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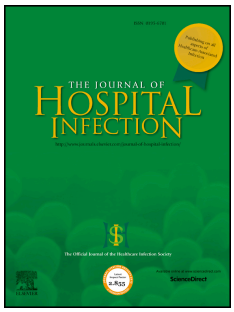

Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: Epidemiology, characteristics and public health implications

Kyung Hee Kim, Ph.D., Tinyami Erick Tandi, Ph.D., Jae Wook Choi, MD, PhD., Jiwon Monica Moon, BA., Min Soo Kim, BSC.

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Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015 : Epidemiology, characteristics and public health implications

Kyung Hee Kim, Ph.D.[1]: kyonghee80@korea.ac.kr
Tinyami Erick Tandi, Ph.D.[1-4]: ttandi2002@yahoo.com
Jae Wook Choi, MD[1-3, 5*]: shine@korea.ac.kr
Jiwon Monica Moon,BA. [1-2]: monicajmoon@korea.ac.kr
Min Soo Kim, BSC.1[-2]:kimmins6@korea.ac.kr
[1)] Institute for Occupational and Environmental Health, Korea University, Seoul, Korea
[2)] Graduate School of Public Health, Korea University, Seoul, Korea
[3)] Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea
[4)] Ministry of Public Health Yaounde, Yaounde Cameroon
[5)] MERS Policy Committee of the Korean Medical Association, Seoul, Korea
Address for correspondence: Jae Wook Choi, MD, PhD.
Department of Preventive Medicine, College of Medicine, Korea University
73, Inchon-ro, Seongbuk-gu, Seoul 02841, Korea
Tel: +82-2-926-4704; Fax: +82-2-927-7220 E-mail: shine@korea.ac.kr

Running title: MERS-CoV outbreak in South Korea

Summary

Background: Since South Korea reported its first Middle East respiratory syndrome coronavirus (MERS-CoV) cluster on May 20 2015, there had been 186 confirmed cases, 38 deaths, and 16,752 suspected cases. Previously published research on South Korea's MERS outbreak has been limited to the early stages when limited data were available. Now that the outbreak has ended, albeit unofficially, a more comprehensive review is appropriate.

Methods: Data were obtained through the MERS Portal, by the Ministry for Health and Welfare (MOHW), and Korea Centers for Disease Control and Prevention, press releases by MOHW, and reports by the MERS Policy Committee of the Korean Medical Association. Cases were analyzed for general characteristics, exposure source, timeline, and infection generation. Gender, age, and underlying diseases were analyzed for the 38 deaths.

Findings: Beginning with the index case that infected 28 others, an in-depth analysis was conducted. The average age was 55, a little higher than the global average of 50; as in most other countries, more men than women were affected. The case fatality rate was 19·9%, lower than the global rate of 38.7%, and that ins Saudi Arabia (36·5%). 184 patients were infected nosocomially, while none were intra-community infections. The main underlying diseases were respiratory diseases, cancer, and hypertension. Main contributors to the outbreak were late diagnosis, quarantine failure of “super-spreaders”, familial care-giving and visiting, nondisclosure by patients, poor communication by the Government, inadequate hospital infection management, and "doctor shopping”. The outbreak was entirely nosocomial, and was largely attributable to infection management and policy failures, rather than biomedical factors.

Keywords: MERS-CoV outbreak, epidemiology, public health, South Korea.

Introduction

Middle East Respiratory Syndrome (MERS), first reported in Saudi Arabia in 2012, is increasingly becoming a threat to global health security, much like Ebola or swine flu.[1] Been March 2012 and November 1 2015, the World Health Organization (WHO) reported 1,611 confirmed MERS-cases and 575 deaths worldwide.[2] MERS outbreak countries include Saudi Arabia (1,255 cases and 539 deaths), South Korea (185 cases and 36 deaths), and the United Arab Emirates (81 cases and 11 deaths).[3]

