



ORIGINAL ARTICLE

Middle East Respiratory Syndrome Coronavirus Outbreak in the Republic of Korea, 2015

Korea Centers for Disease Control and Prevention*

Korea Centers for Disease Control and Prevention, Cheongju, Republic of Korea.

Received: July 31, 2015
Accepted: August 27, 2015

KEYWORDS:

coronavirus,
epidemiology,
Middle East respiratory
syndrome

Abstract

Objectives: The outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea started from the index case who developed fever after returning from the Middle East. He infected 26 cases in Hospital C, and consecutive nosocomial transmission proceeded throughout the nation. We provide an epidemiologic description of the outbreak, as of July 2015.

Methods: Epidemiological research was performed by direct interview of the confirmed patients and reviewing medical records. We also analyzed the incubation period, serial interval, the characteristics of superspreaders, and factors associated with mortality. Full genome sequence was obtained from sputum specimens of the index patient.

Results: A total of 186 confirmed patients with MERS-CoV infection across 16 hospitals were identified in the Republic of Korea. Some 44.1% of the cases were patients exposed in hospitals, 32.8% were caregivers, and 13.4% were healthcare personnel. The most common presenting symptom was fever and chills. The estimated incubation period was 6.83 days and the serial interval was 12.5 days. A total of 83.2% of the transmission events were epidemiologically linked to five superspreaders, all of whom had pneumonia at presentation and contacted hundreds of people. Older age [odds ratio (OR) = 4.86, 95% confidence interval (CI) 1.90–12.45] and underlying respiratory disease (OR = 4.90, 95% CI 1.64–14.65) were significantly associated with mortality. Phylogenetic analysis showed that the MERS-CoV of the index case clustered closest with a recent virus from Riyadh, Saudi Arabia.

Conclusion: A single imported MERS-CoV infection case imposed a huge threat to public health and safety. This highlights the importance of robust preparedness and optimal infection prevention control. The lessons learned from the current outbreak will contribute to more up-to-date guidelines and global health security.

*Correspondence.

E-mail: korea.cdc.mers@gmail.com.

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License (<http://creativecommons.org/licenses/by-nc-nd/4.0>) which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Middle East respiratory syndrome (MERS) is a viral respiratory illness caused by a novel human beta-coronavirus (CoV) [1,2]. Since it was first reported from Saudi Arabia in September 2012, 1,211 patients have been detected worldwide, as of June 5, 2015 [3]. Secondary infection through human-to-human transmission was confirmed from previous outbreaks [4,5,6], and outbreaks in healthcare settings comprise a large proportion of the outbreak [4,7]. Although the exact route of transmission is still unclear, the respiratory droplet route is currently most likely [8]. Until June 2015, most of the cases of MERS-CoV infection occurred in the Middle East. Although a few cases were reported in other countries, none exceeded five [3].

The outbreak of MERS-CoV infection in the Republic of Korea started when a 68-year-old South Korean man developed fever and myalgia on May 11 after returning from a business trip to Bahrain, United Arab Emirates, and Saudi Arabia. MERS-CoV infection was diagnosed on May 20. However, by then he had already contacted approximately 600 people during his visits to two clinics and admission to a secondary hospital (Hospital C) located in Pyeongtaek, Gyeonggi-do. Twenty-six cases of MERS-CoV infection were confirmed among these initial contacts, and consecutive transmission based on nosocomial infection rapidly proceeded throughout the nation.

This unprecedented nationwide MERS-CoV outbreak in the Republic of Korea imposed a huge threat not merely to public health and safety, but also to the economy, the tourist industry, and social activity. The forecast for gross domestic product was downgraded by 0.3%, >135,000 foreign tourists canceled their visit to the Republic of Korea, >2,700 schools were closed, and >16,000 people underwent house quarantine. These highlight the importance of appropriate infection control intervention. However, although evidence-based investigation is essential for effective intervention, information concerning the epidemiology of MERS-CoV infection is currently limited. Herein, we provide an overall epidemiologic description of the MERS-CoV infection outbreak in the Republic of Korea, which is the largest outbreak outside of the Arabian Peninsula.

2. Materials and methods

2.1. Definitions

A person was defined as a confirmed MERS-CoV infection case when there was laboratory evidence of MERS-CoV infection, irrespective of clinical signs and symptoms. The onset of illness was defined as the time when a patient newly developed any symptom relating to MERS-CoV infection such as fever, chills, myalgia, shortness of breath, cough, sore throat, headache, nausea,

vomiting, diarrhea, or abdominal pain. Cases were classified into healthcare personnel (doctor, nurse, and radiologic technologist), patient, caregiver (both paid and family caregivers), and others. Close contact was defined as a person who did not wear appropriate personal protective equipment (gloves, gown, N95 mask, goggles, or face mask), and: (1) stayed within 2 m of the patient; (2) stayed in the same room or ward with the patient; or (3) directly contacted respiratory secretions of the patient [9]. In order to describe patients who caused sizable subsequent infection transmission, we arbitrarily defined a super-spreading event as one patient transmitting the infection to more than four patients. The patient who caused the super-spreading event was defined as a superspreader.

