

MERS epidemiological investigation to detect potential mode of transmission in the 178th MERS confirmed case in Pyeongtaek, Korea

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Most cases of Middle East Respiratory Syndrome (MERS) infection in Korea (outbreak: May 11-July 4, 2015) occurred in hospital settings, with uncertain transmission modes in some cases. We performed an in-depth investigation epidemiological survey on the 178th case to determine the precise mode of transmission. A 29-year-old man living in Pyeongtaek presented on June 16 with a febrile sensation, chills, and myalgia. Upon confirmatory diagnosis on June 23, he was treated in an isolation room and discharged on July 2 after cure. An epidemiological investigation of all possible infection routes indicated two likely modes of transmission: exposure to MERS in Pyeongtaek St. Mary's Hospital during a visit to his hospitalized father (May 18-29), and infection through frequent contact with his father between the latter's referral to Pyeongtaek Good Samaritan Bagae Hospital for treatment without confirmatory diagnosis until his death (May 29-June 6). Although lack of clear proof or evidence to the contrary does not allow a definitive conclusion, all other possibilities could be excluded by epidemiological inferences. While it is impossible to trace back the modes of transmission of all cases in a large-scale outbreak, case-by-case tracking and isolation of infected individuals and those in close contact with them is important in preventing the spread. Efforts should be made to establish a methodology for rapid tracking of all possible contacts and elimination-based identification of the precise modes of transmission.

KEY WORDS: Middle East Respiratory Syndrome, Epidemiologic investigation, Mode of transmission, Outbreak, Korea

INTRODUCTION

Middle East Respiratory Syndrome (MERS) was first detected in South Korea (hereafter Korea) in May 2015, and resulted in a death toll of 36, with 186 confirmed cases between May 11

and July 4, the symptom onset dates of the first and last cases, respectively [1]. MERS is caused by a recombinant coronavirus strain (MERS-CoV) that was first identified in 2012; accumulating evidence points to dromedary camels as the likely major reservoir. While camel-to-human infection and subsequent human-to-human infection have been confirmed, the exact modes of transmission of MERS-CoV have yet to be clarified [2]. The origin of the outbreak in Korea was the arrival of the first case in May 2015 from Saudi Arabia, experiencing a high incidence of MERS. Most infections have been confirmed to occur in hospital settings [3]. However, some cases have unclear routes or symptom onset dates, necessitating an in-depth investigation. While it is difficult to clearly trace back all cases in a large-scale outbreak, an exclusion-based rapid investigation after mapping of all possibilities is indispensable to control outbreak.

The present study relates to an in-depth investigation perform-

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ed on the 178th case with confirmed MERS (hereafter referred to as #178) who was infected during the 2015 outbreak in Korea. #178 was followed starting from June 23, the date of confirmed diagnosis, and measures were taken to prevent further spread, with concerted efforts by an epidemiological investigation team of the Korea Centers for Disease Control and Prevention (KCDC) and civil professionals.

MATERIALS AND METHODS

This survey was performed using elimination methods after mapping all possible routes. As #178 did not have direct contact with MERS patients, we investigated the possibilities for exposure from the 2-week incubation period (June 2-16) to the date of symptom onset. #178 frequently visited his father during the latter's treatment in Pyeongtaek St. Mary's Hospital (PSMH) from May 18-29, and Pyeongtaek Good Samaritan Bagae Hospital (GSBH) from May 29 through June 6. We reviewed the investigation data of these hospitals and performed additional surveys on patients and related persons with whom #178 may have come into contact. All persons with whom #178 may have had contact during the 2-week incubation period, e.g., his family, and colleagues, were asked in person or by phone whether they had MERS-related symptoms or visited a hospital for similar symptoms. Moreover, initial symptoms onset of #178 were reexamined by checking his hospital visit and medical records. The KCDC performed polymerase chain reaction (PCR) assays on sputum samples and serum antibody detection tests on individuals with whom #178 had direct contact, to screen for positive individuals with a confirmatory test.

Because this study was conducted as an outbreak investigation, institutional review board approval was not necessary.

RESULTS

Clinical course

#178 is a 29-year-old man living in Pyeongtaek, Gyeonggi-do, Korea, where the initial outbreak occurred. He was working at a construction site in Asan, Chungcheongnam-do. He was a smoker and had social alcohol drinking, and was in good health without medication. He first noticed a febrile sensation, chills, and myalgia on June 16, and presented to Asan Saewoori Clinic on June 17, where he was prescribed medicine for an upper respiratory tract infection. On June 18, he was administered intravenous fluids for fever (38.5°C) and myalgia in GSBH, again received outpatient treatment at Saewoori Clinic on June 19, and was again administered intravenous fluids on June 20 at GSBH. On June 21, owing to ongoing symptoms, he was ad-

mitted to an isolation room in Pyeongtaek Good Morning Hospital, on referral from GSBH. Upon confirmatory diagnosis of MERS on June 23, he was then referred to Gyeonggi Provincial Medical Center Suwon Hospital.

