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Research paper

Estimates of the risk of large or long-lasting outbreaks of Middle East respiratory syndrome after importations outside the Arabian Peninsula

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ABSTRACT

We quantify outbreak risk after importations of Middle East respiratory syndrome outside the Arabian Peninsula. Data from 31 importation events show strong statistical support for lower transmissibility after early transmission generations. Our model projects the risk of ≥10, 100, and 500 transmissions as 11%, 2%, and 0.02%, and ≥1, 2, 3, and 4 generations as 23%, 14%, 0.9%, and 0.05%, respectively. Our results suggest tempered risk of large, long-lasting outbreaks with appropriate control measures.

1. Introduction

Clusters of patients infected with Middle East respiratory syndrome (MERS) coronavirus continue to occur in countries throughout the Middle East, where the virus is thought to be endemic in camels (Kayali and Peiris, 2015). While rare, countries elsewhere in the world experience importations from infected individuals traveling from the endemic region (Carias et al., 2016). Most identified importations of MERS from travelers have not resulted in documented transmissions in the destination country (Nishiura et al., 2015); however, the recent large cluster of 186 infected patients stemming from a single introduction in the Republic of Korea (ROK) (Korea Centers for Disease Control and Prevention, 2015) demonstrated that explosive outbreaks are possible.

The ROK outbreak, combined with a non-negligible likelihood of further exportations of MERS from Middle Eastern countries (Carias et al., 2016), is cause for continued concern for importation of MERS to other countries. For public health officials requiring quantitative assessment of the risk posed by incoming infected travelers, it is important to have a nuanced understanding of the full spectrum of possible outcomes, especially when they are highly variable (Fisman et al., 2014); modeling studies can play an important role in this regard.

Recent studies (Nishiura et al., 2015; Kucharski and Althaus, 2015; Chowell et al., 2015) have quantified the variability implied by different data sets of MERS cluster sizes resulting from importation of cases. These analyses found that the data are potentially consistent with high transmission variability associated with the occurrence of superspreading events, similar to what was observed during severe acute respiratory syndrome (SARS) outbreaks in 2003 (Lloyd-Smith et al., 2005). These studies quantified transmission probabilities using a negative binomial offspring distribution within a branching process outbreak model, assuming that every infected individual transmits with an average of R_0 transmissions and dispersion parameter k, where $k < 1$ implies high over-dispersion (Lloyd-Smith et al., 2005).

In this paper, we extend the results of the above work to allow the reproductive number R to vary across subsequent generations of transmissions during an outbreak. The ROK outbreak consisted of a large number of transmissions from the initial traveler and from a few patients in the next transmission generation. Then, once local officials determined that a MERS outbreak was occurring and implemented control measures in response, there

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was an extremely rapid decrease in transmissions such that the entire outbreak was extinguished after three total generations of transmission following the introduction (Korea Centers for Disease Control and Prevention, 2015). This type of differential transmissibility before vs. after implementation of control measures has also been observed during localized outbreaks of SARS (Lloyd-Smith et al., 2005; Wallinga and Teunis, 2004) and Ebola (Toth et al., 2015; Shuaib et al., 2014).

A simple way to model a post-control change in average transmissibility is to use one parameter for the reproduction number in early generations (R_0) and another for later generations (R_c, or post-control reproductive number), as assumed in several previous modeling studies of observed outbreaks and public health response for different diseases (Lloyd-Smith et al., 2005; Wallinga and Teunis, 2004; Toth et al., 2015; Chowell et al., 2004). We hypothesized that a model allowing this type of switch would produce a substantially better fit to the data from outbreak clusters caused by MERS importations. Given results from our previous work assessing Ebola importation risk (Toth et al., 2015), we also hypothesized that this model might produce substantially different results for the risk of a very large outbreak compared to a model assuming a single reproductive number across all transmission generations.

