intervals of 6, 7, and 8 days; the curves represent model fits for best-fit parameters. Our estimated R_0 values for Jeddah and Riyadh were in the range of 3.95–6.68 and 1.92–2.52, respectively, using serial intervals of 6–8 days. The estimated R_0 values for the Korea MERS outbreak were 3.96, 4.91, and 5.95 for serial intervals of 6, 7, and 8 days, respectively (Figure 3). Since most cases were related to hospital-acquired infections, the R_0 for each hospital was also considered. The outbreak in the Samsung hospital was larger than that in the Pyeongtaek hospital (the first Korean outbreak). The Pyeongtaek hospital exhibited best-fit R_0 values of 4.04, 4.23, and 4.39 for serial intervals of 6, 7, and 8 days, respectively, while the Samsung hospital exhibited greater R_0 values of 5.0, 6.8, and 8.11 for serial intervals of 6, 7, and 8 days, respectively. Figure 3 shows that the IDEA model provided well-fitted curves for the cumulative data regarding South Korean MERS symptom-onset dates for all cases.

Although the IDEA model seemed to be appropriate, the original data never precisely fit the model. Therefore, the appropriateness of the model was assessed. Error was evaluated using the relative resnorm to find the best-fit parameters. The results indicated that the best-fit R_0 and serial interval values were 4.9 and 7 days for all cases, 4.39 and 8 days for the Pyeongtaek hospital, and 5.0 and 6 days for the Samsung hospital, respectively. Countermeasures (termed "*d*") increased with each serial interval because the daily effort of countermeasures was aggregated by serial interval.

Discussion

The clusters of MERS-CoV cases in KSA healthcare facilities occurred from late March to late May 2014, while the Korean outbreaks occurred from mid-May to early July in 2015. These hospital-based outbreaks exhibited characteristics different from those of community-based outbreaks (higher R_0 values and case fatality rates).[12, 13]

The estimated R_0 is a basic epidemiological variable that is important for selecting appropriate countermeasure efforts. However, an emerging infectious disease often has an unknown epidemiology, making it difficult to mathematically model. Several methods have been proposed to address this issue, including the IDEA model. The Richards model can also estimate the R_0 using the cumulative daily number of cases and the outbreak turning point (or the peak, t_i).[14] In this context, Hsieh used the Richards model to estimate the R_0 values for the Korean outbreak as 7.0–19.3. Yet, the Richards model does not consider any countermeasures implemented during an outbreak; therefore, it can only be used after an outbreak has peaked.

The present study used the IDEA model to estimate the R_0 values from the MERS outbreaks in the KSA and South Korea. The IDEA model exhibited a good fit: the estimated R_0 values for South Korea were 3.9–8.0, and the best-fit R_0 was 4.9 for a serial interval of 7 days. Conversely, the R_0 values for Riyadh and Jeddah were 1.9–2.5 and 3.9–6.9, respectively, using serial intervals of 6–8 days. Majumder et al.[10] used the IDEA model and estimated very similar R_0 values of 2.0–2.8

for Riyadh and 3.5–6.7 for Jeddah, with serial intervals of 6–8 days. However, the estimated R_0 values from the present study were much higher than the previously reported values of <1 for MERS (the threshold for an epidemic).[15] Regardless, the Korean government assumed that the outbreak had an R_0 value of <1 based on the previous research. The initial criterion for quarantine, therefore, was limited to cases of "close contacts," which were defined as people who were within 2 metres of a MERS patient for ≥1 hour.[16] These quarantines—established using an incorrectly assumed R_0—resulted in more MERS patients and greater hospital-to-hospital transmission.[16]