On May 20 2015, the first case of MERS in South Korea occurred in a 68 years old male who had contracted the disease while on a business trip to multiple Middle East countries. Subsequently, 186 cases were confirmed, with 38 deaths; 16,752 suspected cases had substantial impact on the education, tourism, political, and economic sectors.[5] Domestic, and international media sources have attributed the spread of MERS in South Korea to many factors. Reuters reported that South Korea's MERS situation would not be abated without information transparency and cooperation with international virus-hunters, pointing out the South Korean government's refusal to seek help from international parties as particularly troubling.[6] Science Insider highlighted problems such as inadequate in-hospital ventilation, extensive transmission caused by unmanaged super-spreaders, poor infection control measures, and refusal to disclose the names of hospitals where confirmed MERS patients had been treated or sought treatment.[7] The Korea Center for Disease Control (KCDC) reported that problems with South Korea's initial response could be attributed to inconsistent definition and isolation of close contacts, the subsequent failure to conduct preemptive quarantines, and the Government's failure to implement appropriate crisis communication measures.[4]

In the face of such speculation about the main reasons for the initial failure to contain the MERS outbreak in South Korea we undertook a comprehensive review of the temporal progression of the outbreak, and the infection histories of confirmed patients. An overview of worldwide publications on MERS between January 1 2010 and May 31 2015 did not include all of the South Korean cases,[8] whilst previous reports from South Korea have not comprehensively reviewed the outbreak.[4,9,10] The

main objective of our study was to compare the South Korean experience to that of other countries, including clinical outcomes and infection control processes.

Methods

General characteristics, outbreak sites, and source of exposure of patients diagnosed with MERS

The timeline from the first confirmed MERS case in South Korea, and the first death to the latest death is outlined in Figure 1. Data were analyzed based on the South Korean Government MERS Information Portal site, and policy briefings officially managed by the MOHW, and KCDC.[11, 12] The official daily briefing reports included patient serial number, day of diagnosis, infection route, gender, age, and hospital. The gender and age of all 186 South Korean cases were determined. Outbreaks were defined as occurring in hospital, within the family, or occurring in the community. Sources of exposure were divided into three groups: 1) healthcare professionals (doctors, nurses, medical technicians such as radiologist, and medical transport staff), 2) infections contracted in hospitals by inpatients or outpatients, and infections acquired through visiting hospitalized patients or family care-giving.

Analysis of fatalities in patients with MERS

38 deaths were identified via the official daily briefings from the MOHW, and KCDC. We recorded the gender, age, and underlying diseases in these cases. Where patients had multiple underlying diseases duplicate aggregation was permitted, with each disease treated as one case.

Distribution of transmission of MERS clusters, and suspected super-spreader in South Korea

Super-spreading events are found to occur during infectious disease events in which, according to the Pareto principle, 20% of the infected population is the cause of transmitting the disease to the other 80%.[13, 14] We identified three super-spreaders: Patient 1, who infected 28 patients

at St. Mary's Hospital, Pyeongtaek; Patient 14, who infected 85 patients at Samsung Medical Center, Seoul; and Patient 16, who infected 23 patients at Konyang University Hospital and Daejeon Hospital.

Results

General characteristics of confirmed MERS cases, outbreak sites, and sources of exposure

The 186 MERS cases comprised 111 (59.7%) males and 75 (40.3%) females. Overall, the 50 to 59 years age group was most affected (22.6% of all cases), followed by the 60 to 69 and 70 to 79 year age groups. Females with MERS tended to be older than males (Table 1). The 186 cases comprised the index case, his wife who was infected in the household setting, and 184 nosocomially acquired cases. The most common route of exposure was through hospital visiting (including family members who acted as care-givers) which accounted for 103 (55.7%) cases. 54 (29.2%) cases occurred in patients who were hospitalized for other reasons, and 25 (13.5%) cases were occupationally acquired in healthcare workers (Table 1).

Fatality rate and analysis of underlying disease of patients who died of MERS in South Korea

26 of the 38 fatalities were in males; the fatality rate in males (23.4%) was higher than in females (16.0%). The average age of patients who died was 67.9 years (Table 2). 29 patients had underlying diseases. The most common underlying diseases were respiratory disorders (11 cases, 30.5%), followed by cancer (11 cases. 28.9%), hypertension (8 cases, 22.2%), cardiovascular diseases (5 cases, 13.9%), and diabetes (4 cases, 11.1%) (Table 3).