2. Data

We developed a data set of cluster sizes from MERS importations to countries entirely outside of the Arabian Peninsula (Table 1); we excluded data from Jordan, the Kingdom of Saudi Arabia, Kuwait, Oman, Qatar, the United Arab Emirates, and Yemen, countries where it was not always clear whether the initial or subsequent cases within clusters acquired infection from exposure to MERS cases or animals (camels). The data were extracted from World Health Organization reports (World Health Organization, 2015) as well as published accounts of individual clusters (Yavarian et al., 2015; Puzelli et al., 2013; Abroug et al., 2014; The Health Protection Agency U. K. Novel Coronavirus Investigation team, 2013). Our data set consists of 31 importation events, of which 23 resulted in no confirmed or suspected transmissions (clusters of size 1) and the other 8 resulted in clusters of size 2–186. Following Nishiura et al. (2015), we also recorded the total number of generations of transmission that occurred after the introduction.

Table 1
Cluster data from reported Middle East respiratory syndrome importations outside the Arabian Peninsula.

Country	Cluster size[a]	Transmission generations[b]
Algeria	1	0
Algeria	1	0
Austria	1	0
China	1	0
Egypt	1	0
France	2	1
Germany	1	0
Germany	1	0
Germany	1	0
Greece	1	0
Iran	7	3
Iran	2	1
Italy	3	1
Lebanon	1	0
Malaysia	1	0
Netherlands	1	0
Netherlands	1	0
Philippines	1	0
Philippines	1	0
Philippines	1	0
Republic of Korea	186	3
Spain	1	0
Thailand	1	0
Tunisia	2	1
Tunisia	1	0
Turkey	1	0
United Kingdom	3	1
United Kingdom	1	0
United States	2	1
United States	1	0
United States	1	0

Each row represents a unique individual infected traveler to the indicated country.
[a] Cluster size includes the initial infected traveler and any subsequent infected persons epidemiologically linked to that traveler; a cluster of size 1 indicates no known transmission from the traveler in the destination country.
[b] Transmission generations are the maximum number of transmission links from an infected person in the cluster back to the initial traveler.

3. Methods

For each generation of transmission, we assumed a negative binomial offspring distribution with parameter set $\theta_i = (R_i, k_i)$, where i is the generation of transmission ($i = 0$ from the initial traveler). This assumption results in the following equations.

First, the probability that x independent cases in generation i produce a total of y cases in generation $i+1$ is

$$p_{\theta_i}(x, y) = \frac{\Gamma(k_i x + y)}{y!\,\Gamma(k_i x)} \left(\frac{R_i}{R_i + k_i}\right)^y \left(\frac{k_i}{R_i + k_i}\right)^{k_i x}.$$

Next, given n independent introductions (generation 0), the joint probability of a cluster of total size j consisting of exactly g generations of transmission, under parameter set $\theta = (\theta_0, \theta_1, \theta_2, \theta_3)$, is

$$q_\theta(n, j, g) = \begin{cases} p_{\theta_0}(n, 0), & g = 0 \\ p_{\theta_0}(n, j-n)\, p_{\theta_1}(j-n, 0), & g = 1 \\ \sum_{\mathrm{x}=1}^{j-n-1} p_{\theta_0}(n, x)\, p_{\theta_1}(\mathrm{x}, \mathrm{j}-\mathrm{n}-\mathrm{x})\, p_{\theta_2}(\mathrm{j}-\mathrm{n}-\mathrm{x}, 0), & g = 2 \\ \sum_{x=1}^{j-n-2} [p_{\theta_0}(n, x) \sum_{y=1}^{j-n-x-1} p_{\theta_1}(x, y)\, p_{\theta_2}(y, j-n-x-y)\, p_{\theta_3}(j-n-x-y, 0)], & g = 3. \end{cases}$$

We used the above equations to evaluate ten different models. In Model 0, we assumed constant parameter values across all generations of transmission, i.e.,$\theta_0 = \theta_1 = \theta_2 = \theta_3 = (R, k)$. In Models 1a, 1b, and 1c, we assumed the initial patient transmitted with reproductive number R_0 and dispersion parameter k_0, and all subsequent patients transmitted with a post-control reproductive number R_c and dispersion parameter k_c i.e., $\theta_0 = (R_0, k_0)$; $\theta_1 = \theta_2 = \theta_3 = (R_c, k_c)$. Because we found that allowing k_c to range freely in the optimization scheme resulted in wide uncertainty (due to few multi-generation clusters in the data), we chose to test three differ-