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# Risk Factors for Transmission of Middle East Respiratory Syndrome Coronavirus Infection During the 2015 Outbreak in South Korea

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***Background.*** Transmission heterogeneity was observed during the 2015 Korean outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Only 22 of 186 cases transmitted the infection, and 5 super-spreading events caused 150 transmissions. We investigated the risk factors for MERS-CoV transmission.

***Methods.*** Epidemiological reports were used to classify patients as nonspreaders, spreaders, or those associated with a super-spreading event (5 or more transmissions). Logistic regression analyses were used to evaluate the factors for MERS-CoV transmission.

***Results.*** Compared to nonspreaders, spreaders exhibited a longer interval from symptom onset to isolation (7 days vs 3 days) and more frequent pre-isolation pneumonia diagnoses (68.2% vs 17.1%). Spreaders also exhibited higher values for pre-isolation contacts (149 vs 17.5), pre-isolation hospitalization (68.2% vs 16.5%), and emergency room (ER) visits (50% vs 7.3%). Spreaders exhibited lower cycle thresholds for the *upE* and *ORF1a* genes (22.7 vs 27.2 and 23.7 vs 27.9, respectively). In multivariate analysis, transmission was independently associated with the cycle threshold (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.75–0.96) and pre-isolation hospitalization or ER visits (OR, 6.82; 95% CI, 2.06–22.84). The super-spreading events exhibited higher values for pre-isolation contacts (777 vs 78), pre-isolation ER visits (100% vs 35.3%), and doctor shopping (100% vs 47.1%) compared to non-super-spreading events.

***Conclusions.*** These findings indicate that transmission is determined by host infectivity and the number of contacts, whereas super-spreading events were determined by the number of contacts and hospital visits. These relationships highlight the importance of rapidly enforcing infection control measures to prevent outbreaks.

**Keywords.** epidemiology; South Korea; Middle East respiratory syndrome coronavirus; super-spreading event; transmission.

Transmission heterogeneity was a significant characteristic of the 2015 South Korean outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection [1]. Transmission heterogeneity describes a state in which most transmissions are related to a few patients and most patients do not transmit the disease. Numerous other infectious diseases exhibit transmission heterogeneity [2], and this concept is important for understanding epidemics. The course of an epidemic is influenced by the basic reproduction number ($R_0$ = the average number of cases that 1 case produces in a susceptible population) and transmission heterogeneity [3]. As $R_0$ represents an average quantity, it is often insufficient to explain individual variation, and as transmission heterogeneity reflects individual variation, it can help predict the likelihood of super-spreading events. Even in instances with a low $R_0$, a disease with high transmission heterogeneity (eg, severe acute respiratory syndrome [SARS]) can cause super-spreading events [2], such as the super-spreading that occurred during the 2003 SARS outbreak [2, 4].

Transmission heterogeneity was observed during early MERS-CoV outbreaks [1] and became prominent during the 2015 South Korean outbreak. Among the 186 confirmed Korean cases of MERS-CoV infection, >80% of the transmissions were epidemiologically associated with 5 patients [5], and almost 90% of the cases caused no transmission. Furthermore, a recent study revealed that MERS has greater transmission heterogeneity compared to SARS [6]. Therefore, to successfully control MERS-CoV infection, it is essential to identify high-risk patients and perform targeted infection control [2]. However, these patients are difficult to identify, as an individual's infectiousness is affected by complex interactions between

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the pathogen, host, and environment. Several researchers have attempted to identify risk factors for super-spreading events during the SARS outbreak [3, 4, 7], although there is little information regarding the high-risk group(s) from the MERS-CoV outbreak.

The recent South Korean MERS-CoV outbreak was triggered by a single imported case, and epidemiological tracing was performed for all laboratory-confirmed cases and their close contacts [5, 8–13]. Thus, it is possible to precisely reconstruct the transmission chain and identify patients who transmitted MERS-CoV infection. Therefore, we analyzed the epidemiological characteristics that were associated with MERS-CoV transmission and super-spreading events.