Timeline of confirmed MERS cases in South Korea in 2015

Following occurrence of the first MERS patient to mid-June 2015 numbers of confirmed and suspected MERS cases rapidly increased. The first death from MERS occurred on June 1. On June 17 the number of suspected cases being isolated peaked at 6,729. Up to October 26 2015, a total of 16,752 people had been isolated. The 186th confirmed case was diagnosed on July 4 2015; no further

cases were confirmed. The last death occurred on November 25 2015.

Distribution of MERS clusters, and suspected super-spreaders in South Korea

The MERS outbreak in South Korea involved both intra-hospital and inter-hospital transmission.[9] The index case visited four hospitals whilst symptomatic between May 11 and May 20, when he was diagnosed with MERS. During this period, he infected 28 people. Patient 14 is suspected of becoming infected during his stay at St. Mary's Hospital, Pyeongtaek between May 15 and 17. He was subsequently admitted to the emergency room at Samsung Medical Center on May 20, and was diagnosed with MERS on May 30. During his stay at Samsung Medical Center, he infected 81 patients; he then infected a further four patients at Good-morning Hospital, Pyeongtaek). Patient 16 was also infected at St. Mary's Hospital, Pyeongtaek between May 15 and 16; he then infected a total of 23 people at Konyang University Hospital and Daejeon Hospital (Figure 2).

Discussion

South Korea has the world's second highest number of confirmed MERS cases following Saudi Arabia. While South Korea officially reported that the number of confirmed MERS cases is 186, the WHO reports that, the number of confirmed MERS cases in South Korea were 185.[2] This discrepancy is due to the fact that the South Korea government included a South Korean patient who was diagnosed with MERS in China during a business trip despite the fact that he was a suspected case while still in South Korea. As in Saudi Arabia, MERS in South Korea was more common in males than in females.[15]

MERS-CoV has the same coronavirus lineage as the severe acute respiratory syndrome coronavirus (SARS-CoV).[20] Zumla and Chowell, compared the general characteristics between MERS, and SARS.[8,10] They reported that more than 90% of both MERS and SARS the patients were adults. However, whereas 64.5% of MERS cases were in males, 57% of SARS cases were in females.[8, 9, 10] The reason for this apparent difference between the two infections is unknown; possibly it is related to differences in the sex distribution the total populations exposed to risk of the two

infections.[16] The average age of confirmed MERS patients in South Korea was 55 years, a little higher than that reported by Zumla *et al* (50 years)[8,9] The latter study also reported a MERS case in a one-year old, although only 2% of cases were in children.[8] The youngest confirmed case in South Korea was a 16-year-old male (case #67, who was the son of case # 46).[11, 12]

The South Korean fatality rate for MERS was 19.9%. By contrast, the European Centre for Disease Prevention, and Control (ECDC) reported that the global MERS fatality rate between March 2012 and October 2015 was 38.6% (1,616 confirmed cases, and 624 deaths). There were marked regional differences in mortality rates: 41·1% in the Middle East, 53·3% in Europe and 40·0% in Africa, compared with 19·2% in Asian countries.[3] Among probable SARS cases that occurred during 2002 and 2003 the global case fatality rate was lower at 9.6% (774 deaths in 8,098 cases), but again there was considerable regional variation.[17] One of the reasons why South Korea has a lower fatality rate than other MERS outbreak countries may be accessibility to a high level of emergency medical treatment. The difference does not appear attributable to mutations in the virus.[19] There was also a difference in the types of underlying conditions associated with fatal MERS in South Korea compared with Saudi Arabia. In the latter country diabetes mellitus (74% of patients), followed by end-stage renal disease (52%), lung diseases (43%) cardiac conditions (39%) were commonest underlying conditions in fatal cases.[18] However, in South Korea respiratory disease (30.5%), cancer (27.8%) and hypertension (22·2%) were the commonest underlying conditions.

