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Short Communication

Estimating the risk of Middle East respiratory syndrome (MERS) death during the course of the outbreak in the Republic of Korea, 2015

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SUMMARY

Objectives: A large cluster of the Middle East respiratory syndrome (MERS) linked to healthcare setting occurred from May to July 2015 in the Republic of Korea. The present study aimed to estimate the case fatality ratio (CFR) by appropriately taking into account the time delay from illness onset to death. We then compare our estimate against previously published values of the CFR for MERS, i.e., 20% and 40%.
Methods: Dates of illness onset and death of the MERS outbreak in the Republic of Korea were extracted from secondary data sources. Using the known distribution of time from illness onset to death and an integral equation model, we estimated the delay-adjusted risk of MERS death for the South Korean cluster.
Results: Our most up-to-date estimate of CFR for the MERS outbreak in South Korea was estimated at 20.0% (95% confidence intervals (CI): 14.6, 26.2). During the course of the outbreak, estimate of the CFR in real time appeared to have decreased and become significantly lower than 40%.
Conclusions: The risk of MERS death in Korea was consistent with published CFR. The estimate decreased with time perhaps due to time-dependent increase in case ascertainment. Crude ratio of cumulative deaths to cases underestimates the actual risk of MERS death because of time delay from illness onset to death.

1. Introduction

A cluster of the Middle East respiratory syndrome (MERS) was observed from May to July 2015 in the Republic of Korea. More than 14,000 contacts had to be traced for monitoring.[1] As of 31st July 2015, there have been a total of 185 confirmed cases and 36 deaths reported from this cluster.[2]

To assess the clinical seriousness of an infection, it is vital to estimate the case fatality ratio (CFR), the proportion of deaths among cases. The real-time estimation involves two epidemiological biases. A well-known issue during the course of an epidemic is right censoring; i.e., many of cases have not passed through the time required for themselves to die, and thus, the crude ratio of the cumulative numbers of deaths to cases could underestimate the CFR.[3–5] Another issue for the estimation of CFR is the ascertainment bias; i.e., the reported cases may not represent a substantial part of the total number of infections, and thus, the ratio of confirmed deaths to cases may overestimate the actual risk of death that might be perceived as the risk among all infected individuals.[6,7] So far, the CFR among diagnosed cases for MERS is 40%,[8] but that among secondary cases may be around 20%.[9]

The purpose of the present study is to estimate the CFR for MERS in the Republic of Korea by accounting for the time-delay from illness onset to death and comparing the estimate against published values.

2. Materials and Methods

Our analysis rests on secondary data concerning the number of confirmed cases and deaths of MERS in the Republic of Korea.[10–13]

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Confirmed diagnosis was made based on laboratory diagnosis by detecting viral nucleic acid or serological test, regardless of the presence of clinical signs and symptoms.

For the estimation of the CFR in real time, we employed an integral equation model, the mathematical details of which were described elsewhere.[14,15] To adjust the right censoring, the time of illness onset to death was assumed to follow a gamma distribution, f_s, with the median of 11 days, and the coefficient of variation was assumed at 50.0%.[16] Maximum likelihood estimate of the CFR was obtained by adjusting the time delay from illness onset to death, and the 95% confidence interval (CI) was computed by using the profile likelihood. To test the difference between the estimate in the Republic of Korea against published two estimates, i.e., p_{ref}=0.20 and 0.40, a two-sided binomial test was employed. The level of statistical significance was set to be α=0.05.

3. Results

Cumulative numbers of cases and deaths are illustrated in Figure 1. An increase in the number of deaths is delayed as compared to that in cases. Figure 2 A and 2B show the estimates of the risk of death using the abovementioned method. The most recent estimate of the CFR in the Republic of Korea appeared to be 20.0% (95% CI: 14.6, 26.2). During the course of the outbreak, the crude ratios of deaths to cases without accounting for the time delay from illness onset to death was smaller than our delay-adjusted estimates (Figure 2A). Estimate of the CFR in real time appeared to have decreased and become significantly lower than 40% (Figure 2B). The most up-to-date CFR among those aged 60 years or older was estimated at 39.5% (95% CI: 28.9, 51.0), while that among those aged from 0-59 years was as small as 6.6% (95% CI: 2.9, 12.4).