A serial interval is the interval between successive cases of an infectious disease. This time period depends on the temporal relationship between the infectiousness of the disease, the clinical onset of the source case, and the incubation period of the receiving case.[17] As MERS becomes infectious with the onset of clinical symptoms, the MERS latency period equals the incubation period. Therefore, the shortest serial interval could be the same as the incubation period, and the longest serial interval could be the sum of the incubation period and the maximum duration of infectiousness. During the Korean MERS outbreak, several super-spreading events occurred because the MERS cases were not immediately isolated upon presentation of clinical symptoms.[18] Thus, these cases contacted susceptible individuals for up to 1 week after the onset of their clinical symptoms. However, most MERS cases with laboratory confirmation were isolated immediately after clinical-symptom onset.[19, 20] In this study, since the incubation period was 2–14 days (median: 6 days), the serial interval was slightly longer than the incubation period. The IDEA model with several serial intervals (4–12 days) was used and found that intervals of 6–8 days provided the best fit. For the KSA data, even though the reported date was used instead of the onset date, the R_0 was not affected because aggregated data by serial intervals was used in the analysis.

The IDEA model is limited by the fact that the countermeasures term (*d*) cannot be compared with the *d* of another model. In this context, an increasing *d* in accordance with increasing serial intervals indicates that the countermeasure efforts are increasing. However, the size of *d* cannot be compared between two or more models of different outbreaks. Nevertheless, the strength of the IDEA model is its simplicity because the R_0 value can be estimated using only the cumulative number of cases according to the serial interval.

Conclusions

The estimated R_0 values from the KSA outbreaks (Riyadh and Jeddah) ranged from 1.9 to 6.9, whereas the estimated values from the South Korean outbreaks ranged from 3.9 to 8.0. Based on these findings, it appears that nosocomial MERS-CoV outbreaks in the KSA and South Korea had higher R_0 values than the previously assumed values of <1. Although community-acquired infections are caused by contact, nosocomial infections are caused by a combination of contact and aerosol transmission; therefore, R_0 values for hospital infections can be higher than those for community-acquired infections. Hence, more comprehensive countermeasures are needed to address nosocomial MERS infection and prevent its spread.

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Tables

Table I. Characteristics of selected MERS outbreaks in Saudi Arabia and South Korea

		Saudi Arabia		South Korea		
		Jeddah	Riyadh	Total	Pyeongtaek Hospital	Samsung Hospital
Outbreak	Onset date	28/3/2014	20/3/2014	11/5/2015	15/5/2015	25/5/2015
	Duration (day)	67	71	55	23	45
	No. of cases	180	142	186	36	91
Exposure	Hospital	80[1]	70[1]	180	36	88
	Household			4	0	3
	Zoonotic	1	1	0	0	0
	Unknown	99	69	2	0	0
Status[2]	Healthcare worker	40	8	39	3	15
	Patient			82	20	36
	Family or visitor			63	13	40
	Unknown	140	134	2	0	0
Date[3]	Onset date	75	66	178	36	85
	Hospitalized date	85	79	186	36	91
	Reported date	180	142	186	36	91

[1] Hospital exposure cases included healthcare workers and individuals who were in contact with a healthcare worker or hospitalized patients.

[2] The status of cases when they were exposed to MERS.

[3] The number of cases with information for onset date, hospitalization date, and reported date of MERS.