Oboho *et al* reported that 109 (97.3%) of 112 patients in the Jeddah area of Saudi Arabia, and who were not healthcare workers contracted MERS through contact with someone in healthcare facilities.[18] Likewise, we found that 99.4% of cases were nosocomially acquired. South Korea's MERS infection routes are characterized not only by intra-hospital transmission but also by hospital-to-hospital transmission.[9] Cases of intra-community transmission were not found, corroborating the findings of the WHO report that there was no evidence of transmission outside hospitals in South Korea.[20-22] However, it noted that MERS testing was only available to cases where there has been known close contact with a confirmed or suspected case; thus more casual contacts of MERS cases

may have been missed because they were not tested. However, global experience does point to MERS being predominantly a nosocomially acquired infection.[17] Thus restrictions on visitors probably has a key role in controlling MERS.[23]

Immediately after the MERS outbreak in South Korea, many researchers reported various problems with the South Korean Government's MERS control measures. It was reported that South Korea's MERS outbreak has been caused by poor hospital infection control standards, and lack of monitoring close contacts, which was also the case in Saudi Arabia.[19] It was pointed out that public risk communication was delayed because the South Korean government made determining all the details of the outbreak a priority rather than information disclosure. This resulted in widespread panic during the MERS crisis.[24] Jack pointed out that while the biological basis for the initial failure to contain MERS is unclear, a number of factors contributed significantly, including “doctor shopping” behavior (which means a patient seeks treatment from various hospitals for the same ailment); lack of epidemiology experts; the culture of frequent hospital visiting, and family care-giving; and the South Korean Government's steadfast stance on keeping information contained.[25] WHO experts have indicated that problems with the initial spread of MERS in South Korea included prevalent occurrences among medical staff; lack of hospital infection management procedures; extremely crowded emergency rooms, and multi-bed rooms in some hospitals; “doctor shopping” behavior; and the spread of infection through patient's family members or friends during their visits to hospitals.[26] Finally, Choi *et al* reported that South Korea's initial failure to control MERS was caused by South Korea's rigid application of MERS control guidelines which failed to isolate all close contacts; failure to recognize super-spreading events; environmental factors such as inadequate ventilation; insufficient infectious disease management capacity in secondary hospitals; and, once again, the South Korean government's inadequate crisis management communication.[4]

Many healthcare professionals in South Korea reported that South Korea's MERS spread can

be characterized by the fact that hospitals acted as the main infection location, and by super-spreading events, where one case infects a number of others. [4,9,10] The occurrence of super-spreading events are known to be determined by physiological factors of the host, transmissibility of the pathogen, and the environment (such as crowding) [27]. Lim pointed out that since the MERS-CoV isolated in South Korea did not differ from those isolated in other countries, there is a lack of biological evidence to support the occurrence of super-spreading events.[28] Thus, super-spreading events must have been caused by environmental factors, including the South Korean government's failure of crisis response management. Other countries should be aware of this in their response to imported MERS cases. The debate on MERS infection handling in South Korea continues, with many local experts proposing improvement measures locally to prevent future national outbreaks of infectious diseases. [29-33]

Conclusion

This narrative account of the South Korean experience of MERS describes some issues that be only be of local importance, but it also contains some important lessons that should be of wider relevance. First, the importance of early detection of cases; second the role of super-spreaders of the virus; and third, the importance of restricting visitors to hospital as a control measure. We also suggest that hospitals need to be prepared for eventualities such as MERS, in particular by ensuring that they have the necessary facilities and equipment for patient isolation. For countries such as South Korea where medical care is insurance-based there should be inclusion of insurance coverage for infectious diseases in insurance plans to ensure that there are no delays in clinical care.

Declaration of Interest

The authors have declared that no competing interests exist.

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Table 1. Epidemiological characteristics of MERS in South Korea (May 20 to November 25, 2015)

N = 186

		Total number of cases	%
Sex	Total	186	100
	Female	75	40.3
	Male	111	59.7
Age	<19	1	0.5
	20-29	13	7.0
	30-39	26	14.0
	40-49	29	15.6
	50-59	42	22.6
	60-69	36	19.4
	70-79	30	16.1
	80-89	9	4.8
Average age	55 years old	-	-
Number of cumulative quarantine/isolate cases	16,693		
Outbreak sites 1) 2)	Infection in hospital (including health professionals)	184	99.4
	Infection within household	1	0.6
	Infection within communities	0	0
Route of infection spread 1) 3)	Infection through medical staff or allied health professionals*	28	15.1
	Infection at hospitals for the purpose of own treatment †	54	29.2
	Infection due to hospital visitation or care-giving ‡	103	55.7

1) This analysis targets 185 cases, excluding the index case.