2.2. Data source and assessment of exposure

We carried out an epidemiological research by direct interview of the patients who were confirmed with MERS-CoV infection. Data concerning demographic characteristics, the initial symptom and date of its onset, healthcare facilities for the case visited, presence of personal protective equipment, and a list of contacts were collected. The duration and route of exposure were further determined through reviewing closed circuit television and tracking the health insurance review and assessment service, global positioning system of the patient's cellular phone, and recent credit card inquiry transactions. Based on these data, potential exposures were identified for each confirmed case. When a confirmed case had multiple potential exposures, the most probable exposure was determined through the consensus of the authors. Simultaneously, we thoroughly reviewed the medical records of the patients in order to identify underlying comorbidities, radiological evidence of pneumonia, aerosol generating procedures, and final prognosis. National health insurance data was used to validate underlying diseases of the confirmed patients.

2.3. Clinical samples and laboratory confirmation

Sputum or tracheal-aspirate samples of the patients were collected in a sterile cap and transferred to qualified national, local, or commercial facilities immediately. For patients whose sputum specimen was not acquirable, a specimen from a nasopharyngeal or oropharyngeal swab was obtained. Laboratory diagnosis was performed according to the World Health Organization guidelines of the MERS laboratory test [10]. For molecular detection of MERS-CoV RNA, two real-time reverse-transcription polymerase chain reaction assays targeting an upstream of MERS-CoV envelope protein gene and the open reading frame 1a (ORF 1a) gene were used [11].

2.4. Sequencing and phylogenetic analysis

Full genome sequence using Sanger and Illumina sequencing was obtained from direct polymerase chain reaction products using sputum specimens from the

index patient. Imported high quality reads were mapped against the JX869059 reference sequence using the CLC Genomic Workbench Version 8.0.1 (CLC bio, Aarhus, Denmark). Fasta consensus sequences obtained from deep sequencing and a group of 15 MERS-CoV complete genome sequences retrieved from GenBank were aligned using MAFFT (Multiple Alignment using Fast Fourier Transform) algorithm [12]. Phylogenetic reconstructions were performed by maximum likelihood criterion using RAxML (Randomized Axelerated Maximum Likelihood) version 8.2.6 (<https://github.com/stamatak/standard-RAxML>) [13]. Trees were visualized using FigTree v.1.4 (<http://tree.bio.ed.ac.uk/software/figtree>).

2.5. Statistical analysis

The incubation period was estimated by identifying the earliest and latest time of possible exposure and the time of symptom onset for each case. Treating these times as interval-censored estimates of the incubation period for each person, we fit a log-normal distribution to these data using maximum-likelihood techniques. We then examined the robustness of our estimates with multiple definitions of onset and with the exclusion of particular cases. The serial interval was estimated by identifying the times of symptom onset in the patient and in the person who transmitted the infection (infected–infectior pairs) and then fitting a log-normal

distribution to these interval-censored data [14]. We estimated the medians and 5th and 95th percentiles of the incubation period and the serial interval using the quintiles of log-normal distribution fit to each data set. The Chi-square test and Fisher's exact test were used, as appropriate, to compare variables such as age, sex, symptoms at presentation, and underlying disease in association with mortality. Risk factors associated with mortality were assessed using logistic regression analysis. All statistical tests were two-tailed and were considered statistically significant at $p < 0.05$. Statistical analysis was performed using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA), SPSS Statistics Software, version 20.0 (IBM Corp., Armonk, NY, USA), and R statistical package, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Description of the outbreak

A total of 186 confirmed patients of MERS-CoV infection were identified in the Republic of Korea between May 20, 2015 and July 13, 2015. The outbreak proceeded with three phases of transmission and spread to 16 healthcare facilities (Figure 1). The median age of confirmed MERS-CoV patients was 55 years

