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# Objective Determination of End of MERS Outbreak, South Korea, 2015

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**To the Editor:** After not finding any additional cases of Middle East respiratory syndrome (MERS) for several weeks in South Korea, in July 2015, the South Korean government and the World Health Organization (WHO) discussed the appropriate time to declare the end of the outbreak in July 2015 (*1*). This declaration would enable allocation of human resources to healthcare facilities to return to normal and would help restore international travel to the country. A widely acknowledged criteria of WHO to determine the end of an epidemic has been twice the length of the incubation period since the most recently diagnosed case (*2*). For MERS, the longest incubation period is 14 days. Thus, adopting 28 days as the waiting period, and counting days from diagnosis of the most recent case on July 4, 2015, the earliest date the South Korean government could have declared the end of outbreak was August 2 if it adhered to WHO criteria (*1*). However, to emphasize safety to the nation and to international travelers at an earlier time, the South Korean government originally decided to announce the end of the MERS outbreak on July 27, the date the last quarantined MERS patient was released from movement restriction. Because we are concerned about the validity of strict adherence to the WHO criteria, we objectively calculated the probability of observing additional cases at a given time and compared that probability with the WHO criteria.

To clearly define the end of the outbreak, we excluded reintroduction of imported cases and cases of MERS coronavirus infection resulting from a zoonotic reservoir. We defined the end of the outbreak as the end of continued chains of transmission. The probability of observing additional cases was derived by using the serial interval; that is, the time from illness onset in the primary case-patient to illness onset in a secondary case-patient, and the transmissibility of MERS (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/22/1/15-1383-Techapp1.pdf). Both of these epidemiologic variables were estimated by using case data in South Korea (*3,4*). As practiced in the determination of the length of quarantine (*5*), the end of outbreak can be declared if that probability is <5%, a threshold value.

Our analysis showed that the first date on which the posterior median probability decreased to <5% was July 21 (Figure, panel A). The first date on which the posterior median decreased to 1% was July 23. Compared with August 2 as calculated from the WHO criteria, the end of the outbreak could have been declared 11 and 9 days earlier, respectively. Because the choice of 5% or 1% as the threshold
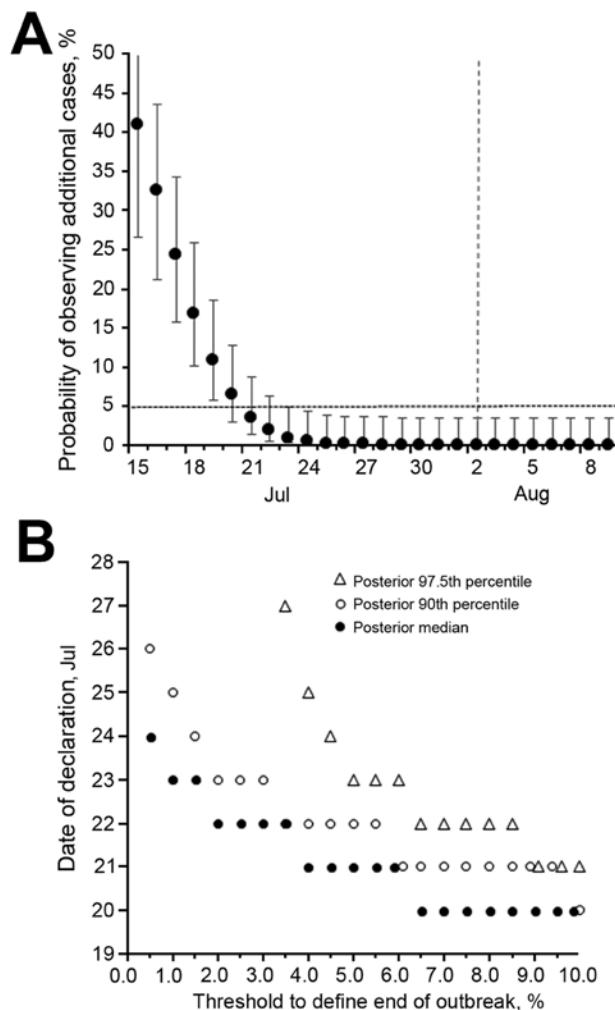
probability is arbitrary (as practiced in determining the p value in any hypothesis testing) and because of the need to account for parameter uncertainties, we also measured the sensitivity of the first date on which the South Korean government could declare the end of the outbreak to a variety of threshold values (Figure, panel B). Examination of the probability of observing additional cases in the range of 0.5% to 10% indicated the end of the outbreak could have been declared from July 21 to July 24 (i.e., 9–12 days earlier than August 2).