## METHODS

### Definitions

Cases of MERS-CoV infection were confirmed using real-time reverse-transcription polymerase chain reaction (RT-PCR) assays, regardless of their clinical manifestations. The epidemiological reports were analyzed by epidemic intelligence service officers who participated in the MERS-CoV outbreak investigation. When a case was exposed to multiple confirmed cases, the transmission was attributed to the case with the highest likelihood of transmission, and any conflicts were resolved through the consensus of the epidemic intelligence service officers. Spreaders were defined as confirmed cases of MERS-CoV infection that were epidemiologically suspected of transmitting MERS-CoV to 1 or more persons. Super-spreading events were arbitrarily defined as transmission of MERS-CoV infection to 5 or more cases. The patient who triggered the outbreak was defined as patient zero. Cases that were infected by patient zero were defined as first-generation cases; cases that were infected by first-generation cases were defined as second-generation cases; and cases that were infected by second-generation cases were defined as third-generation cases [14]. Isolation was defined as separating symptomatic patients from others to prevent spreading, and quarantine was defined as separating or restricting the movement of healthy individuals who may have been exposed to the infection within the maximum incubation period. The transmission date was defined as the date of contact between the spreader and suspected secondary case during the spreader's infectious period. In cases with an exposure duration of longer than 1 day, the transmission date was defined as the day with the highest likelihood of transmission or as the median day during the exposure period in cases with consistent contact throughout the exposure. The date of sampling was the day on which the first positive respiratory specimen was collected. Close contacts were defined using the Guidelines on Middle East Respiratory Syndrome [15], which include persons who stayed in a room or ward with a confirmed case, who directly contacted respiratory secretions from confirmed cases, or who stayed within 2 m from the confirmed cases without wearing appropriate personal protective equipment. Pre-isolation pneumonia diagnoses were based on radiographic evidence. Doctor shopping was defined as visiting multiple healthcare facilities without an official interhospital transfer after developing MERS-CoV symptoms [16].

### Data Collection

Epidemiological reports from the outbreak were evaluated to collect data regarding basic demographic characteristics, medical history, MERS-CoV exposure, symptoms and their onset date(s), sampling date(s), contact history, and post-exposure infection control. The reports were drafted during the outbreak based on direct interviews with the confirmed cases and follow-up epidemiological investigations that were performed to identify the exposure route and close contacts. Hospital information systems were reviewed to identify patients who stayed in the hospital during the exposure period and healthcare providers who contacted the patient(s). Persons who contacted confirmed cases outside healthcare facilities were also traced. Data from closed circuit television, credit card transactions, and health insurance services were also reviewed [5]. The numbers of close contacts were calculated based on the number of quarantines during the outbreak. All data were collected as part of the public health response and in accordance with the Infectious Disease Control and Prevention Act [17].

### Laboratory Confirmation

Clinical specimens were collected in sterile containers and immediately transferred to qualified facilities. Sputum samples were mixed with 0–1× phosphate-buffered saline and vortexed vigorously to reduce their viscosity. Viral RNA was extracted from the clinical specimens using a Qiagen viral RNA mini kit (Qiagen, Hilden, Germany). All laboratory diagnoses of MERS-CoV were confirmed using the World Health Organization guidelines [18] and results from real-time RT-PCR assays that target upstream of the MERS-CoV envelope protein gene (*upE*) and the open reading frame 1a gene (*ORF1a*) [19]. Cycle threshold (Ct) values for the *upE* and *ORF1a* genes were obtained during testing. We analyzed the Ct value from the first positive MERS-CoV specimen (or the specimen obtained immediately after a positive screening test).

### Statistical Analyses

Categorical variables were compared using the $\chi^2$ test and Fisher exact test, and the Mann–Whitney test was used for continuous variables. The variables' associations with MERS-CoV transmission were evaluated using multiple logistic regression analyses, and covariates were selected based on a $P$ value of $< .1$ in the univariate analyses. A $P$ value of $< .05$ was considered statistically significant. All analyses were performed using R software (version 3.2.2; R Foundation, Vienna, Austria).

## RESULTS

### Transmission Chain

We identified 186 cases of confirmed MERS-CoV infection. Patient zero infected 28 first-generation cases. Among the 28 cases, 8 were responsible for transmission to 121 second-generation cases. Among the 121 cases, 12 infected 30 third-generation cases. One patient with an unclear source of infection (case 119) transmitted the infection to another patient. Four patients exhibited unclear sources of transmission (cases 43, 178, 184, and 185). Each confirmed case transmitted the infection to 0–83 secondary cases (Figure 1). There were 164 nonspreaders and 22 spreaders (1 or more transmission). Of the spreaders, 5 cases transmitted the infection to 5 or more cases (super-spreading event).

