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Institutional Preparedness to Prevent Future Middle East Respiratory Syndrome Coronavirus-Like Outbreaks in Republic of Korea

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A year has passed since the Middle East respiratory syndrome (MERS) outbreak in the Republic of Korea. This 2015 outbreak led to a better understanding of healthcare infection control. The first Korean patient infected by Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was diagnosed on May 20, 2015, after he returned from Qatar and Bahrain. Thereafter, 186 Korean people were infected with the MERS-CoV in a short time through human-to-human transmission. All these cases were linked to healthcare settings, and 25 (13.5 %) infected patients were healthcare workers. Phylogenetic analysis suggested that the MERS-CoV isolate found in the Korean patient was closely related to the Qatar strain, and did not harbor transmission efficiency-improving mutations. Nevertheless, with the same infecting virus strain, Korea experienced the largest MERS-CoV outbreak outside the Arabian Peninsula, primarily due to the different characteristics of population density and the healthcare system. We aimed to review the epidemiological features and existing knowledge on the Korean MERS outbreak, and suggest methods to prevent future epidemics.

Key Words: Middle East respiratory syndrome coronavirus; Awareness; Preparedness

Mode of transmission issue during the 2015 outbreak [1]

The suspected transmission route for human Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection was a direct contact with the saliva of infected camels, or through consumption of unpasteurized milk or undercooked meat [2]. Kayali et al. showed that the seroprevalence of MERS-CoV was several times higher in persons with regular exposure to camels than in the general population [3]. Further, Muller et al. reported a 15- and 23-times higher seroprevalence of MERS-CoV antibodies in shepherds and in slaughter-

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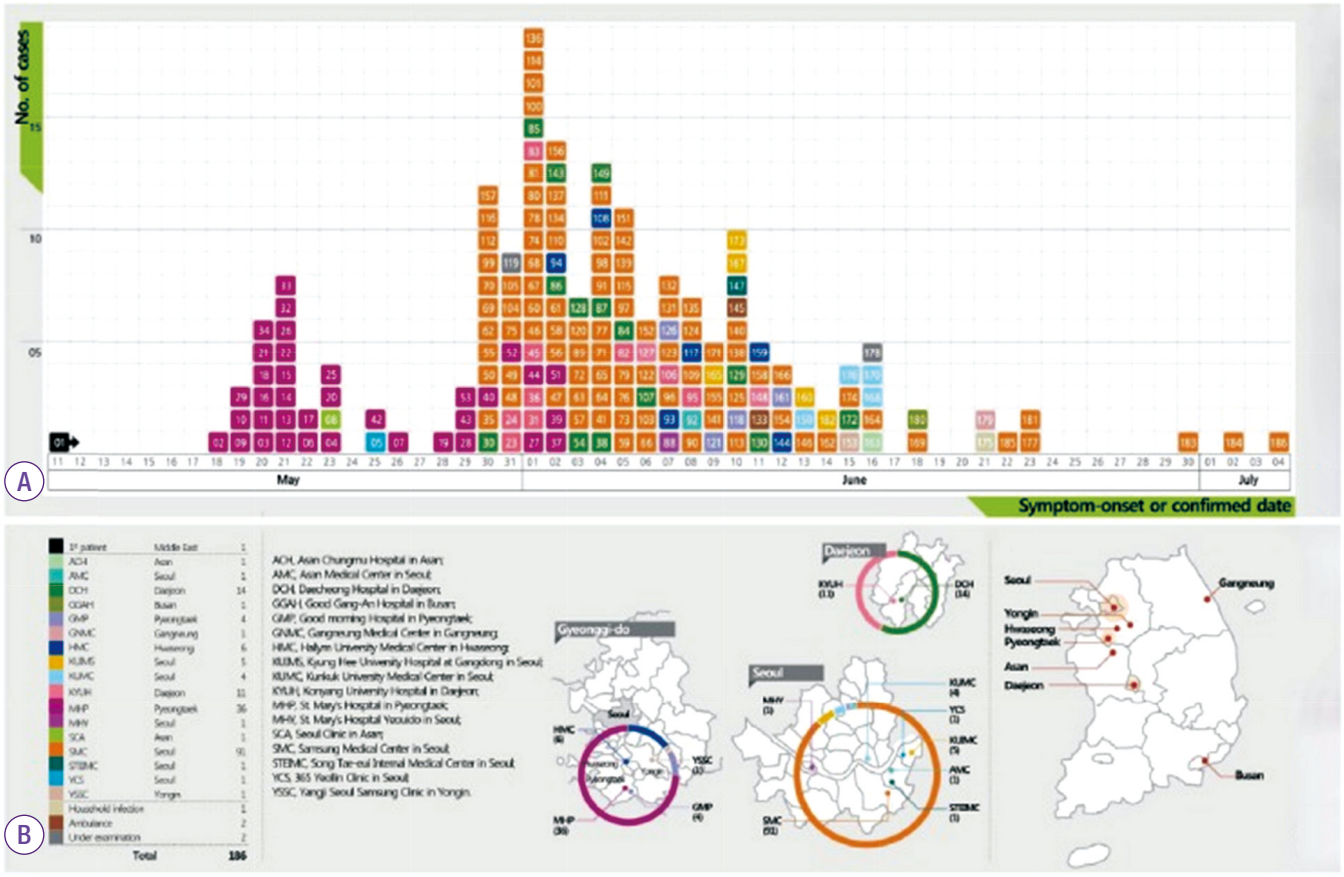