Our proposed method does not account for missing undiagnosed or mild cases, and underdiagnosis would considerably extend the time to declare the end of an outbreak (and thus the proposed method is not directly applicable to, for example, Ebola virus disease in West Africa, for which we are currently developing an alternative method). All possible contact with diagnosed case-patients in the late phase of the MERS outbreak in South Korea were traced (*6,7*); thus, we believe it was appropriate to ignore ascertainment bias in this specific setting. Although our proposed approach is simplistic, adopting the WHO criteria could have added >1 week to the elevated state of tension, and the use of the incubation period distribution would be fully supported only when the exact times of infection were known for exposed potential contacts. Although it is a posteriori reasoning, the original decision made by the South Korean government at an earlier date was ironically supported by our proposed method. Rather than adopting the use of "twice" and the "incubation period," which has not been theoretically justified, an objective decision of the end of an outbreak should explicitly rest on the risk of observing at least 1 more case on or after a specified date.

**Figure.** Estimated probability of observing additional cases of Middle East respiratory syndrome coronavirus infection, South Korea, 2015. A) Estimated probability of observing additional cases on each calendar date, given that no illness onset has been observed by the specified date. Circles represent posterior median values; whiskers extend to upper and lower 95% credible intervals. Horizontal dashed line represents 5%, a threshold level. Vertical line indicates August 2, 2015, on which the end of the outbreak might be declared if World Health Organization criteria were followed. B) Calendar date to declare the end of outbreak for different threshold probabilities and percentile points of posterior distribution. Horizontal axis corresponds to the probability of observing additional cases. Vertical axis shows the date of declaration which is calculated as 1 day plus the date at which the probability of observing additional cases lowered the specified threshold probability.

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# Surveillance for Coronaviruses in Bats, Lebanon and Egypt, 2013–2015

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**To the Editor:** Coronaviruses (CoVs) in bats are genetically diverse, and evidence suggests they are ancestors of Middle East respiratory virus CoV (MERS-CoV), severe acute respiratory syndrome CoV, and human CoVs 229E and NL63 (*1–4*). We tested several bat species in Lebanon and Egypt to understand the diversity of bat CoVs there.

Samples were collected during February 2013–April 2015. A total of 821 bats were captured live in their caves; sampled (oral swab, rectal swab, serum); and released, except for 72 bats that died or were euthanized upon capture. Lungs and livers of euthanized bats were harvested and homogenized. Caves were in proximity to human-inhabited area but not in proximity to camels.

In Egypt, we sampled 3 bat species (online Technical Appendix 1, http://wwwnc.cdc.gov/EID/article/22/1/15-1397-Techapp1.pdf). Eighty-two Egyptian tomb bats (*Taphozous perforatus*) tested negative for CoV. We also sampled 31 desert pipistrelle bats (*Pipistrellus deserti*) and detected an HKU9-like betacoronavirus (b-CoV) in the liver of 1 bat (prevalence 3.2%). From 257 specimens from Egyptian fruit bats (*Rousettus aegyptiacus*), we detected b-CoV in 18 samples from 18 different bats (prevalence 7%). A murine hepatitis virus–like CoV was detected in the lung of 1 bat. HKU9-like viruses were detected in 5 oral, 2 lung, 5 liver, and 5 rectal samples. Overall, 5.1% of the bats tested positive.