### The Spreaders' Epidemiological Characteristics

After excluding the 5 cases with unclear infection sources, we identified 180 transmissions generated by 22 spreaders. A total of 150 transmission events (83.3%) were epidemiologically linked to the 5 super-spreading events. Twenty-five transmission events (13.9%) occurred within 3 days after symptom onset, 136 transmissions (75.6%) occurred 4–7 days after symptom onset, and 19 transmissions (10.6%) occurred >7 days after symptom onset. A total of 170 transmission events (94.4%) occurred on the day of or after a radiographically confirmed diagnosis of pneumonia. A total of 173 transmissions (96.1%) occurred before appropriate in-hospital isolation. Seven transmissions (3.9%) occurred between confirmed cases and healthcare personnel after in-hospital isolation: 4 (cases164, 169, 181, and 183) were doctors or nurses who managed confirmed cases, 1 (case148) participated in cardiopulmonary resuscitation of a confirmed case, 1 (case 162) involved portable radiography for a confirmed case, and 1 (case 179) rode in an ambulance with a confirmed case during a hospital transfer.

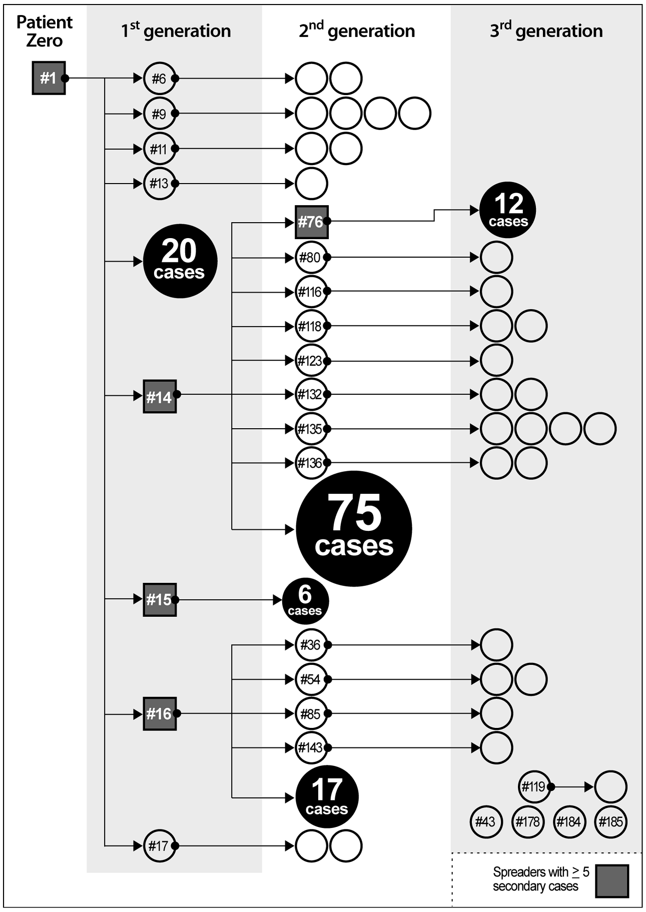


**Figure 1.** Transmission chain for the 186 laboratory-confirmed cases of Middle East respiratory syndrome coronavirus infection in South Korea during 2015. Figures in squares indicate the spreaders that transmitted the infection to 5 or more cases. One case with an unclear infection generation (case 119) transmitted the infection to an additional case. The source of infection was unclear in 4 additional cases (cases 43, 178, 184, and 185).

### Comparing the Spreaders and Nonspreaders

Table 1 shows the spreaders' and nonspreaders' epidemiological characteristics. These individuals exhibited similar values for age, sex, and presence of cough at symptom onset. However, spreaders exhibited significantly more frequent underlying respiratory disease (27.3% vs 11%; $P = .044$). The spreaders also had significantly lower Ct values (*upE*: median [interquartile range], 22.7 [19.5–29.1] vs 27.2 [23.5–30.4]; $P = .004$ and *ORF1a*: 23.7 [20.3–29.8] vs 27.9 [24.9–30.8]; $P = .009$). The intervals from symptom onset to diagnosis or obtaining a respiratory specimen were also significantly longer among spreaders (to diagnosis: 9 [5.5–10] days vs 5 [3–8] days; $P = .008$ and to sampling: 8 [5–9.3] days vs 4 [2–6] days; $P < .001$). Furthermore, the interval from symptom onset to isolation was longer among spreaders (7 [4.5–9] days vs 3 [1–6] days; $P = .002$). Spreaders exhibited a significantly higher proportion of pre-isolation pneumonia diagnoses (68.2% vs 17.1%; $P < .001$) and a longer interval from the pneumonia diagnosis to isolation (4 [3–7] days vs 1 [0–3] days; $P = .008$). The overall number of contacts was significantly larger among spreaders compared to nonspreaders (149 [22.3–640.5] vs 17.5 [2–92.5]; $P = .004$). Compared to nonspreaders, spreaders exhibited a significantly higher proportion for pre-isolation hospitalization (68.2% vs 16.5%; $P < .001$), visiting outpatient clinics (59.1% vs 33.5%; $P = .019$), and visiting emergency rooms (ERs; 50% vs 7.3%; $P < .001$).