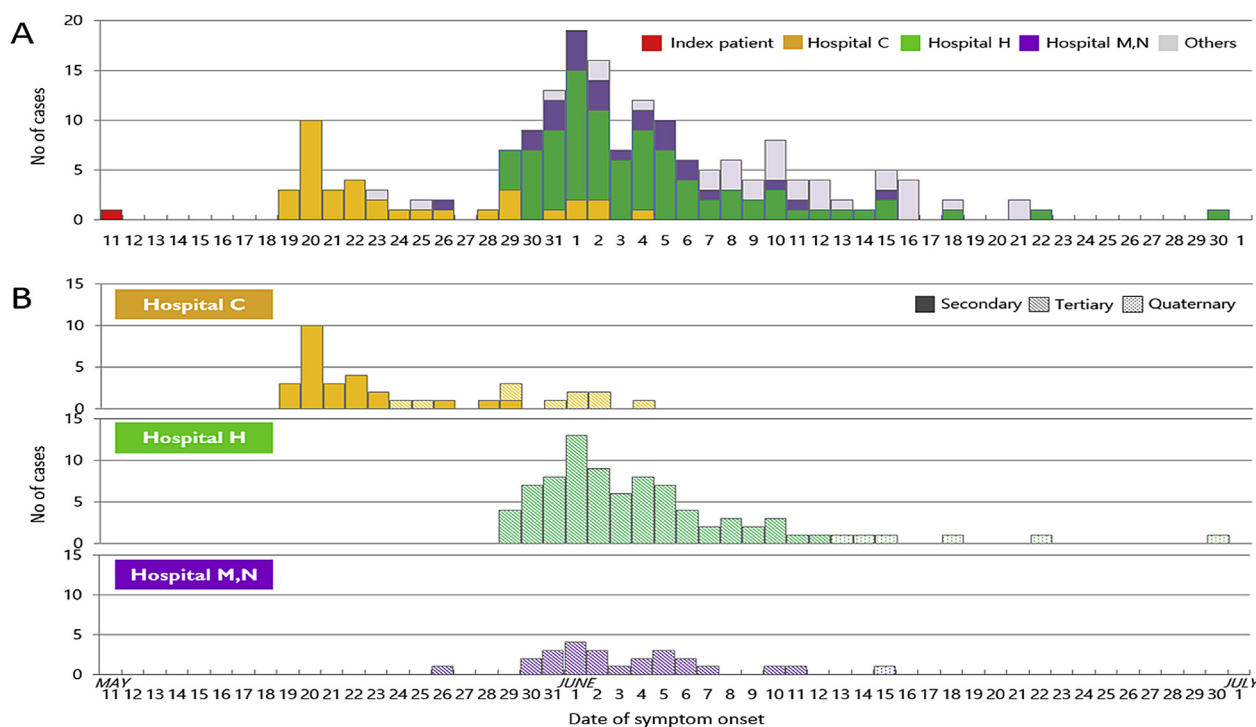


Figure 1. Epidemiologic curve of 178 confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea, 2015. Panel A (integrated curve) depicts the overall epidemiologic curve by date of symptom onset. Red color indicates the index patient, and three main clusters (Hospital C, Hospital H, and Hospital M and N) are depicted with yellow, green, and purple, respectively. Eight cases whose date of symptom onset is uncertain or who are still under investigation are excluded. Panel B shows the epidemic curve of each of the three main clusters. Stages of transmission are expressed by different patterns. An additional case in Hospital H whose stage of transmission is uncertain is excluded.

Table 1. Demographic and clinical features of 186 cases of laboratory-confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infection, Republic of Korea, 2015.

Characteristics	No. of patients
Sex, <i>n</i> (%)	
Male	111 (59.7)
Female	75 (40.3)
Age (y), median (IQR)	55 (42–66)
≥65y, <i>n</i> (%)	55 (29.6)
Case classification, <i>n</i> (%)	
Healthcare personnel	25 (13.4)
Patient	82 (44.1)
Caregiver	61 (32.8)
Others*	18 (9.7)
Symptoms at presentation, <i>n</i> (%)	
Fever/chills	138 (74.2)
Cough	33 (17.7)
Dyspnea	10 (5.4)
Myalgia	47 (25.3)
Headache	16 (8.6)
GI symptoms [†]	24 (12.9)
Sputum	14 (7.5)
Sore throat	8 (4.3)
Comorbidities, <i>n</i> (%)	
Any [‡]	102 (54.8)
Respiratory disease [§]	23 (12.4)
Diabetes mellitus	52 (28.0)
Cardiac disease	42 (22.6)
Chronic kidney disease	9 (4.8)
Malignancy	43 (23.1)
Known setting of contact, <i>n</i> (%) [¶]	
Healthcare facility	178 (98.0)
Household	1 (0.5)
Ambulance	3 (1.5)
Time from symptom onset to laboratory confirmation in days, median (IQR)	5 (3–9)
Time from symptom onset to death in days, median (IQR)	15 (10–20)
Outcome as of July 13, 2015, <i>n</i> (%)	
Recovered	131 (70.4)
Ongoing treatment in hospital	19 (10.2)
Died	36 (19.4)

*Includes visitors, hospital security agents etc; [†]Any one or more among the following symptoms: nausea, vomiting, diarrhea, gastric discomfort, loss of appetite; [‡]Any one or more among respiratory diseases, including chronic obstructive pulmonary disease and asthma, diabetes mellitus, cardiac disease, chronic kidney disease, and malignancy; [§]Includes chronic obstructive pulmonary disease and asthma; ^{||}Includes ischemic heart disease, arrhythmia and heart failure; [¶]With exclusion of the index patient and three cases of which the precise setting of contact is unidentified. IQR = interquartile range.

(Interquartile range 42–66), and 111 patients (59.7%) were male (Table 1). Twenty-five (13.4%) cases were healthcare personnel, 82 (44.1%) were patients who had been exposed during admission or at clinics, and 61(32.8%) were caregivers. Common symptoms at presentation were fever/chills (74.2%) and myalgia

(25.3%). Diabetes mellitus was the most common comorbidity (28.0%), followed by malignancy (23.1%). The majority (98%) of patients were infected with MERS-CoV in healthcare facilities.

3.2. Incubation period and serial interval

The incubation period of confirmed cases was 6.83 days [95% confidence interval (CI), 6.31–7.36] (Figure 2); distributions that were fit to our observed data indicated that 95% of infected patients would have an onset of symptoms by Day 13.48 (95% CI of 95th percentile, 12.23–14.73), whereas 5% would have an onset of symptoms by Day 2.27 (95% CI of 5th percentile, 1.98–2.48). We estimated that the serial interval was 12.5 days (95% CI, 11.8–13.2) (Figure 3). The distributions that were fit to our observed data indicate that the serial interval was 20.65 days in 95% of cases (95% CI of 95th percentile, 19.15–22.15) and 6.15 days in 5% of cases (95% CI of 5th percentile, 3.65–8.65).

