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A dynamic compartmental model for the Middle East respiratory syndrome outbreak in the Republic of Korea: A retrospective analysis on control interventions and superspreading events

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HIGHLIGHTS

- A dynamic transmission model for the 2015 MERS outbreak in the Republic of Korea is proposed.
- Our model incorporates the superspreading events by pulses of infections.
- We explore the impact of the timing for hypothetical control scenarios.
- We analyze uncertainties focused on the role of superspreading events.

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ABSTRACT

The 2015 Middle East respiratory syndrome (MERS) outbreak in the Republic of Korea has provided an opportunity to improve our understanding of the spread of MERS linked to healthcare settings. Here we designed a dynamic transmission model to analyze the MERS outbreak in the Republic of Korea based on confirmed cases reported during the period May 20–July 4, 2015. Our model explicitly incorporates superspreading events and time-dependent transmission and isolation rates. Our model was able to provide a good fit to the trajectory of the outbreak and was useful to analyze the role of hypothetical control scenarios. Specifically, we assessed the impact of the timing of control measures, especially associated with a reduction of the transmission rate and diagnostic delays on outbreak size and duration. Early interventions within 1 week after the epidemic onset, for instance, including the initial government announcement to the public about the list of hospitals exposed to MERS coronavirus (MERS-CoV), show a promising means to reduce the size (>71%) and duration (>35%) of the MERS epidemic. Finally, we also present results of an uncertainty analysis focused on the role of superspreading events.

1. Introduction

Middle East respiratory syndrome (MERS) is a fatal respiratory disease caused by a coronavirus that emerged in Saudi Arabia in 2012 (Zaki et al., 2012). The major reservoir of MERS virus (MERS-CoV) responsible for infections in the human population is likely to be associated with dromedary camels (Cauchemez et al., 2014; Zumla et al., 2015; Sabir et al., 2015). Most individuals infected with MERS-CoV develop a severe respiratory illness accompanied by cough, fever, shortness of breath, and pneumonia. As of 28 July 2016, a total of 1791 laboratory-confirmed cases including 640 deaths in 27 countries have been reported to the World Health Organization (WHO) (World Health Organization, 2015c). Although countries in Africa, Asia, Europe, and North America have experienced sporadic importations of MERS from the Middle East, these have not generated local outbreaks thus far. The largest MERS outbreak outside Saudi Arabia occurred in the Republic of Korea as a result of a single importation from the Arabian Peninsula in May 2015. As of 4 July 2015, a total of 186 cases have been reported, including 38 deaths.

Although the person-to-person transmission risk of MERS is thought to be not self-sustaining (Cauchemez et al., 2014; The Health Protection Agency (HPA) UK Novel Coronavirus Investigation team, 2013; Chowell et al., 2014; Breban et al., 2013), it has shown potential to be explosive in the nosocomial setting (Assiri et al., 2013; Oboho et al., 2015). Out of 186 confirmed cases in the

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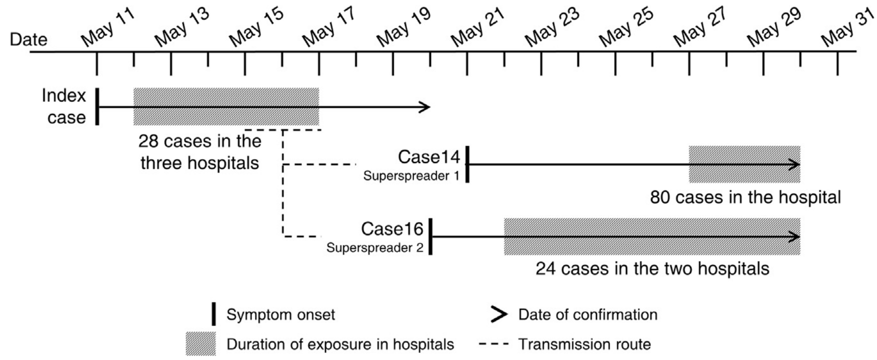

Fig. 1. Schematic timeline for the two superspreaders (Case 14 and Case 16) in the MERS outbreak in the Republic of Korea in 2015. The thick bar indicates the date of symptom onset, and the gray diagonal patterned square represents the duration of exposure when the superspreader with symptoms visited or stayed in hospitals. The arrowhead represents the date of confirmation. The length of the arrow means the duration from symptom onset to confirmation. The dashed line means the transmission route from the index case to Case 14 and Case 16.

Republic of Korea, 178 cases (98%) were related to nosocomial transmission in 17 MERS-affected healthcare facilities (Korea Centers for Disease Control and Prevention, 2015, 2016; Ki, 2015) and 80 cases (43%) were generated by only one infected case at the same hospital (Korea Centers for Disease Control and Prevention, 2015, 2016) (Fig. 1).