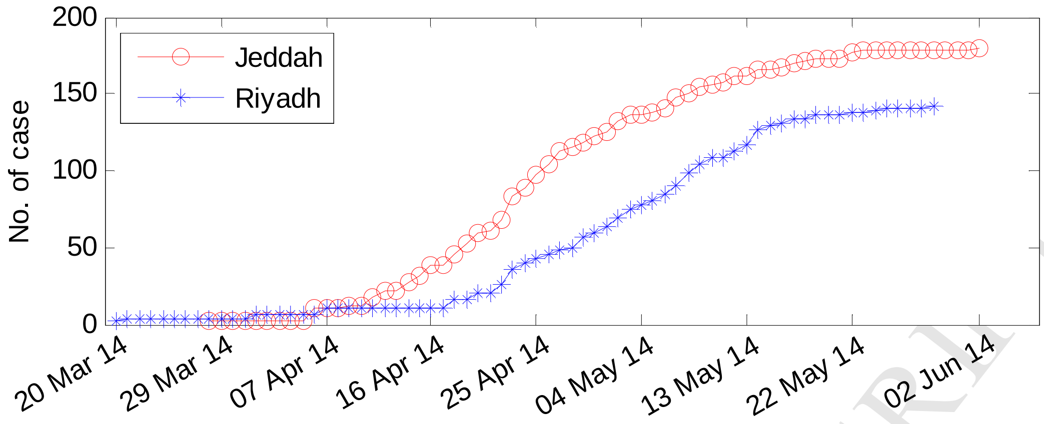
Figures

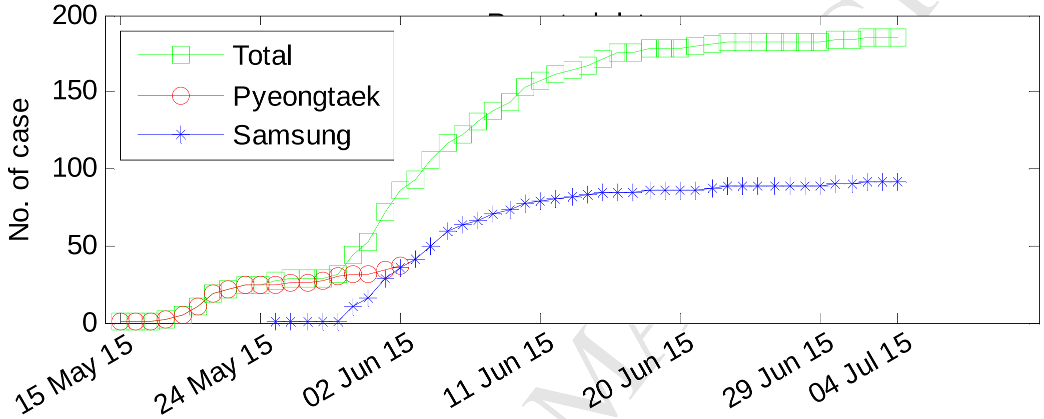
Legends

Figure 1. Epidemic curves of cumulative cases by selected MERS outbreaks in Saudi Arabia and South Korea.

Figure 2. Best-fit R_o by serial intervals of MERS in Jeddah and Riyadh, Saudi Arabia, 2014, using the IDEA model.

Figure 3. Best-fit R_o by serial intervals of MERS in South Korea, 2015, using the IDEA model.