2) If a case was infected while care-giving a family member who was admitted while showing symptoms of MERS, this case was classified as an in-hospital infection. We cannot determine if the infection had occurred during the MERS latent period. In the case of in-hospital infections, 25 medical staff were included.

3) * Including doctors, nurses, medical technologists such as radiologists, and patient transfer personnel in hospitals; † Outpatients or inpatients; ‡ Including hospital visitation, and care-giving by family member

Table 2. Fatality rate of patients who died of MERS in South Korea (May 20 to October 25, 2015)

Gender	Total number of death	Fatality rate (%)[1)]	Average age (year)
Total	38	20.4	67.9
Male	26	23.4	67.2
Female	12	16.0	69.6

1) (Total number of death/ Total number of cases) X 100

2) This is the result of an analysis of the underlying diseases of cases that have died from MERS. For cases with multiple underlying diseases, each disease was counted as one case.

Table 3. Epidemiological characteristics of 37 deaths from MERS in South Korea (May 20 to October 25, 2015)

case	Sex	Age	Date of death	Confirmed date	Underlying diseases
1	female	57	1 June	1 June	Asthma, Hypertension, Cushing's syndrome
2	male	71	2 June	28 May	COPD, Nephrectomy
3	male	82	3 June	4 June	Asthma, Hypertension
4	male	76	4 June	21 May	Cholangiocarcinoma, Asthma, COPD
5	male	75	5 June	6 June	Gastric cancer
6	female	68	8 June	6 June	Valvular disease
7	male	80	8 June	7 June	Pneumonia
8	female	75	10 June	7 June	Multiple myeloma
9	male	62	10 June	8 June	Hepatic cirrhosis, Liver cancer
10	male	65	11 June	7 June	Lung cancer
11	male	73	12 June	1 June	COPD, Asthma
12	male	78	12 June	1 June	Asthma, Hypertension
13	female	72	12 June	6 June	Pneumonia, ARF
14	female	67	13 June	10 June	Hypothyroidism, Hypertension
15	male	58	14 June	2 June	DM
16	male	61	14 June	6 June	None
17	male	49	15 June	5 June	Alcoholic cirrhosis of liver, DM
18	male	58	15 June	9 June	None
19	male	65	15 June	11 June	None
20	male	69	17 June	4 June	TB, Hypertension
21	female	54	17 June	5 June	Bronchiectasis, Hypertension
22	male	64	17 June	7 June	Hypertension, Asthma, Necrotizing pancreatitis, Abdominal infection
23	female	82	17 June	7 June	Hypertension, Cataract surgery
24	male	75	19 June	10 June	None
25	male	63	20 June	10 June	Myocardial ischemia, DM
26	male	84	22 June	9 June	Lung cancer
27	male	87	22 June	12 June	AF, Heart failure, cancer, Stroke
28	male	65	24 June	6 June	None
29	female	70	24 June	22 June	None
30	female	79	25 June	7 June	DM, Cerebral infarction
31	female	80	26 June	13 June	Bladder cancer
32	male	55	27 June	9 June	None
33	female	81	29 June	06 June	Hypertension, Cardiac valvular disease, Cerebral infarction
34	female	50	7 July	23 June	Lymphoma, TB
35	male	70	8 July	12 June	None
36	male	60	10 July	16 June	Lung cancer
37	male	66	25 October	15 June	None
38	male	35	25 November	5June	Cutaneous lymphoma

1. COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; TB, Tuberculosis; ARF, Acute Renal Failure; AF, Atrial Fibrillation