The chest radiography taken on June 21 revealed that pneumonia had developed over a few days, and he was treated primarily for pneumonia. With negative results from two sputum tests and complete disappearance of symptoms, he was discharged on July 2 (Figure 1).

Suspected exposure events and transmission routes

#178's father

#178's father (a resident of Jeollanam-do) was receiving post-operative pain management and chemotherapy. He had a history of liver cancer operation in Chonnam National University Hospital in 2008, and hepatic artery embolization for recurrent liver cancer and lung metastasis in Seoul Asan Medical Center in June 2014. He was hospitalized in PSMH from May 18-29, 2015 because of poor general condition. He was referred to GSBH on May 29 and died there on June 6. He was tested twice for MERS-CoV (sputum on May 29 and endotracheal aspiration on June 1) before his death, with negative results, and chest radiography (May 29) did not yield clear pneumonia findings. However, he developed fever on June 2 and the chest radiography taken on June 4 showed findings suspicious pneumonia. And no additional MERS test was performed after then. He was completely bed-ridden throughout hospitalization. He was admitted to Room 8104 in PSMH the day after discharge of #1 from the same room. For the next 2 days, he shared Room 8112 with the #9. There was no MERS patient in Room 7110, where he stayed for the next 8 days (Tables 1 and 2, Figures 2 and 3).

Pyeongtaek St. Mary's Hospital

During the time when #178 visited his father in PSMH (May 18-29), he might be exposed to MERS patients (#6, #9, #11, #12, #13, #14, #21, #28, #29, #32, #42, #43, and #53). If #178 was infected in PSMH by May 29, the incubation period had exceeded 2 weeks due to showing the symptoms on Jun 16 (Tables 1 and 2, Figures 2 and 3).

Pyeongtaek Good Samaritan Bagae Hospital

The possibility that #178 was infected by other MERS patients in GSBH during the period he visited his father (May 29-June 6) was investigated. Three cases (#22, #52, and #119) were hospitalized or visited emergency room during this time. Considering #178's visiting times and movements with closed-circuit television data, #52 and #119 could be safely excluded. #22 stayed for 14 hours in the room just opposite the room of #178's father. However, #22 did not leave the room, and there was no contact between #22 and #178 (Tables 1 and 2, Figure 2).

No.	Exposure	Infection	Contact (n)	Transmission
178	#178's father or PSMH	Symptom onset	#178's wife	None
		16 Febrile sensation, chills, and myalgia		
		17 Visit Saewoori Clinic for chills and myalgia	Medical staff (4) and patient (1) of Saewoori Clinic, pharmacy (1), colleagues (8) and wife.	None
		18 Visit GSBH for fever (38.5°C) and myalgia	Medical staff (2) and patients (4) and wife	None
		19 Visit Saewoori Clinic for continuous symptoms	Medical staff (4) of Saewoori Clinic, pharmacy (6), colleagues (7) and wife	None
		20 Visit GSBH for continuous symptoms	Medical staff (2) and patients (6) of GSBH and wife	None
		21 Visit GSBH for continuous symptoms Admitted & isolated at Good Morning Hospital PCR for MERS	Patients (9) of GSBH and wife	None
		23 PCR for MERS (+) Isolated and treated at GPMC Suwon		
July 03 Discharged				

Figure 1. Main events by date for the 178th MERS case in Korea. MERS, Middle East Respiratory Syndrome; PSMH, Pyeongtaek St. Mary's Hospital; GSBH, Good Samaritan Bagae Hospital; PCR, polymerase chain reaction; GPMC Suwon, Gyeonggi Provincial Medical Center Suwon Hospital.

#178's wife and mother

Because #178's wife and mother provided care for #178's father during hospitalization, we evaluated the possibility that they became infected and transmitted MERS-CoV to #178. In particular, #178's wife received outpatient treatment for upper respiratory symptoms 4 times (May 25, 27, 30, and June 3), which raised the suspicion that she was a mild case of MERS [4]. However, four sputum samples (June 26-July 2) from her yielded negative results, as did the serum test (June 25). And #178's mother had no symptoms and showed negative sputum result, without no serum test (Tables 1 and 2, Figure 2).