Figure 1. Epidemic curve of the Korean Middle East respiratory syndrome outbreak.
Adapted from Epidemiol Health 2015; 37: e2015033.

house workers, respectively, compared with the general population [4].

Person-to-person transmission of zoonotic disease has been reported for only a limited number of diseases [5]. The incapability of MERS-CoV to infect animal models like hamsters, mice, and ferrets, indicates the presence of a species barrier. However, an experimental study showed that human cell lines were susceptible to MERS-CoV infection [6], and the reports of human-to-human transmission have increased [7-9]. The modes of human-to-human MERS-CoV spread are incompletely defined [10]. However, some experts have suggested the occurrence of secondary infections through droplets, or direct contact with infected patients or fomites [11]. Furthermore, an epidemiological study reported the potential for MERS-CoV nosocomial transmission through contaminated surfaces of bed sheets, bed controllers, bedrails, medical devices, and even air-ventilation equipment [12].

Although the school-going children of the community were not initially a suspected at-risk population for virus transmission, growing public fear finally resulted in closure of more than 1,160 kindergartens, schools, and even some universities. During this time, people riding subways, buses, and other public transports while wearing face masks, was a common sight. Increasing public fear resulted in cancellation of social meetings, and the downtowns were no longer crowed [13]. However, there still are no strong evidences supporting MERS spread in community-settings, and therefore, the usefulness of these social efforts to prevent MERS spread in the community remains uncertain.

Super-spreading events: epidemiological perspective

Chowell et al. suggested that a few early super-spreading events fueled the MERS outbreak in Republic of Korea [1]: the index patient who infected 30 secondary cases, and another two second generation cases who infected 80 and 23 secondary cases, respectively (Fig. 1). These cases were termed as "super-spreaders," while the vast majority of cases induced

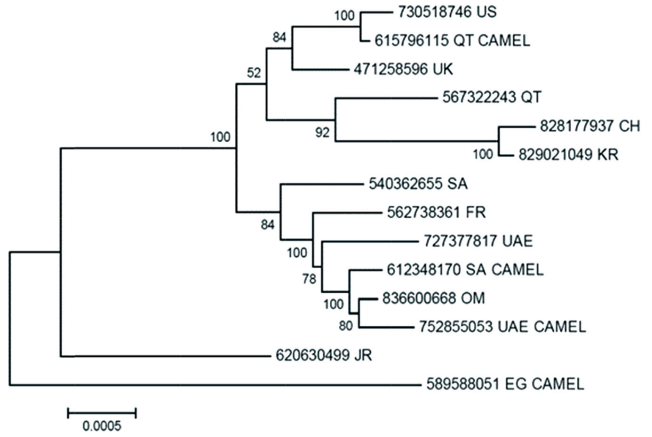

Figure 2. Phylogenetic analysis of the complete Middle East respiratory syndrome-coronavirus genomes using the maximum-likelihood method based on Tamura-Nei model implemented in MEGA5.
CH, China; EG, Egypt; FR, France; KR, Republic of Korea; OM, Oman; QT, Qatar; SA, Saudi Arabia; UAE, United Arab Emirates; UK, United Kingdom; US, United States; JR, Jorda.
Adapted from Exp Mol Med. 2015;47:e181.

relatively few secondary infections. According to some researchers, super-spreading events follow the 20/80 rule [14], where approximately 20% of the infected individuals are responsible for 80% of the transmissions. Moreover, Lloyd-Smith et al. reported that super-spreading is a normal feature of disease transmission [15].

Stein et al. summarized the contributing factors resulting in a super-spreader as follows: pathogen's virulence factors, co-infections, decreased host immunity, misdiagnosis, delayed hospital admission, inter-hospital transfers, host behaviors such as ignoring instructions regarding infection control, and poor environmental conditions such as crowding, poor ventilation, etc. [16]. An observational, laboratory-based study of outbreaks in Jeddah and Riyadh reported that the MERS super-spreading events and the observed overdispersion of MERS transmission may similarly result from a combination of factors, including individual viral shedding and contact rates, hospital procedures and locations, as well as population structure and density [17].