In Lebanon, we sampled 4 bat species. Four *Rhinolophus hipposideros* bats and 6 *Miniopterus schribersii* bats tested negative. One of 3 *Rhinolophus ferrumequinum* bats sampled was positive. We sampled 438 *Rousettus aegyptiacus* bats from 10 different locations and detected HKU9-like viruses in 24 rectal swab specimens (prevalence 5.5%). Overall, 5.5% of the bats tested positive.

A subset of the samples (696 samples: 516 from Egypt, 180 from Lebanon) were tested for MERS-CoV by using the specific upstream of E quantitative reverse transcription PCR; all tested negative. Serum samples from 814 bats tested negative for MERS-CoV antibodies.

Phylogenetic analysis revealed that the RNA-dependent RNA polymerase (*RdRp*) genes of viruses detected in *R. aegyptiacus* bats in Lebanon and Egypt were closely related to the *RdRp* gene of HKU9 CoV (Figure). Our viruses clustered in 3 groups: A, B, and C. Group A viruses were closely related to HKU9-10-2 virus and included viruses from Egypt. Group B included viruses from both countries and were closely related to HKU9-1 and HKU9-4 viruses. Group C also included viruses from both countries that were related to HKU9-3 and HKU9-5 viruses. The *RdRp* fragments sequenced had <90% nt similarity among groups A, B, and C. Within-group nucleotide similarity was >90%, and amino acid variability was 2%–4% (online Technical Appendix 2, http://wwwnc.cdc.gov/EID/article/22/1/15-1397-Techapp2.xlsx). The phylogenetic tree of the N gene also showed proximity of the viruses detected in our study to HKU9 viruses (online Technical Appendix 1). Viruses from Lebanon clustered together as did the viruses from Egypt.

Most of the positive samples were detected in Egyptian fruit bats. These are cave-dwelling species that inhabit regions of East Africa, Egypt, the Eastern Mediterranean, Cyprus, and Turkey (*5*). This species is a reservoir for several viruses, including Marburg, Kasokero, and Sosuga

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# Objective Determination of End of MERS Outbreak, South Korea, 2015

**Technical Appendix**

**Epidemiologic Data**

We analyzed the date of illness onset among persons who had laboratory-confirmed Middle East respiratory syndrome (MERS) cases in South Korea during 2015 (*1–3*). The latest date on which the data were compiled was October, 1, 2015 with a total of 185 confirmed cases in South Korea (excluding 1 case in a person who traveled overseas). Whenever the date of illness onset was missing, we substituted it with the date of laboratory confirmation. In total, there have been 4 cases with unknown dates of illness onset since June 15, but this substitution actually enabled us to conservatively argue the time to declare the end of outbreak: counting the waiting period from the date of diagnosis elevates the actual probability of the freedom from infection (*4*). Considering that illness developed in 2 persons on July 2, the end of MERS outbreak could be declared on July 31, at the earliest, following the WHO criteria. Nevertheless, to be conservative with the WHO method, counting the diagnosis date of 1 of the latest cases, July 4, as the first day, the earliest date to declare the end of outbreak may be August 2 (*5*).

To propose a more objective approach, 2 pieces of epidemiologic information were used. First, we used the distribution of the serial interval, i.e., the time from illness onset of a primary case to illness onset of the secondary case in a person who directly acquired infection from the primary case-patient (*6*). An analysis of epidemiologic data in South Korea estimated the mean

and SD of the serial interval at 12.6 and 2.8 days, respectively (*3*). In the following, the cumulative distribution function of the serial interval is denoted by $F(t)$ which was assumed to follow a gamma distribution. Second, we used parameters that govern the transmissibility of MERS, i.e., $R_0$ at 0.75 and dispersion parameter $k$ at 0.14 of a negative binomial distribution (*7*), which did not significantly deviate from published estimates in earlier studies (*8,9*). By using the estimated reproduction number and dispersion parameter, the cluster size of >150 cases was not unexpected (*10*). These parameters are applicable to an initial exponential growth phase without interventions, and not specifically applicable to a nonlinear phase under contact tracing practice. Thus, it should be remembered that the use of these parameters would lead to an overestimation of the probability of observing additional cases, and thus, the proposed approach is deemed conservative. To address parameter uncertainties, we used a bivariate normal distribution that accounts for parameter dependence and resampled randomly drawn combinations of $R_0$ and $k$ as practiced before (*7*). The similar resampling was conducted for the serial interval distribution (i.e., the mean and the standard deviation) (*3*).