Pyeongtaek community

During the incubation period for #178, many MERS patients were in Pyeongtaek. Therefore, the possibility of infection in community was evaluated. We investigated the movements of 4 cases (#32, #40, #53, and #119) who were possibly active in the downtown of the same district around June 2-6. We considered the time of symptom onset (June 16) in #178, and compared this with the times of possible exposure. The period between June 6 (afternoon) and June 15 was excluded because #178 was in Jeollanam-do for his father's funeral. The comparison of movements yielded the following results: while there

Table 1. The possible modes of transmission by exposure for the 178th MERS case

No.	Exposure	Mode of transmission	Supporting evidence	Refuting evidence	Conclusion
1	#178's father	#178's father infected in PSMH (5/18-5/29) → father to #178 in GSBH (5/29-6/6)	Incubation period, chest radiography (r/o pneumonia), mild fever	Vague results on chest radiography, only mild fever, 2 times PCR (-) of father, all PCR (-) of other family members	Possible but unknown due to limitation of serum test
2	PSMH	#178 infected in PSMH with long incubation period	Statistically possible	Only suggestion	Possible
3	GSBH	#178 infected in GSBH from other cases (#52, #119) #178 infected in GSBH from other case (#22)	Within incubation period Incubation periods, rooms of father and #22 are near	Staying in hospital in different time and different room No contact between #178 and #22 on CCTV	Unlikely Unlikely
4	#178's wife	#178's wife infected in PSMH (5/18-5/29) and transmitted to #178	Her upper respiratory symptoms (5/25-6/3), incubation period, order	MERS PCR (-) 4 times, but late exam (6/26-7/2), MERS serology (-)	Unlikely
5	#178's mother	#178's mother infected in PSMH (5/18-5/29) and transmitted to #178	Within incubation period	MERS PCR (-) and no upper respiratory symptoms	Unlikely
6	Pyeongtaek community	Community acquired infection of #178	Four MERS cases were in Pyeongtaek at that period.	No evidence of staying in same area of community	Unlikely

MERS, Middle East Respiratory Syndrome; PSMH, Pyeongtaek St. Mary's Hospital; GSBH, Good Samaritan Bagae Hospital; r/o, rule out; PCR, polymerase chain reaction; CCTV, closed-circuit television.

Table 2. Flow chart of the 178th MERS case and his family members

Date	#178	#178's father (liver cancer patient)	#178's wife	
May	18	Visit father/Room 8104	Admission at Room 8104 of PSMH ¹	
	19	Visit father	Room 8104 of PSMH	
	20	Visit father	Move to Room 8112	
	21	Visit father/Room 8112	Room 8112	Takes care of father-in-law/Room 8104 of PSMH
	22-24	Visit father/Room 7110	Move to Room 7110	Nursing/Room 8112
	25	Visit father	Room 7110	R/Sx OPD
	26	Visit father	Room 7110	Takes care of father-in-law/Room 7110
	27	Visit father	Room 7110	R/Sx OPD
	28	Visit father	Room 7110	
	29	Visit father/GSBH	Transfer to GSBH	R/Sx OPD
June	30	Visit father	MERS PCR (-)/GSBH	
	31	Visit father	GSBH	Takes care of father-in-law/GSBH
	1	Visit father	MERS PCR (-)/GSBH	R/Sx OPD
	2	Visit father	GSBH	
	3	Visit father	CXR pneumonia, vague result/GSBH	Takes care of father-in-law/GSBH
	4	Visit father	GSBH	
	5	Visit father	GSBH	
	6	Visit father	Death	Nursing/GSBH
	7-14	Residence in Jeollanam-do for funeral		Residence in Jeollanam-do for funeral
	15	Return to Pyeongtaek		Return to Pyeongtaek
16	MERS symptom onset			

MERS, Middle East Respiratory Syndrome; PSMH, Pyeongtaek St. Mary's Hospital; R/Sx OPD, respiratory symptom, positive, outpatient department; GSBH, Good Samaritan Bagae Hospital; PCR (-): polymerase chain reaction, negative; CXR, chest radiography.

¹Patient zero (#1) was in Room 8104, May 15-17.

was no overlapping area with #40, contacts with #32 (June 2), #53 (June 2 and 3), and #119 (June 2 and 4) could not be excluded because they were not isolated, and movement analyses could not clearly prove that they had no overlapping zones (Tables 1 and 2, Figure 2).