We used logistic regression analyses to evaluate the risk factors for transmission (Table 2). In the univariate analyses, transmission was associated with underlying respiratory disease, Ct value, interval from symptom onset to diagnosis, number of contacts, and pre-isolation hospitalization or ER visits. In the multivariate analyses, transmission was independently associated with a low Ct value for *upE* (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.75–0.96) and pre-isolation hospitalization or ER visits (OR, 6.82; 95% CI, 2.06–22.84).

**Table 1. Comparing the Demographic and Epidemiological Characteristics of Middle East Respiratory Syndrome Coronavirus Infection Spreaders and Nonspreaders During the 2015 South Korean Outbreak**

| Variables, n (%) or median [interquartile range] | Spreaders (n = 22) | Nonspreaders (n = 164) | *P* Value |
|---|---|---|---|
| *Host factors* | | | |
| Age, y | 55.5 [35.0–67.0] | 55 [42.5–66.0] | .938 |
| Sex, male | 16 (72.7) | 95 (57.9) | .184 |
| Case classification | | | .013[a] |
| Healthcare personnel | 0 (0) | 25 (15.2) | |
| Patients | 9 (40.9) | 74 (45.1) | |
| Family members | 5 (22.7) | 46 (28.0) | |
| Paid caregivers | 2 (9.1) | 7 (4.3) | |
| Others[b] | 6 (27.3) | 12 (7.3) | |
| Stage of transmission[c] | | | <.001[a] |
| Patient zero | 1 (4.8) | 0 (0) | |
| 1st generation | 8 (38.1) | 20 (12.5) | |
| 2nd generation | 12 (57.1) | 111 (69.4) | |
| 3rd generation | 0 (0) | 29 (18.1) | |
| Underlying respiratory disease[d] | 6 (27.3) | 18 (11.0) | .044[a] |
| Cough at symptom onset | 5 (22.7) | 30 (18.3) | .571[a] |
| Cycle threshold value (reverse transcription polymerase chain reaction) | | | |
| *upE* | 22.7 [19.5–29.1] | 27.2 [23.5–30.4] | .004 |
| *ORF1a* | 23.7 [20.3–29.8] | 27.9 [24.9–30.8] | .009 |
| *Duration* | | | |
| Symptom onset to sampling, days | 8 [5.0–9.3] | 4 [2.0–6.0] | <.001 |
| Symptom onset to diagnosis, days[e] | 9 [5.5–10.0] | 5 [3.0–8.0] | .008 |
| Symptom onset before isolation[e] | 21 (95.5) | 124 (78.0) | .083[a] |
| Onset to isolation, days | 7 [4.5–9.0] | 3 [1.0–6.0] | .002 |
| Diagnosis of pneumonia before isolation[f] | 15 (68.2) | 28 (17.1) | <.001 |
| Pneumonia to isolation, days | 4 [3.0–7.0] | 1 [0–3.0] | .008 |
| *Contacts* | | | |
| Contact with other persons before isolation | 21 (95.5) | 138 (84.1) | .209[a] |
| Number of contacts | 149 [22.3–640.5] | 17.5 [2.0–92.5] | .004 |
| *Hospital visit before isolation* | | | |
| Hospitalization | 15 (68.2) | 27 (16.5) | <.001[a] |
| Duration of hospitalization, days | 5 [4.0–8.0] | 4 [2.0–7.0] | .354 |
| Outpatient clinic visit | 13 (59.1) | 55 (33.5) | .019 |
| Frequency of visits | 2 [1.0–2.0] | 2 [1.0–3.0] | .472 |
| ER visit | 11 (50.0) | 12 (7.3) | <.001[a] |
| Frequency of visits | 2 [1.0–2.0] | 1.5 [1.0–2.0] | .499 |
| Number of hospitals visited | 2 [1.0–2.3] | 0 [0–1.0] | <.001 |
| For hospitalization or ER visit | 1 [0–2.0] | 0 [0–0] | <.001 |
| For outpatient clinic visit | 1 [1.0–2.0] | 1 [1.0–2.0] | .364 |

*P* values were obtained using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney test for continuous variables.