3.3. Chains of transmission

From May 15 through May 17, the index patient infected 26 secondary cases in Hospital C (Figure 4). An initial epidemiological investigation focused on the healthcare personnel, family members, and the patients who either had prolonged close contact or shared the same hospital room with the index patient. On May 28, as MERS-CoV infection was diagnosed among patients in other rooms, investigation was extended to those who stayed in the same ward. However, eight secondary patients who had not been detected already moved to another ward and infected 10 tertiary patients. Some of

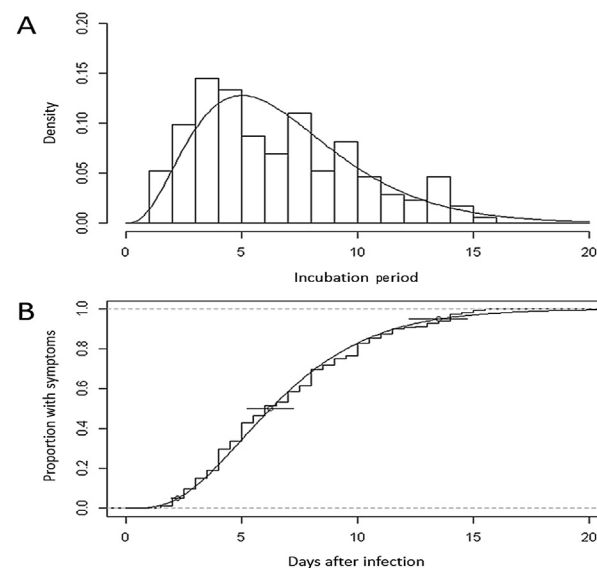


Figure 2. Incubation period of Middle East respiratory syndrome coronavirus (MERS-CoV) infection outbreak in the Republic of Korea, 2015. Panel A shows the density estimation of incubation periods with gamma distribution. Panel B shows the empirical cumulative density estimation of incubation period.

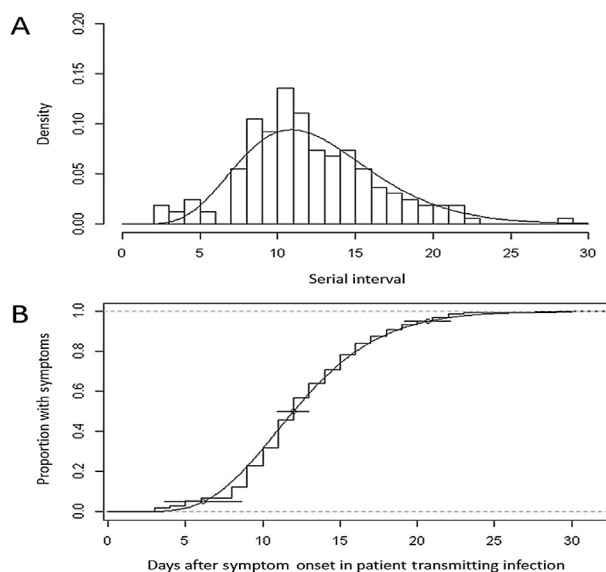


Figure 3. Serial interval of Middle East respiratory syndrome coronavirus (MERS-CoV) infection outbreak in the Republic of Korea, 2015. Panel A shows the density estimation of serial intervals using gamma distribution. Panel B shows the empirical cumulative density estimation of serial intervals.

the patients had been discharged before May 28. Active surveillance was performed to trace these patients and we were able to find tertiary transmission across seven different hospitals. Patient 14 infected 80 tertiary cases in Hospital H, Patient 15 infected six tertiary cases in Hospital L, and Patient 16 infected 24 tertiary cases in Hospitals M and N, respectively. After the implementation of infection control interventions, a small number of quaternary transmissions occurred, and nearly half of these cases were caused by Patient 76 who was infected in Hospital H.

3.4. Characteristics of superspreader

Five patients met the definition of a superspreader (Table 2). A total of 83.2% of the transmission events were epidemiologically linked to these five patients. The median age of the superspreaders was 41 years (range, 41–68 years). Four were men and the median body mass index was 24 (range, 19–30). Comorbidity was observed in two cases; asthma in Patient 1 and multiple myeloma and diabetes mellitus in Patient 76. All cases were febrile and had pneumonia at presentation. Patient 1, Patient 14, and Patient 16 who had a severe cough infected 28 cases, 85 cases, and 23 cases, respectively. By contrast, Patient 15 and Patient 76 who rarely coughed infected six cases and 11 cases, respectively. Patient 14 mostly stayed in the emergency department, Patient 1, Patient 15, and Patient 26 were mainly hospitalized in multipatient rooms, and Patient 76 stayed in both. The median duration of hospitalization was 10 days (2–11 days) and the number of close contacts ranged from 277 to 805. Patient 14 wore an N95 mask intermittently, whereas other superspreaders did not wear any type of mask.

3.5. Mortality cases

As of July 13, 36 deaths have occurred and the mortality rate was 19.4%. In the univariate analysis, older age (≥ 65 years) was strongly associated with mortality (Table 3). History of diabetes mellitus, malignancy, and the presence of underlying respiratory disease (i.e., asthma, chronic obstructive pulmonary disease), cardiac disease (i.e., ischemic heart disease, arrhythmia, and/or heart failure), and chronic kidney disease were also significantly associated with mortality. However, in the multivariate regression analysis, adjusted for sex, age, and underlying diseases, only older age [odds ratio (OR) = 4.86, 95% CI 1.90–12.45] and underlying respiratory disease (OR = 4.90, 95% CI 1.64–14.65) appeared to be significant.