The potential for high variability in the number of secondary cases or superspreading events (SSEs) is a notable characteristic of infectious diseases (Lloyd-Smith et al., 2005; Galvani and May, 2005). Cases that generate a disproportionate number of secondary cases tend to occur during the early stage of an epidemic (Transmission Dynamics and Control of Severe Acute Respiratory Syndrome, 2003; Goh et al., 2006). Conversely, unlike "superspreaders", the typical individuals tend to infect only a few or no cases at all. In recent works on the MERS outbreak (Chowell et al., 2015; Nishiura et al., 2015; Kucharski and Althaus, 2015; Blumberg and Lloyd-Smith, 2013), this individual variation has been described by transmission heterogeneity. Based on the stochastic approach, it is assumed that the number of secondary cases caused by each infected individual is negative binomial distributed with mean $\mathcal{R}_0$ and dispersion parameter k (with lower value representing higher heterogeneity, and vice versa). In this framework, SSEs during the recent MERS outbreaks can be explained by the high dispersion nature of the distribution of the number of secondary cases per case. For example, Chowell et al. (2015) estimated that the mean $\mathcal{R}_0$ for the MERS outbreaks was below the epidemic threshold value of 1 while the dispersion parameter k was estimated at 0.06, indicating high heterogeneity in the potential number of secondary cases. Simulations indicated that the probability of observing outbreaks larger than the MERS outbreak in the Republic of Korea is only of the order of 1%. However, this requires careful interpretation because SSEs during outbreaks might be treated as outliers rather than observations stemming from a highly over dispersed distribution. At the same time, infectious diseases with subcritical $\mathcal{R}_0$ and overdispersed k are more likely to subside within just a few disease generations.

Currently, no vaccine or antiviral treatment against MERS-CoV infection (World Health Organization, 2015b) is available. Although early intervention strategies such as fast diagnosis and quarantine of suspected cases have proved to be the most effective control measures for rapidly mitigating a MERS outbreak (The Health Protection Agency (HPA) UK Novel Coronavirus Investigation team, 2013; Breban et al., 2013; Nishiura et al., 2015; Kucharski and Althaus, 2015; Banik et al., 2015). The mean duration from symptom onset to diagnosis of MERS-CoV infection of the outbreak in the Republic of Korea was estimated in the range of 4–8 days (Korea Centers for Disease Control and Prevention, 2015; Ki, 2015; Cowling et al., 2015). Although it decreased once intense contact tracing activities were implemented, a significant delay in diagnosis was observed in the early stage of the outbreak in the Republic of Korea, which is one of the critical features that facilitated the outbreak.

Most studies on the MERS outbreak in the Republic of Korea have focused on inferring the probability of a large outbreak size by analyzing the distribution of cluster sizes (Nishiura et al., 2015; Kucharski and Althaus, 2015). To the best of our knowledge, there is no dynamic compartmental model for the MERS outbreak in the Republic of Korea that incorporates the role of SSEs and the time-dependent parameters associated with the impact of early interventions. In this work, we develop a mathematical model that is consistent with consolidated retrospective investigations of previous MERS outbreaks. Our calibrated model provides a basis to analyze the hypothetical impact of intervention strategies. Furthermore, by analyzing the variation in infectiousness of the superspreaders, we explore the uncertainty associated with the SSEs.

2. Materials and methods

2.1. Epidemic data

Data on daily laboratory-confirmed MERS cases for the outbreak in the Republic of Korea were obtained from the Korea Center for Disease Control and Prevention (KCDC) (Korea Centers for Disease Control and Prevention, 2016). The KCDC reported 186 cases including a case confirmed in China and 38 deaths since May 20, 2015, which is the day the index case was confirmed. No additional confirmed cases have been reported since 4 July, and the Korean government declared the end of MERS-CoV transmission in the Republic of Korea on December 23, 2015 by WHO standards (Korea Centers for Disease Control and Prevention, 2016).

The index case of the MERS outbreak in the Republic of Korea was a businessman who took a trip to the Middle East and returned on May 4 (Chowell et al., 2015; Cowling et al., 2015; World Health Organization, 2015a). Showing symptoms of respiratory problems on May 11, he visited several hospitals, was admitted to a hospital on May 15 and discharged on May 17, and finally diagnosed with MERS on May 20. Consequently, the index case generated multiple exposures, infecting 28 people including the two patients, Case 14 and Case 16, who in turn generated over 50% of the total cases reported in the Republic of Korea.

Most cases were related to nosocomial transmission or hospital-to-hospital transmission in 17 MERS-affected healthcare facilities (Korea Centers for Disease Control and Prevention, 2015, 2016; Ki, 2015). Of the 186 cases, 82 were inpatients who shared the same room, ward, or emergency room; 65 were their family