Abbreviation: ER, emergency room.

[a]Fisher exact test.

[b]Includes hospital security agents in the emergency department, emergency medical technicians, visitors, police officers, and hospital office workers.

[c]Excludes 5 cases with unclear stages of transmission.

[d]Includes chronic obstructive pulmonary disease, asthma, pulmonary tuberculosis, and pneumonia before the exposure to Middle East respiratory syndrome coronavirus.

[e]Excludes 5 cases with unclear symptom onset dates.

[f]Cases with radiographic evidence of pneumonia before their isolation.

#### Comparing the Spreaders With 5 or More Transmissions and Spreaders With 4 or Fewer Transmissions

We compared the epidemiological characteristics of the 5 spreaders with 5 or more transmissions and the 17 spreaders with 4 or fewer transmissions (Table 3). Both groups exhibited similar host factors and contact durations. However, spreaders with 5 or more transmissions exhibited higher values for pre-isolation contacts (777 [459.5–862] vs 78 [8.5–281.5]; $P = .017$), pre-isolation ER visits (100% vs 35.3%; $P = .035$), and the number of healthcare facilities that each patient visited for hospitalization or ER treatment (2 [2.0–2.5] vs 1 [0–1.5]; $P = .009$). In addition, super-spreading events were marginally associated with doctor shopping (100% vs 47.1%; $P = .054$).

**Table 2. Epidemiological Factors Associated With Middle East Respiratory Syndrome Coronavirus Transmission During the 2015 South Korean Outbreak**

| | Univariate Logistic Regression | | | Multivariate Logistic Regression | | |
|---|---|---|---|---|---|---|
| Variable (reference) | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Underlying respiratory disease (no) | 3.04 | 1.06–8.76 | .039 | 3.02 | 0.80–11.40 | .103 |
| Cycle threshold value (*upE*) | 0.85 | 0.76–0.94 | .002 | 0.84 | 0.75–0.96 | .007 |
| Symptom onset to diagnosis (days) | 1.13 | 1.01–1.27 | .031 | 1.02 | 0.87–1.18 | .846 |
| Number of contacts (<10) | | | .004 | 1.49 | 0.75–2.97 | .260 |
| 10–99 | 1.03 | 0.27–4.03 | .963 | | | |
| ≥100 | 4.86 | 1.61–14.65 | .005 | | | |
| Hospitalization or emergency room visit before isolation (no) | 10.59 | 3.84–29.15 | <.001 | 6.82 | 2.06–22.84 | .002 |

There was no multicollinearity between the independent variables (all variables: R score of <0.5).

Abbreviations: CI, confidence interval; OR, odds ratio.

## DISCUSSION

We evaluated the epidemiological characteristics of patients who transmitted MERS-CoV during the recent South Korean outbreak. Among the 186 confirmed MERS-CoV cases, only 22 cases transmitted the infection to other individuals. These spreaders had higher host infectivity and wider and prolonged contacts compared to nonspreaders. The risk factors for super-spreading events included a larger number of contacts and a pre-isolation ER visit. Doctor shopping was marginally associated with a super-spreading event. However, both spreaders with 5 or more transmissions and spreaders with 4 or fewer transmissions exhibited similar levels of host infectivity. It appears that both host infectivity and the number of contacts influenced MERS-CoV transmission, whereas super-spreading events were mostly associated with a greater likelihood of encountering other people under diverse environmental conditions.

During the 2015 outbreak, approximately 75% of the transmissions occurred during days 4–7 after symptom onset, and this may be a period when the risk of transmission is particularly high. Furthermore, this high-risk period was temporally associated with other epidemiological factors. First, the period overlapped with the confirmed cases' visits to healthcare facilities, as hospitalization and ER visits peaked during days 4–7 after symptom onset. It is well known that MERS-CoV outbreaks generally occur in the healthcare setting [1, 5, 13, 20], and the high-risk period may be associated with healthcare-seeking behaviors. Second, the high-risk period was several days (1–4 days) after the radiographic diagnoses of pneumonia, which generally occurred on days 3–4 after symptom onset. Although the significance of pre-isolation pneumonia has not been discussed previously, a radiographic diagnosis of pneumonia may influence transmission in 2 ways. First, it may directly increase the chance of transmission by actively generating lower respiratory tract secretions and a productive cough. Second, it may be an indirect index of disease severity and hospital visiting status. In our study, cases with pre-isolation pneumonia had lower Ct values and more frequent pre-isolation hospital visits.