3.6. Phylogenetic analysis

The MERS-CoV of the index case produced the best match with the virus from an outbreak in Riyadh, Saudi Arabia in February 2015 (Riyadh_KKUH_0708_20150225) by pairwise comparisons (Figure 5). The nucleotide identity was 99.61%. Phylogenetic analysis of the 16 MERS-CoV complete genomes showed that MERS-CoV/KOR/KNIH/001_05_2015 and Riyadh_KKUH_0708_20150225 are the closest relatives of viruses from Qatar and Hafr-Al-Batin in the 2013 outbreak.

4. Discussion

The outbreak of MERS-CoV infection in the Republic of Korea is the first of its kind and the largest known outbreak outside the Arabian Peninsula [15]. Because knowledge on the nature of the virus and its mode of transmission was limited, the extensive spread of MERS-CoV infection in the early phase of the outbreak raised great concern. However, the present outbreak could be understood within the range of knowledge from previous outbreaks. The outbreak progressed in the manner of human-to-human transmission, was amplified under the healthcare setting, and showed heterogeneity in transmission. However, delayed diagnosis and the unique medical and patient-care system of the Republic of Korea caused super-spreading events.

Nosocomial transmission has been a main characteristic of MERS-CoV infection. The rapid increase of MERS cases since 2013 resulted from healthcare-associated outbreaks in the Middle East [4,8]. Transmission occurred during admission or outpatient visits, at emergency departments, or at outpatient facilities including renal dialysis units [4,7,16]. In addition to the transmission between patients or healthcare personnel, transmission to hospital visitors was also reported [6,7]. Nosocomial transmission was also predominant in the present outbreak. Of 182 confirmed cases of MERS-

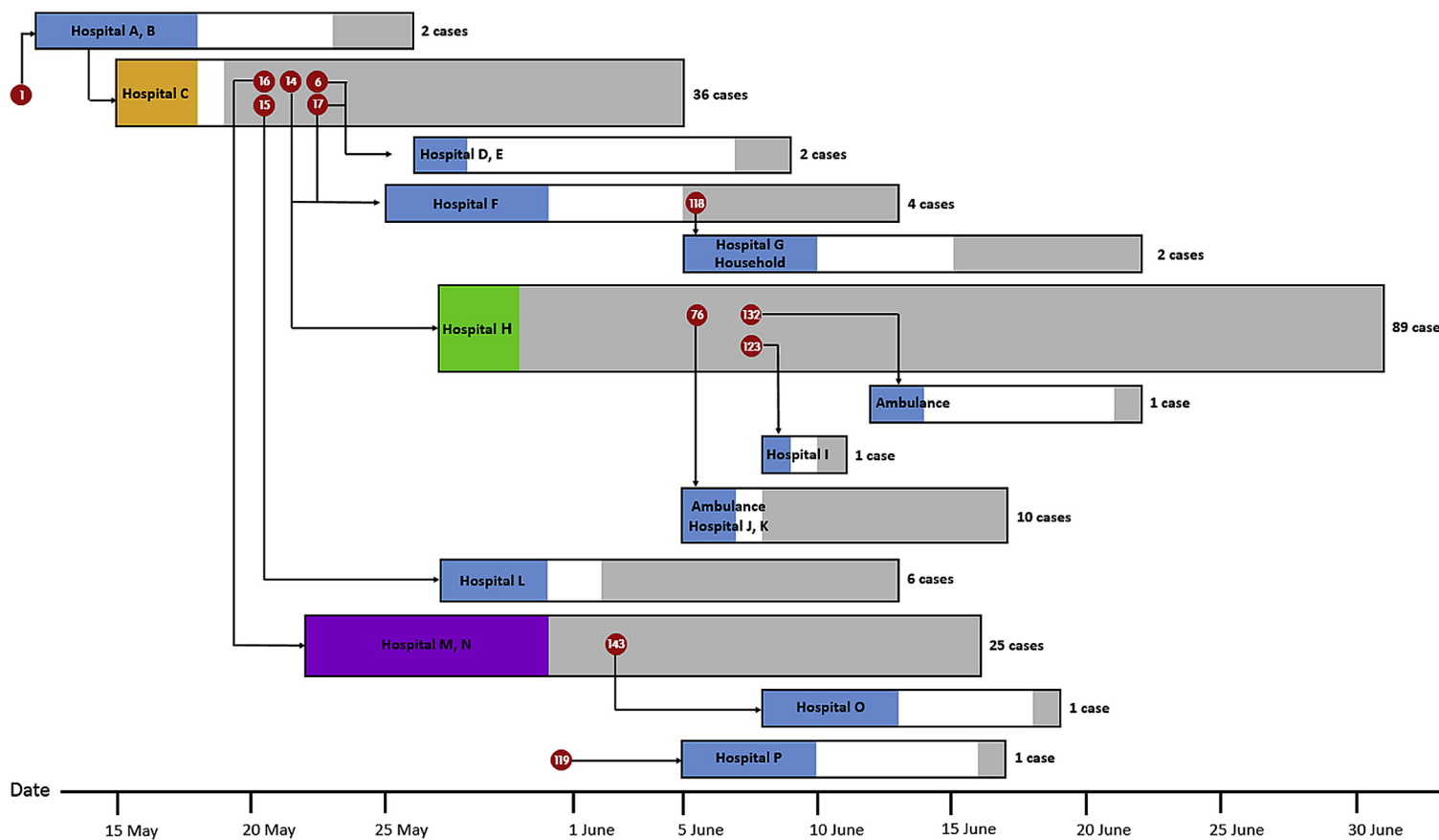


Figure 4. Transmission map of 182 confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea. The numbers within the red circles are identifiers of notable patients who caused succeeding MERS-CoV infection. The site and the duration of exposure by these patients are indicated in colored boxes. Gray boxes depict the time periods that new cases occurred by date of symptom onset at each site. Black arrows represent how each spreader moved to the next site of transmission. The transmission route of Patient 119 is uncertain. Four cases still under investigation are excluded.