Preventive measures for those in contact with #178

Eighty-one individuals who had contact with #178 after symptom onset, including his wife, colleagues, and medical staffs, were quarantined. No additional MERS transmission was observed through the maximum possible incubation period (Figure 1).

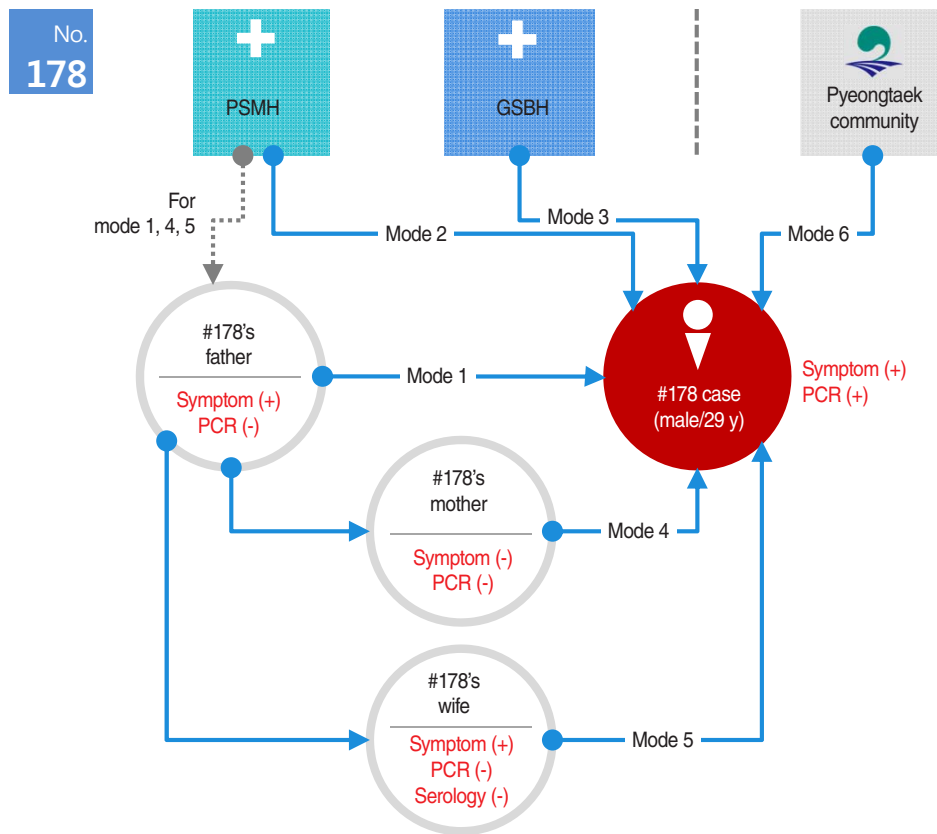


Figure 2. Possible modes of transmission of the 178th MERS case (see Table 2 for the number of transmission mode). MERS, Middle East Respiratory Syndrome; PSMH, Pyeongtaek St. Mary's Hospital; GSBH, Good Samaritan Bagae Hospital; PCR, polymerase chain reaction.