The epidemiological significance of the high-risk period could also be observed when we compared the spreaders and nonspreaders. The spreaders were typically isolated after the high-risk period (median, 7 days after symptom onset and 4 days after a diagnosis of pneumonia), whereas nonspreaders were typically isolated before this period (median, 3 days after symptom onset and 1 day after a diagnosis of pneumonia). Similar results were observed in a study of the SARS outbreak, which revealed that late admission to healthcare facilities (especially >4 days after symptom onset) was associated with super-spreading events [21]. Thus, infection prevention measures should target isolation before this critical period (ie, within 4–7 days after symptom onset and within 1 day after the detection of pneumonia). Interestingly, the average duration from symptom onset to isolation dropped to <4 days during the first week of June 2015, and reports of new cases have rapidly decreased since that time.

Among the host factors that were associated with transmission, only the Ct value was statistically significant in the multivariate analyses. The Ct value is a semiquantitative continuous variable that is inversely proportional to the viral load. Ct values are associated with the severity of MERS-CoV infection [22], although its relationship with transmission has rarely been studied. In the present study, spreaders had significantly lower Ct values compared to nonspreaders, which suggests that Ct values might reliably predict transmission. Moreover, the cases with very low Ct values (Ct <23) tended to transmit the infection in uncommon circumstances. In both the present study and previous studies, MERS-CoV transmission usually occurred in the hospital setting [1, 11, 13, 23]. In contrast, cases with very low Ct values transmitted the infection in more diverse settings in the present outbreak (eg, their household, in an ambulance, in an outpatient clinic, or to healthcare personnel after in-hospital isolation). These findings suggest that cases with very low Ct values can potentially transmit the infection in unexpected conditions. However, our data regarding the Ct values have several limitations. First, various amounts of phosphate-buffered saline were added to dilute the respiratory specimens, and this

Table 3. **Comparison of the Epidemiological Characteristics of Spreaders With 5 or More Cases and Spreaders With 4 or Fewer Cases**

| Variables, n (%) or Median [interquartile range] | Spreaders With 5 or More Cases (n = 5) | Spreaders With 4 or Fewer cases (n = 17) | *P* Value |
|---|---|---|---|
| *Host factors* | | | |
| Underlying respiratory disease[a] | 2 (40) | 4 (23.5) | .585[b] |
| Cough at symptom onset | 3 (60) | 2 (11.8) | .055[b] |
| Cycle threshold value (reverse transcription polymerase chain reaction) | | | |
| *upE* | 22.2 [17.4–29.9] | 22.8 [20.7–26.9] | .820 |
| *ORF1a* | 23.2 [18.2–32.2] | 23.9 [21.3–28.1] | .880 |
| *Duration* | | | |
| Symptom onset to sampling, days | 9 [4.5–10.5] | 6 [5.0–8.5] | .284 |
| Symptom onset to diagnosis, days | 9 [5.5–11] | 8 [5.0–9.5] | .320 |
| Symptom onset before isolation | 5 (100) | 16 (94.1) | 1[b] |
| Onset to isolation, days | 8 [4.0–9.5] | 6.5 [4.3–8.8] | .453 |
| Diagnosis of pneumonia before isolation[c] | 5 (100) | 10 (58.8) | .135[b] |
| Pneumonia to isolation, days | 5 [2.0–8.0] | 3.5 [2.3–6.3] | .419 |
| *Contacts* | | | |
| Contact with other persons before isolation | 5 (100) | 16 (94.1) | 1[b] |
| Number of contacts | 777 [459.5–862] | 78 [8.5–281.5] | .017 |
| *Hospital visit before isolation* | | | |
| Hospitalization | 5 (100) | 10 (58.8) | .135[b] |
| Duration of hospitalization, days | 5 [2.5–9] | 4.5 [3.5–8.3] | .852 |
| Outpatient clinic visit | 3 (60) | 10 (58.8) | 1[b] |
| ER visit | 5 (100) | 6 (35.3) | .035[b] |
| Frequency of visits | 2 [2–2.5] | 1.5 [1.0–2.0] | .054 |
| Number of hospitals visited | 2 [2.0–3.5] | 1 [1.0–2.0] | .055 |
| For hospitalization or ER visit | 2 [2.0–2.5] | 1 [0–1.5] | .009 |
| For outpatient clinic visit | 1 [0–1.5] | 1 [0–1.0] | .966 |
| Doctor shopping | 5 (100) | 8 (47.1) | .054[b] |

*P* values were obtained using the $\chi^2$ test or Fisher exact test for categorical variables, and the Mann–Whitney test for continuous variables.