Table 2. Characteristics of superspreaders of Middle East respiratory syndrome coronavirus infection outbreak in the Republic of Korea, 2015.

Patient number	1	14	15	16	76
Infected no. of patients	28	85	6	23	11
Age (y)	68	35	35	41	75
Sex	Male	Male	Male	Male	Female
Body mass index	27	30	24	24	19
Underlying disease	Hypertension, asthma	No	No	Familial adenomatous polyposis	Diabetes mellitus, multiple myeloma
Exposed duration (d)*	10	9	10	11	2
Exposed setting	GW (27 cases) OPD (1 case)	ER (78 cases) GW (4 cases) Other (3 cases)	GW (6 cases)	GW (22 cases) Other (1 case)	ER (4 cases) GW (3 cases) Other (4 cases)
Number of close contacts	626	594	304	277	805
Personal protective equipment	No	Intermittent	No	No	No
Pneumonia [†]	Present	Present	Present	Present	Present
Cough	Frequent	Frequent	Rare	Frequent	Rare
Prognosis	Survived	Survived	Survived	Survived	Expired
Aerosol-generating procedure	No	No	No	No	No

*Exposed duration is defined as the period from symptom onset to the date of proper isolation; [†]Pneumonia detected from chest radiograph at the moment of investigation. ER = emergency room; GW = general ward; OPD = outpatient department.

CoV infection whose setting of contact is identified, all but one case were infected in healthcare facilities or in ambulances. However, the range of exposure was more extensive than that of outbreaks in the Middle East, infecting multiple visitors, radiologic technologists, hospital security agents in emergency departments, emergency medical technicians, and caregivers. To date, there was no evidence of sustained transmission in the community.

MERS-CoV transmission showed heterogeneity of infectiousness as observed in severe acute respiratory syndrome [4,17,18,19]. Similarly, the majority (91.3%) of cases resulted in no transmission and the remaining small proportion caused most of the transmission events

in this outbreak. However, superspreading events were more prominent than previous reports. Prolonged duration of exposure before diagnosis and proper isolation, practice of seeking care at multiple healthcare facilities, frequent interhospital transfer, significant numbers of paid caregivers, and large numbers of contacts in large crowded tertiary referral hospitals might have contributed to multiple spreading events. Moreover, the custom of family members and friends to accompany or visit patients, and to provide care with staying in the same hospital rooms (mostly multibed rooms) or in the crowded emergency rooms, may have also contributed to the increased number of contacts. Regarding clinical manifestation, all patients who resulted in multiple

Table 3. Risk factors associated with in-hospital mortality in 186 patients with laboratory-confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infection, 2015.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR	95%CI	<i>p</i>	OR	95%CI	<i>p</i>
Sex, male	1.44	0.67–3.11	0.434	1.56	0.62–3.91	0.33
Age, ≥ 65 y	7.67	3.45–17.04	<0.0001	4.86	1.90–12.45	0.001
Case classification, patient	3.17	1.47–6.83	0.003	0.82	0.27–2.50	0.73
Respiratory disease* [†]	6.27	2.48–15.83	<0.0001	4.90	1.64–14.65	0.004
Diabetes mellitus	2.91	1.436–6.20	0.006	1.37	0.55–3.45	0.49
Cardiac disease [†]	4.43	2.02–9.70	<0.0001	2.21	0.86–5.67	0.09
Chronic kidney disease	5.84	1.48–23.0	0.012	2.30	0.44–11.94	0.32
Malignancy	2.63	1.20–5.76	0.015	1.92	0.75–4.86	0.16

*Includes chronic obstructive pulmonary disease and asthma; [†]Includes ischemic heart disease, dysrhythmia, and heart failure. Multivariate analysis adjusted by gender, age, and underlying diseases. CI = confidence interval; OR = odds ratio.