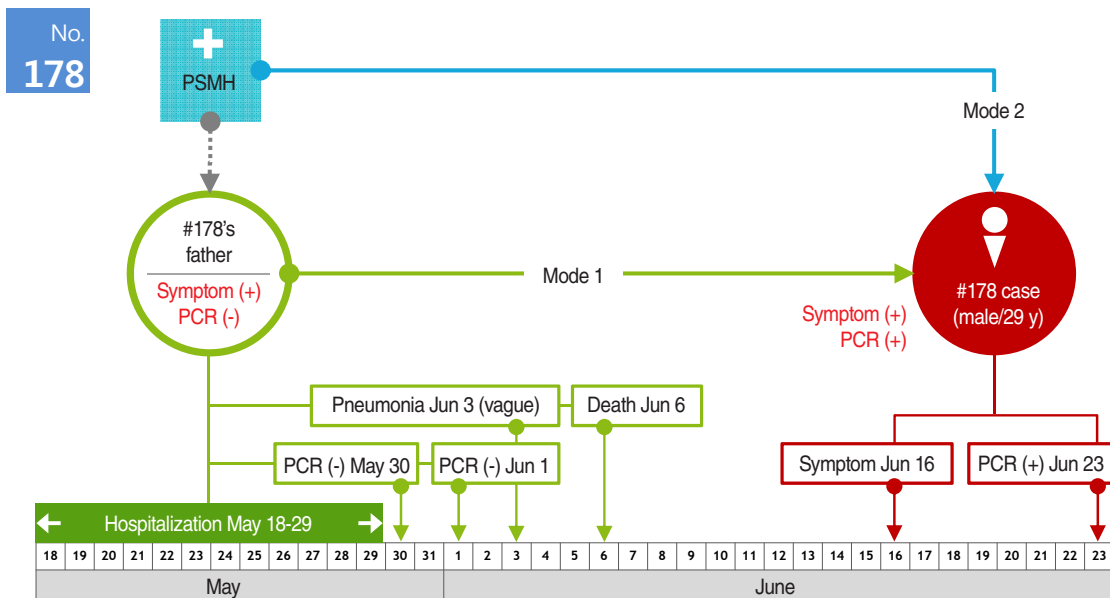


Figure 3. Two probable modes of transmission of 178th MERS case (see Table 2 for the number of transmission mode). MERS, Middle East Respiratory Syndrome; PSMH, Pyeongtaek St. Mary's Hospital; PCR, polymerase chain reaction.

DISCUSSION

We performed an in-depth investigation on #178 who had unclear modes of transmission. The results yielded two possibilities: infection during visits to his father who was a suspected false negative patient, and infection from other MERS patients in the hospital under the assumption that the incubation period was exceptionally long (Figure 3).

If it is postulated that #178 was infected through his father, three scenarios may be considered for his father's infection: i) from the contaminated environment during the 2 days in Room 8104; ii) from the other patients during the 2 days in Room 8112; and iii) from repeated exposure to MERS-CoV in other areas within the hospital. If his father was actually a false negative patient, a plausible scenario would be that #178 was infected from his father during visits, especially around June 6, the date of his father's death. The scenario is plausible in terms of an incubation period of 2-14 days [2]. However, except for vague findings of pneumonia, his father showed no clear MERS symptoms, and the sputum test was negative, as were those of 5 other family members contacted his father. As his father is dead, it could not be verified whether he was a patient. On a related note, there was a comparable case in Tunisia in 2013. A 66-year-old man developed high fever on returning home after meeting his 30-year-old daughter in Qatar, and died 5 days after hospitalization (12 days after symptom onset). The MERS PCR test performed the day before his death was negative. His 34-year-old son took care of him during his illness, developed MERS symptoms with high fever 3 days after the funeral, and was confirmed. The son had no foreign travel, and as this was the first MERS case in Tunisia, the only possibility was infection from the father. The Tunisian public health office sent the father's serum taken before his death to the US Centers for Disease Control, and it was MERS-positive [4]. In Korea, there was also a #119 case in which a negative diagnosis on the first test was corrected to positive with additional tests. This suggests that it is possible #178 was infected from his father. Unlike the Tunisian case, a confirmatory test was not possible because the father's serum was not stored [5].

The second scenario assumes a long incubation period. The estimated incubation period in this scenario is 18 days, which is considerably longer than the known 2-14 days, but is statistically possible.

Other modes of transmission were evaluated and excluded. First, the possibility of being infected from the other 3 MERS patients in GSBH could be excluded by confirming no direct contact. The possibility of #178's wife or mother infecting him after being infected from his father could be excluded, considering the investigation results. Community-acquired infection is possible, but it is less plausible than others, more so considering

the MERS-specific transmission patterns are in hospital settings and through close contact [6]. The possibility of error regarding #178's symptom onset date was also considered; however, we could exclude this revealing that he did not have any symptoms before June 16, and that he did not visit medical facilities before June 16 (Table 2).

From the standpoint of prevention, there are lessons learned. Although #178 and his family were exposed to MERS-CoV in PSMH, and belonged to the subjects for initial quarantine, they were not closely monitored. Although she received outpatient treatment for respiratory symptoms several times, #178's wife was not subjected to MERS testing. His family kept providing care for #178's father in GSBH without precautionary measures, even after transfer from PSMH. No additional MERS testing was undertaken after the sputum-negative for #178's father. The funeral was held without any precautionary measures. After #178 returned to Pyeongtaek following the funeral, he came into contact with a large number of individuals after symptom onset. Fortunately, no additional MERS cases occurred among those in contact with #178. In addition, those in contact with #178's father, including relatives, GSBH staffs, and those who transported or shrouded the corpse, did not develop any symptoms.

In conclusion, we arrived at two plausible scenarios: intrafamilial spread through the father and a prolonged incubation period from the infection at PSMH.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

SUPPLEMENTARY MATERIAL

Supplementary material (Korean version) is available at <http://www.e-epih.org/>.

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