Abbreviation: ER, emergency room.

[a]Includes chronic obstructive pulmonary disease, asthma, pulmonary tuberculosis, and pneumonia before the exposure to Middle East respiratory syndrome coronavirus.

[b]Fisher exact test.

[c]Cases with radiographic evidence of pneumonia before their isolation.

may have affected the Ct values. Second, the Ct value is influenced by the specimen type and the interval between symptom onset and sample collection [22, 24], but various different types of specimens were collected at different time points in the present study. However, we only evaluated 5 nonsputum specimens, and there was no linear correlation between the Ct values and the interval from onset to sampling.

Our comparison of the spreaders with 5 or more transmissions and spreaders with 4 or fewer transmissions revealed that the spreaders with 5 or more transmissions had an approximately 10-fold higher number of contacts. Furthermore, there were no significant differences in host infectivity. These findings may suggest that the underlying likelihood of transmission has the greatest influence on super-spreading events rather than an intrinsic difference in host infectivity. A similar finding was observed in a previous study of the SARS super-spreading event [4], with those super-spreaders having 11–74 contacts compared to 1–4 contacts for the spreaders with 1–2 transmissions.

Our study also revealed that a pre-isolation ER visit and doctor shopping were associated with super-spreading events. In addition, super-spreading events were associated with the number of healthcare facilities that each patient visited for hospitalization or ER treatment but not with the number of hospitals visited for outpatient treatment. In South Korea, patients who seek hospitalization without prior arrangements tend to visit the ER, and a history of 2 or more ER visits strongly suggests that the patient had been doctor shopping during hospitalization. Specific environmental conditions have been suggested to increase the likelihood of a super-spreading event [3], and doctor shopping may increase the likelihood of encountering these conditions. For example, when a confirmed case changes hospital during hospitalization without an official interhospital transfer, multiple environments are exposed to the infected case (an ambulance, an ER, and a ward). Thus, doctor shopping can greatly increase the likelihood of encountering conditions that are suitable for a super-spreading event. In the present outbreak, 4 of the 5 super spreaders (cases 1, 14, 16, and 76) transmitted the infection at 2 or more hospitals, as they had visited multiple healthcare facilities. Therefore, it is very important to have an early suspicion of MERS-CoV infection and minimize doctor shopping during the early stage of an outbreak.

Our study has several limitations. First, some of the confirmed cases had multiple potential sources of infection, and we attributed the transmission to the case with the highest epidemiological probability. The source of infection was clear in >95% of the transmissions, and we excluded 3 cases that had contact with multiple cases and an unclear source of transmission. However, as the analyses of the epidemiological data are ongoing, the list of spreaders may change if new epidemiological evidence is uncovered. Second, we did not have access to genomic sequencing data, which might have provided information regarding the relatedness of transmitted strains. Third, transmission may be affected by other epidemiological factors, including aerosol-generating procedures, differences in environmental conditions, and variations in crowdedness [3, 13, 25]. However, these factors were not included in the present analysis. Fourth, serological testing was not performed for every close contact, and additional asymptomatic cases may have been present. However, the seropositive rate was 0.7% in a recent serological study of close contacts [26]. Thus, the absence of serological testing likely did not significantly influence our results.

We evaluated the epidemiological risk factors for MERS-CoV transmission during the recent South Korean outbreak. Superspreading events were not related to intrinsic host characteristics and were attributable to the likelihood of transmission. Therefore, strict ER triage and minimizing doctor shopping during an outbreak's early stage may help prevent super-spreading events.

## Notes

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***Author contributions.*** S. W. K. performed the literature search, study design, data collection, analysis, interpretation, and writing. M. K. contributed to the study design, data interpretation, and writing. J. W. P., Y. S. P., C. L., K. M. K., K. J. L., and D. K. contributed to the data collection and interpretation. H. D. J. and J. S. Y. contributed to the data collection, MERS PCR testing, data interpretation, and analysis. Y. J. H. and B. Y. C. contributed to the study design, data interpretation, and revising the manuscript. S. W. K. and M. K. revised the manuscript. All authors contributed to writing and approved the final manuscript.