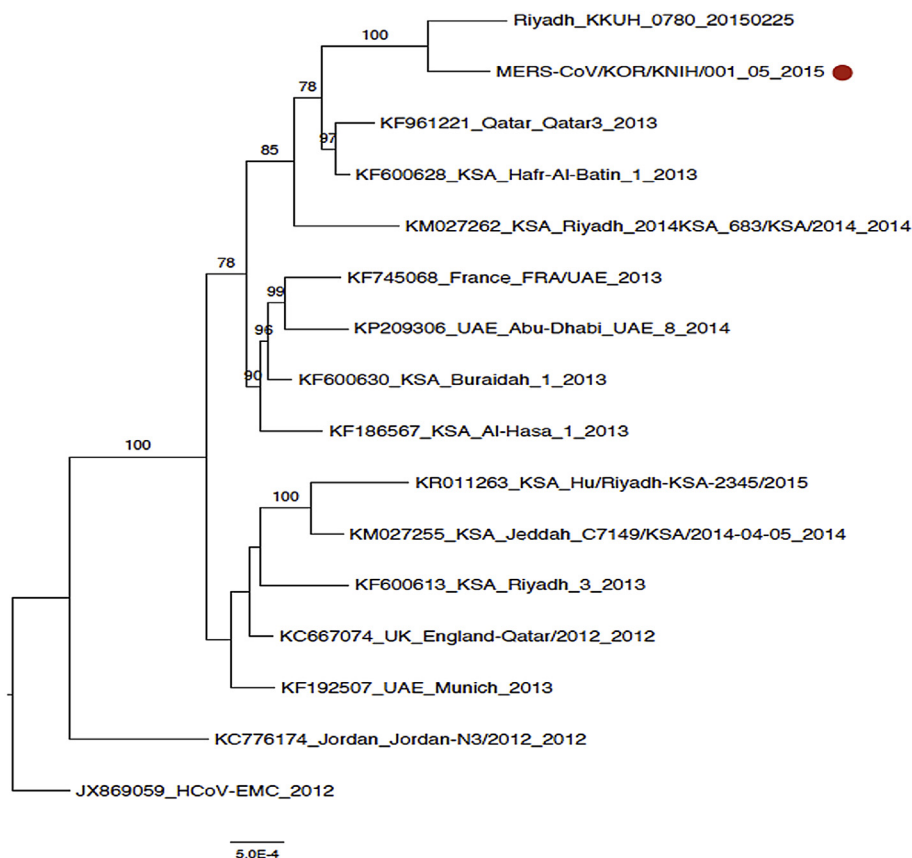


Figure 5. Evolutionary history of the Middle East respiratory syndrome coronavirus (MERS-CoV). A phylogenetic tree was constructed using RAxML. The scale bar shows evolutionary distance inferred by RAxML algorithm. The MERS-CoV in the Republic of Korea outbreak is indicated by a red circle. Support for the ML phylogenetic trees was evaluated using 1,000 bootstrap replicates. Note numbers represent % bootstrap replicates >70%.

transmissions had pneumonia, and those with severe cough infected more cases than others who rarely coughed. There was no evidence of viral mutation which can modify the mode of transmission or virulence [11].

The outbreak progressed in the manner of human-to-human transmission. However, it is still uncertain whether the transmission occurred merely through the respiratory droplet route or through another route of transmission (i.e., airborne transmission). Although the respiratory droplet route is currently regarded as the most likely route of transmission [8], the outbreaks in Hospital C and Hospital H were far more extensive compared with previous hospital outbreaks, and surveillances for other possible routes are under process. Irrespective of the route of transmission, viral transmission actually occurred between rooms in the same ward and throughout the emergency room of Hospital H, which is as wide as 1,970 m². Transmission across rooms has been previously reported [4], but the present outbreak demonstrated its high feasibility and magnitude. To successfully control the MERS-CoV outbreak, it is essential to implement droplet and contact precautions and trace every individual, including patients, healthcare personnel, and visitors, who stayed in the same ward or same emergency room.

Clinical presentation in this outbreak was similar to the previous outbreaks in the Middle East [7]. Fever is the most common symptom along with myalgia. It is noteworthy that only 12.9% of patients had gastrointestinal symptoms, which is relatively lower than its prevalence of 20–30% documented elsewhere [4]. This may partly be explained by the limitation of current data which is based on primary epidemiologic investigation reports. The estimated incubation period of the present outbreak was 6.83 days, which is similar to that of previous outbreaks [4]. Estimated distribution indicated that most of the infected patients would have symptoms by Day 13.48, and this may reinforce the current policy regarding the duration of quarantine. Estimated serial interval was 12.5 days in this outbreak, which was longer than that of 7.6 days in the previous report [4]. Compared with the previous report, our results have strength in the aspect that they are based on a larger sample size and every case is confirmed by a laboratory test. However, we might have wrongly attributed tertiary or quaternary infection to secondary or tertiary infection in the process of determining the most probable exposure, and thus overestimated the serial interval.

Risk factors for mortality include older age and underlying respiratory diseases, which is similar to the

previous study [20]. In our study and other studies alike, patients aged ≥ 65 years were eight to nine times more likely to die from MERS-CoV infection [20]. Although evidence suggests that chronic kidney diseases are known to be associated with a particularly higher fatality in MERS-CoV infected patients [21], this was not evident in our multivariate analysis. Although underlying diseases of the initial epidemiologic report were cross validated with the national health insurance database, complete clinical data needs to be supplemented in order to draw a more accurate picture on the association of underlying diseases and prognosis.

In the early phase of the outbreak, containment measures were conducted in accordance with current international guidelines which recommended identifying and monitoring close contacts [22,23]. Identification and monitoring of contacts were limited to healthcare personnel who directly managed the index patient, and patients and their families who were in the same hospital room with the index patient. However, when a patient was first confirmed beyond this initial criterion, containment measures had to be reestablished to include a wider spectrum of contacts. Unfortunately, this was not timely enough to prevent infected patients, including super-spreaders, from discharging from or transferring to other hospitals. This initial flaw in identifying the appropriate population at risk and delayed response with regards to management of superspreaders, along with suboptimal infection prevention and control in healthcare facilities, eventually culminated in the infection of >180 patients.

Efforts were made to reinforce containment measures. Active surveillance and contact management including contact identification, listing, and follow up on all contacts on a daily basis was conducted. Confirmed cases were isolated and treated in designated hospitals while exposed individuals were quarantined in their homes for 14 days after last exposure. A MERS-CoV test was immediately conducted if the exposed individuals reported suspicious symptoms. Infection control practices in hospitals were reinforced and public awareness was increased. The number of new cases has slowly declined towards the end of June.