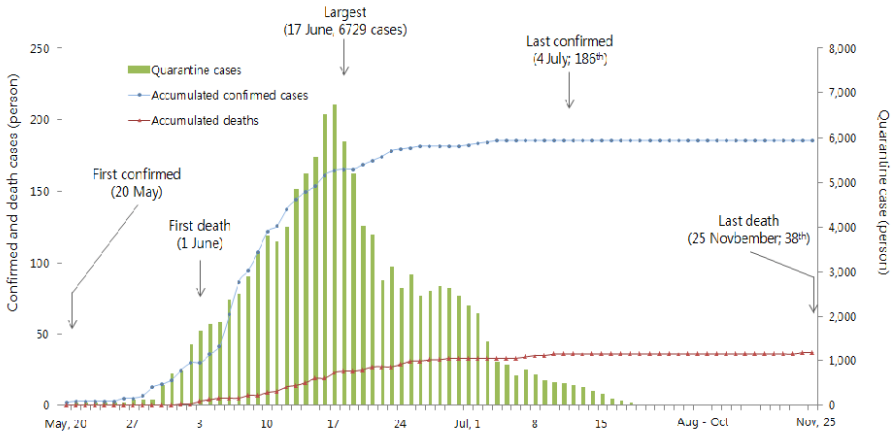

Figure1. Number of confirmed cases, deaths, and quarantines/isolation for MERS-CoV in South Korea (May 20 to November 25, 2015)

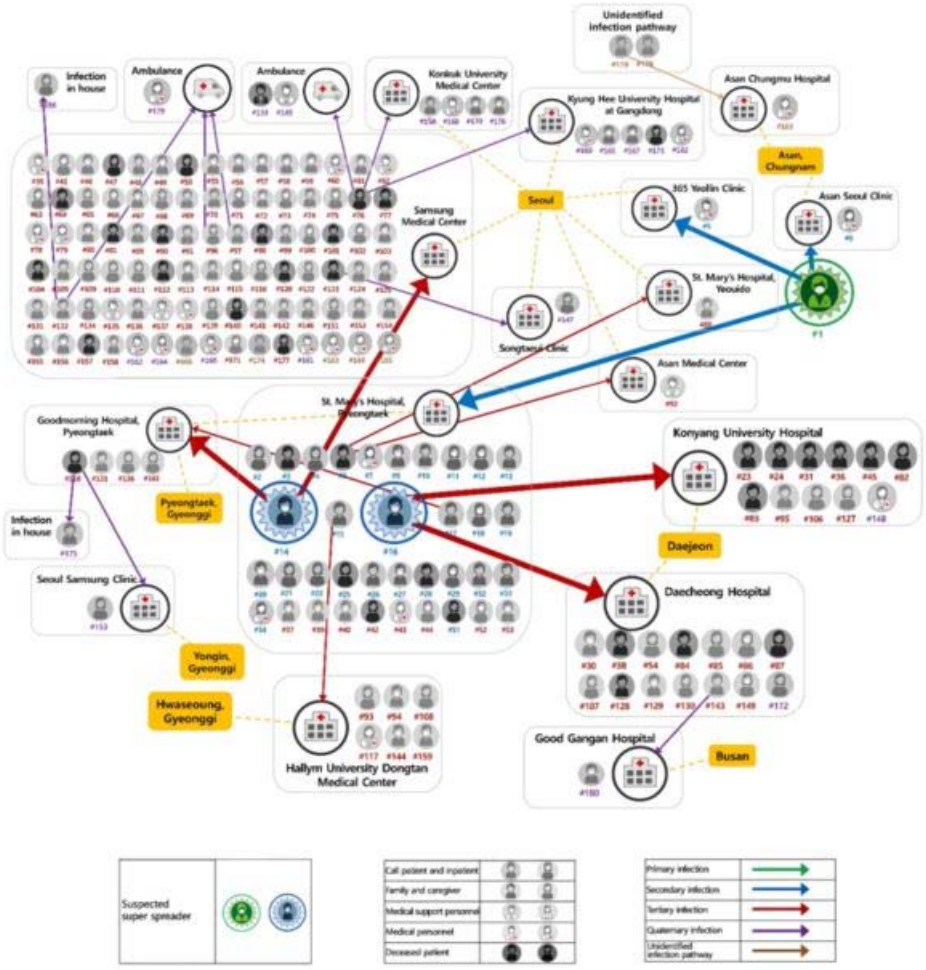

Figure 2. Distribution of transmission of MERS-CoV clusters, and suspected super spreaders in South Korea (May 20 to November 25, 2015)