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## References

1. Assiri A, McGeer A, Perl TM, et al; KSA MERS-CoV Investigation Team. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med **2013**; 369:407–16.
2. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature **2005**; 438:355–9.
3. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis **2007**; 44:1017–25.
4. Shen Z, Ning F, Zhou W, et al. Superspreading SARS events, Beijing, 2003. Emerg Infect Dis **2004**; 10:256–60.
5. Korean Centers for Disease Control and Prevention. Middle East respiratory syndrome coronavirus outbreak in the Republic of Korea, 2015. Osong Public Health Res Perspect **2015**; 6:269–78.
6. Chowell G, Abdirizak F, Lee S, et al. Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. BMC Med **2015**; 13:210.
7. Stein RA. Super-spreaders in infectious diseases. Int J Infect Dis **2011**; 15:e510–3.
8. Ki M. 2015 MERS outbreak in Korea: hospital-to-hospital transmission. Epidemiol Health **2015**; 37:e2015033.
9. Kim KM, Ki M, Cho SI, et al. Epidemiologic features of the first MERS outbreak in Korea: focus on Pyeongtaek St. Mary's Hospital. Epidemiol Health **2015**; 37:e2015041.
10. Choi JH, Yoo B, Lee SY, et al. Epidemiological investigation on the 119th confirmed MERS-CoV case with the indefinite mode of transmission in Pyeongtaek outbreak, Korea. Epidemiol Health **2015**;37: e2015054.
11. Park YS, Lee C, Kim KM, et al. The first case of the 2015 Korean Middle East respiratory syndrome outbreak. Epidemiol Health **2015**; 37:e2015049.
12. Chang K, Ki M, Lee EG, Lee SY, Yoo B, Choi JH. MERS epidemiological investigation to detect potential mode of transmission in the 178th MERS confirmed case in Pyeongtaek, Korea. Epidemiol Health **2015**; 37:e2015036.
13. Cho SY, Kang JM, Ha YE, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. Lancet **2016**; 388:994–1001.
14. Farrington P. Modelling epidemics. Oxford: The Open University, **2003**.
15. Ministry of Health and Welfare. Guidelines on Middle East respiratory syndrome. Sejong, **2015**.
16. Sansone RA, Sansone LA. Doctor shopping: a phenomenon of many themes. Innov Clin Neurosci **2012**; 9:42–6.
17. Korea Ministry of Government Legislation Infectious Disease Control and Prevention Act. [cited 10 Nov 2014]. Available from: http://law.go.kr/ (Korean).
18. World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus. Interim recommendations. Geneva, Switzerland: World Health Organization; **2014**.
19. Kim YJ, Cho YJ, Kim DW, et al. Complete genome sequence of Middle East respiratory syndrome coronavirus KOR/KNIH/002_05_2015, isolated in South Korea. Genome Announc **2015**; 3. pii: e00787–15.
20. Oboho IK, Tomczyk SM, Al-Asmari AM, et al. 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. N Engl J Med **2015**; 372:846–54.
21. Li Y, Yu IT, Xu P, et al. Predicting super spreading events during the 2003 severe acute respiratory syndrome epidemics in Hong Kong and Singapore. Am J Epidemiol **2004**; 160:719–28.
22. Feikin DR, Alraddadi B, Qutub M, et al. Association of higher MERS-CoV virus load with severe disease and death, Saudi Arabia, 2014. Emerg Infect Dis **2015**; 21:2029–35.
23. Drosten C, Muth D, Corman VM, et al. An observational, laboratory-based study of outbreaks of Middle East respiratory syndrome coronavirus in Jeddah and Riyadh, Kingdom of Saudi Arabia, 2014. Clin Infect Dis **2015**; 60:369–77.
24. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. J Infect Dis **2014**; 210:1590–4.
25. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One **2012**; 7:e35797.
26. Kim CJ, Choi WS, Jung Y, et al. Surveillance of the Middle East respiratory syndrome (MERS) coronavirus (CoV) infection in healthcare workers after contact with confirmed MERS patients: incidence and risk factors of MERS-CoV seropositivity. Clin Microbiol Infect **2016**; 22:880–6.