Our study has several limitations. Although clinical features of the infected patients were largely based on information attained through accurate epidemiologic investigation, this does not provide knowledge as to the entire clinical course of respective patients. Given this, information regarding clinical data and underlying diseases was validated and supplemented with other reliable sources such as health insurance data and medical records, to minimize the effect of such limitations. There were also a few patients with atypical or no symptoms and several cases whose dates of onset were unclear, which also warrants further investigation. The strength of this study is that, to our knowledge, this is the first report describing the epidemiologic and clinical features of 186 lab-confirmed patients of the outbreak. A wealth of

information sources such as closed circuit television, location detection technologies, as well as credit card inquiry transactions, were collected and analyzed.

A single MERS-CoV infection case from abroad resulting in a sizable outbreak in the healthcare setting of a developed country highlights the importance of robust preparedness, vigilant surveillance, and optimal infection prevention control in hospitals. Although evidence-based technical guidelines for investigation are an integral part of effective containment, only limited information is currently available on the transmission dynamics of MERS-CoV. It is anticipated that the lessons learned from this outbreak will contribute to more up-to-date guidelines of MERS-CoV investigation and global health security.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

The authors and KCDC EIS officers who contributed to this article are as follows: Seung Woo Kim, Tae Un Yang, Yoolwon Jeong, Jung Wan Park, Keon-Joo Lee, Kyung Min Kim, Jongseok Oh, Yong-shik Park, Woncheol Lee, Jong Rak Jung, Changhwan Lee, Joonkee Lee, Heun Choi, WooSuck Suh, Dae-Won Kim, Hoon gil Jo, Minsung Kim, Jungmo Ahn, Kanghyoung Lee, Sang Hyup Lee, Seongil Park, Kyuchul Lee, Min Kim, Jin Won Mo, Daegwang Lee, Up Huh, Hyungmin Kee, Jaejoon Kim, Jae Young Cheon, John Kwon, Eui Jun Lee, Hyung Joo Lim, Jiung Ryu, Young Woo Ryu, and Jung Rae Cho.

References

1. Hijawi B, Abdallat M, Sayaydeh A, et al. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. *East Mediterr Health J* 2013;19(Suppl. 1):S12–8.
2. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012 Nov;367(19):1814–20.
3. European Centre for Disease Prevention and Control (ECDC). Severe respiratory disease associated with Middle East respiratory syndrome coronavirus (MERS-CoV). 16th update, 05 June, 2015. Stockholm (Sweden): ECDC; 2015.
4. Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 2013 Aug; 369(5):407–16.
5. 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 Feb;60(3):369–77.
6. Health Protection Agency (HPA) UK Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. *Euro Surveill* 2013 Mar;18(11):20427.

7. 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 Feb;372(9):846–54.
8. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet*; 2015 [Epub 2015 June 3].
9. Ministry of Health and Welfare (MOHW), Korea Centers for Disease Control and Prevention (KCDC). Guidelines on Middle East respiratory syndrome Sejong (Republic of Korea): MOHW, KCDC; 2015.
10. World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus. Interim recommendations. Geneva (Switzerland): WHO; 2014.
11. Kim Y-J, Cho Y-J, Kim D-W, et al. Complete genome sequence of Middle East respiratory syndrome coronavirus KOR-/KNIH/002_05_2015 isolated in South Korea. *Genome Announc* 2015 Aug;3(4):e00787–815.
12. Katoh K, Standley DM. MAFFT multiple sequence alignment software version 7: improvements in performance and usability. *Mol Biol Evol* 2013 Apr;30(4):772–80.
13. Stamatakis A. RAxML version 8: a tool for phylogenetic analysis and post-analysis of large phylogenies. *Bioinformatics* 2014 May; 30(9):1312–3.
14. Reich NG, Lessler J, Cummings DA, et al. Estimating incubation period distributions with coarse data. *Stat Med* 2009 Sep;28(22): 2769–84.
15. European Centre for Disease Prevention and Control (ECDC). Middle East respiratory syndrome coronavirus (MERS-CoV). 18th update. Stockholm (Sweden): ECDC; June, 2015.
16. Guery B, Poissy J, el Mansouf L, et al. Clinical features and viral diagnosis of two cases of infection with Middle East respiratory syndrome coronavirus: a report of nosocomial transmission. *Lancet* 2013 Jun;381(9885):2265–72.
17. Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005 Nov;438(7066):355–9.
18. Shen Z, Ning F, Zhou W, et al. Superspreading SARS events, Beijing, 2003. *Emerg Infect Dis* 2004 Feb;10(2):256–60.
19. Stein RA. Super-spreaders in infectious diseases. *Int J Infect Dis* 2011 Aug;15(8):e510–3.
20. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014 Dec;29:301–6.
21. Chan JF, Chan KH, Choi GK, et al. Differential cell line susceptibility to the emerging novel human betacoronavirus 2c EMC/2012: implications for disease pathogenesis and clinical manifestation. *J Infect Dis* 2013 Jun;207(11):1743–52.
22. World Health Organization. WHO guidelines for investigation of cases of human infection with Middle East Respiratory Syndrome Coronavirus(MERS-CoV). Geneva (Switzerland): WHO; 2013.
23. Centers for Disease Control and Prevention (CDC). Middle East respiratory syndrome—interim guidance for healthcare professionals. Atlanta (GA): CDC; 2015.