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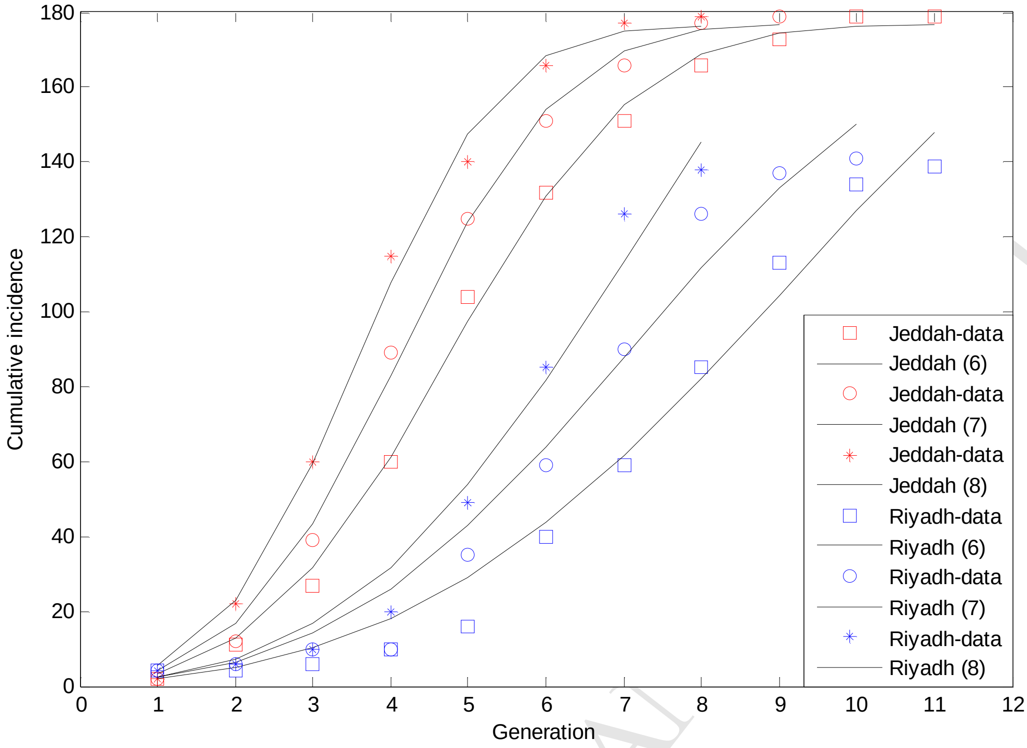
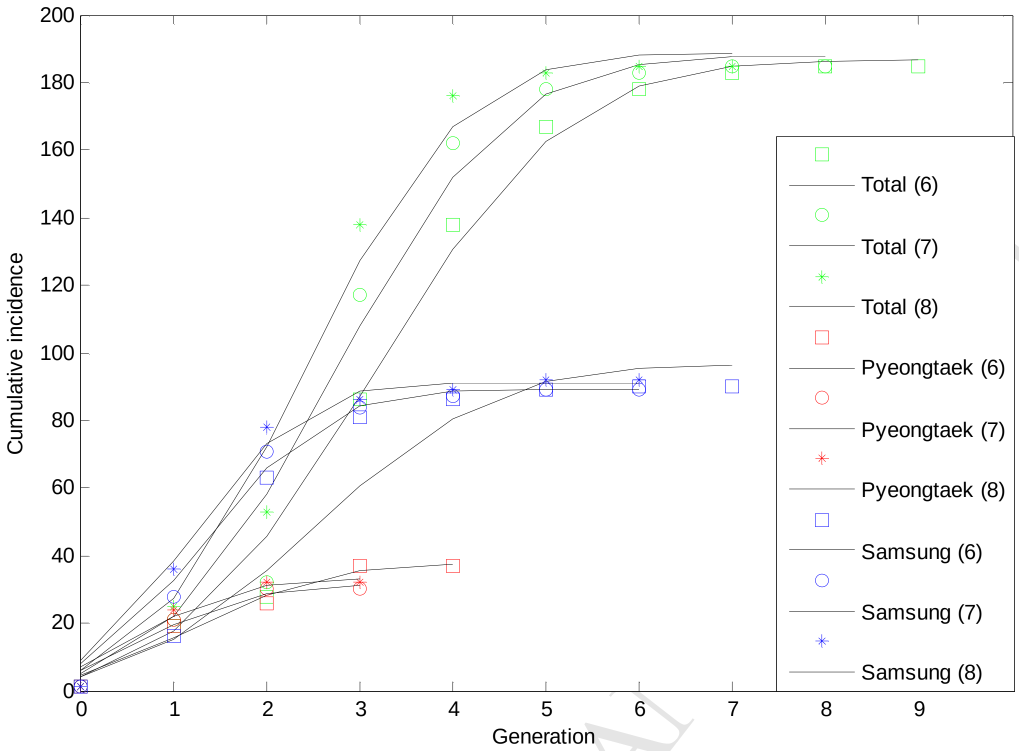


Serial Interval	***R_0***		**Resnorm**	
	Jeddah	Riyadh	Jeddah	Riyadh
6	3.9463	1.9168	2.7971	23.8599
7	5.0505	2.3247	5.6315	32.9805
8	6.6806	2.5252	6.4178	14.3884

Figure 2. Best-fit R_o by serial intervals of MERS in Jeddah and Riyadh, Saudi Arabia, 2014, using the IDEA model.



Serial Interval	R_0			Resnorm		
	Total	Pyeongtaek Hospital	Samsung Hospital	Total	Pyeongtaek Hospital	Samsung Hospital
6	3.9555	4.0426	5.0000	22.6323	14.8974	27.9525
7	4.9125	4.2315	6.8006	40.5951	27.8792	46.7812
8	5.9531	4.3935	8.1151	34.0529	36.2232	64.0210

Figure 3. Best-fit R_o by serial intervals of MERS in South Korea, 2015, using the IDEA model.