4. Discussion

The present study estimated the CFR for the ongoing MERS outbreak in the Republic of Korea. Using the most up-to-date data, the CFR was estimated at 20.0% (95% CI: 14.6, 26.2), which was not significantly different from 20%, agreeing estimates among secondary cases in literature.[8,9,17] The obtained value in real time was greater than that calculated from the crude ratio of deaths to cases, which could have indicated that the risk of death was as small as below 10% during the course of the outbreak. Governments and public health agencies are advised to adopt the suggested method during the real-time announcement of emerging outbreaks.[5,14]

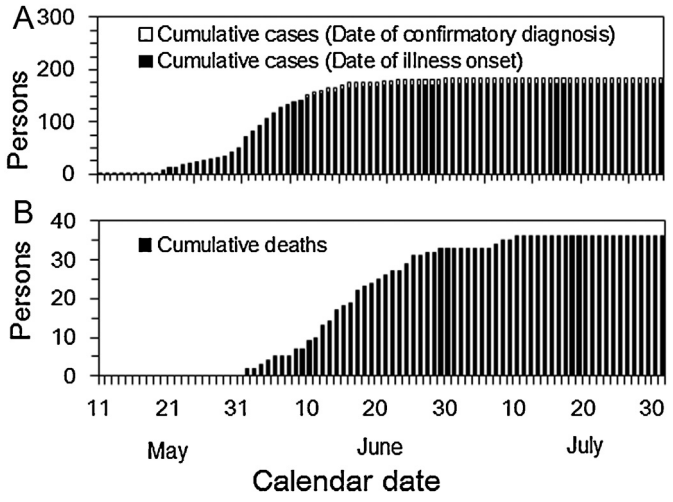

Figure 1. Temporal distribution of cases and deaths due to Middle East respiratory syndrome coronavirus (MERS-CoV) in the Republic of Korea, 2015.
Cumulative numbers of cases (A) and deaths (B) over time. As the dates of illness onset were not fully available from the midst of outbreak, we partially used dates of confirmatory diagnosis for a part of cases (white bars in panel A). Suspicious symptoms of contacts under observation have been closely monitored, and traced suspected cases have been consistently tested during the course of the outbreak.

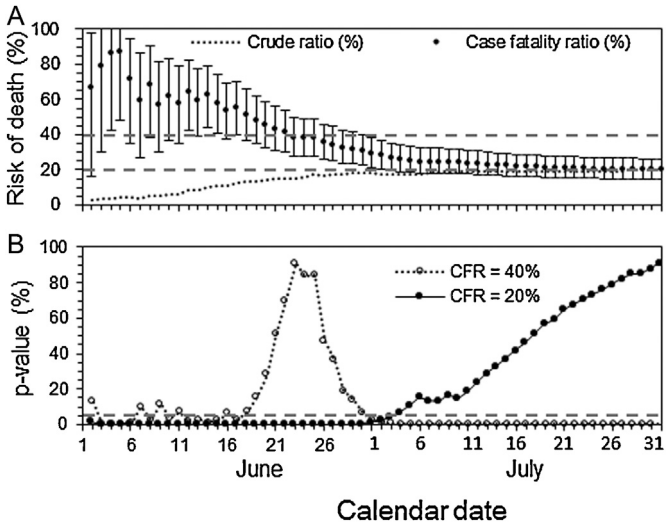

Figure 2. The risk of death caused by Middle East respiratory syndrome coronavirus (MERS-CoV) in the Republic of Korea, 2015.
Estimated case fatality ratio (CFR) as a function of calendar time. The two horizontal dashed grey lines represent published values of CFR, i.e., 20% and 40% [8,9]. The crude ratio is calculated as the ratio of cumulative numbers of deaths to cases, which likely underestimates the risk of death and may increase over the course of calendar time. The whiskers of estimated CFR extend to lower and upper 95% confidence intervals that were computed by the profile likelihood. B. Two-sided binominal test (p-value) as a function of time, comparing adjusted CFR against published values, 20% and 40%. The horizontal dashed grey line corresponds to the threshold value (5%).

The estimated CFR during the early epidemic phase was consistent with 40%, but the estimate has declined over the course of the epidemic. There can be two possible explanations. First, in the Republic of Korea, extensive contact tracing and quarantine have been carried out.[10,11,18,19]. Thus, while our estimate of the CFR was initially consistent with 40% (e.g. in mid-June in Figure 2A), ascertainment rate in Korea could have been improved over time, and increased diagnostic coverage may have been reflected in the CFR estimate during the latter half stage of this outbreak. Second, we have found that the CFR among elderly persons age 60 years or older was as high as 40%, while that among younger individuals was as low as 7%. As an underlying mechanism of the time-dependent decrease in the CFR, our estimate of the CFR in Korea may have been sensitive to the fraction of cases with comorbidities. That is, if the early cluster of cases represents elderly with underlying comorbidity which has transmitted the disease to healthier individuals in the later stage of the outbreak, that could partly explain why the estimated CFR decreased over time.

In conclusion, the risk of MERS death in the Republic of Korea has been shown to be consistent with 20%. Estimation of the CFR has to account for the time delay from illness onset to death.

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