**Probabilistic Model**

Here we devise a model that calculates the probability of observing additional cases at a given calendar time, counting waiting time from dates of illness onset in potential primary cases. If 1 minus this probability is >95% on a given date, one can be 95% sure that the outbreak is over by that date. For simplicity, we ignore potential asymptomatic infection with MERS coronavirus in the following analysis.

If we were concerned with only a single (potential) secondary case, the probability that an outbreak is over at $t$ days since the date of illness onset in the potential primary case would be

given by $F(t)$ (*11*). Nevertheless, an appropriate computation of the probability of observing additional cases on a calendar date involves 3 major obstacles that require some improvements. First, there can be multiple cases on the latest date, which was actually the situation for the MERS outbreak in South Korea. If there are 2 cases, the absence of transmission will be calculated at $(F(t))^2$, assuming that 2 cases independently produce secondary cases, and thus, the probability of observing at least 1 case is calculated as $1-(F(t))^2$. If there are $n$ cases, the probability of observing additional cases is obtained as $1-(F(t))^n$. Second, there can be several persons who developed the illness on different dates around the latest time. Suppose that the days elapsed from 2 persons with different dates of illness onset were $t_1$ and $t_2$, the probability of observing additional cases will have to be calculated as $1-F(t_1)F(t_2)$. Third, we have to address the potential for observing multiple secondary cases produced by a single primary case, e.g., multiple infections among healthcare workers who were exposed to an admitted patient. The variation in the number of secondary cases per single primary case can be addressed by using both $R_0$ and $k$, which could even partially capture the emergence of superspreaders. Let $p_y$ be the probability that the number of secondary cases is $y$, i.e., $p_y = \Pr(Y = y)$. Using the dataset of $t_i$, the calendar date of illness onset of diagnosed cases $i$ ($i = 0,1,..,185$), the probability of observing additional cases in future at calendar date $t$ is calculated as

$$\Pr(one\ or\ more\ cases) = 1 - \prod_{i=1}^{185} \sum_{y=0}^{\infty} p_y [F(t - t_i)]^y$$

(Equation 1)

Equation 1 does not manually subtract all existing secondary transmissions from the model, despite the fact that the observed cases have already generated secondary cases that they were supposed to cause. For that reason, the probability that is derived from the Equation 1 might

be a slight overestimate. Nevertheless, to keep the model structure simple, we let the model to be simple as shown and conservative. At least, observed cases for which illness recently developed did not involve superspreaders (and the bias introduced by the above-mentioned model assumption would be minimal). The simulations with resampled serial interval (mean and SD), $R_0$ and $k$ were run 10,000 times, enabling us to take percentile points for the calculation of uncertainty bounds.

**Supplementary Discussion**

The calculated probability is interpreted as the risk of observing at least 1 more case on or after a specified date and has a good potential to assist objective determination of the end of outbreak. The model efficiently addressed 3 practical problems in objectively calculating the probability that an outbreak leads to the end: 1) multiple cases on the latest date, 2) several recent cases with different illness onset dates, and 3) variations in the number of secondary cases generated by a single primary case.

The cutoff probability is arbitrarily determined, as practiced to determine the length of quarantine period using the incubation period (*4*). Despite arbitrariness, p value in all hypothesis testing is determined in the same fashion. Rather than the issue of adopting a specific threshold probability, the point of devising the proposed model is to explicitly calculate the probability of observing additional cases at a given point in time. Relying on the use of the incubation period can be feasible only when the exact time of exposure is known for all traced contacts, but such situation is usually not the case for directly transmitted diseases, and thus, one should remember that the incubation period is applicable to specific settings with known times of exposure among all potential contacts.

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