Predicting super-spreading events is thus very important in infectious disease management and pandemic preparedness plans [16]. However, it may be difficult to identify the super-spreaders before the onset of an epidemic. In both the French [9] and the German MERS-CoV cases [18], which had similar findings listed above, the exposed healthcare workers did not get infected, although appropriate infection-protection measures were not in place. In the Korean outbreak as well, some non-super-spreaders had similar conditions to those favoring super-spreading events: high viral titer, delayed awareness, narrow and crowded rooms, and unprotected close contact such as intubation. Despite this, no confirmed secondary cases were found amongst thousands of exposed persons (data not published). The consequence of this discrepant transmission can be summarized in a statement by Galvani and May, "heterogeneously infectious emerging disease will be less likely to generate an epidemic, but if sustained, the resulting epidemic is more likely to be explosive" [14] (Fig. 2).

Risks of death and the implication of infection control

A Korean MERS outbreak epidemiological study was undertaken to estimate the case fatality rate (CFR) among senior patients [19]. The CFR for patients aged 60 years or older, with underlying diseases, was estimated at 48.2 %, as of July 31, 2015. The estimated CFR among other cases were as follows: 1.8 % in the lowest risk group (age < 60 years without any underlying diseases); 13.6 % for those aged 60 years or older, without any underlying diseases; and 11.1 % for those younger than 60 years, with underlying diseases. Senior patients were thus 9.3-fold (95 % CI, 5.3–16.9) more likely to die compared to younger patients, while presence of underlying diseases resulted in a 7.8-fold (95 % CI, 4.0–16.7) higher likelihood of fatality [19]. Although the researchers were not able to ensure a systematic and consistent review of all common comorbidities, these findings showed that enhanced hospital infection control practices, protecting the specific at-risk groups from MERS exposure, were very important to reduce associated mortality.

Weakness of the Korean health care system in infection control

The health care system of Republic of Korea is a very unique structure, in which a 39 year-old universal social welfare system; the utilitarian "National Health Insurance System (NHIS)"; and competitive private clinics and hospitals miraculously co-exist. The efficiency of the Korean medical insurance system is among the highest in the world, having even numerous mega-sized hospitals running at relatively low medical costs. Although the reimbursement system of the medical costs are public, there is no limitation to hospital use in different regions, and relatively few restrictions exist in

choosing from large university hospitals or tertiary care centers. Thus, patients can select a medical institution they want to visit, and move easily from one hospital to another. Further, even though accurate transfer notes are mandatory, the patient management and clinical testing information are not adequately shared by the referring hospitals. These factors may make hospital-to-hospital infection transmission more common [20]. In addition, with an aim to restrict over-charging by individual institutions, medical expenditures including institutional safety-related expenditures are strictly controlled by the Health Insurance Review & Assessment Service (HIRA). Consequently, more than 50% of the hospital rooms in Korea have more than 4 beds per room, and family members or privately hired health care aides usually stay with the patients in theses crowded hospital rooms. This situation has not been ameliorated with the recently built large-sized university hospitals, and this increased vulnerability to easier viral transmission as a result of overcrowding has long been considered a common occurrence at the larger hospitals [20].

Future prevention strategies against MERS CoV-like situation in Korea

How can Korean healthcare institutions, with high population density, be better prepared against MERS-CoV-like outbreaks? This question is even more pertinent for large well-constructed hospitals, operating in relatively resource limited settings in terms of safety issues; availability of adequate space; and number of healthcare workers, that cater to severe cases including the critically ill patients. To prevent future infectious disease outbreaks in Korea, several strategies might be adopted, and are summarized as below. These strategies should include not only individual institution-level preparedness, but also the entire healthcare system. Debates are expected on prioritization of infection safety.

1. A higher index of alerting system to find the source-patient earlier

In the Korean MERS outbreak, a number of cases could not be suspected in the first hospital visit, as early clinical manifestations of MERS are non-specific. Consequently, significant secondary exposures were provoked unconsciously. Drostein et al. suggested that viral spread may have been limited by awareness of the disease among healthcare workers and patients [17]. Therefore, an efficient alerting system, including proper education on newly spreading diseases to the healthcare workers is necessary. In addition, medical providers must adopt a mandatory travel history checking policy when screening patients presenting with fever or respiratory symptoms. Thereon, systems to share adequate medical information between hospitals should be established.

2. Appropriate numbers of airborne infection isolation rooms (AIIRs) should be constructed and maintained

The US's Centers for Disease Controls and Prevention (CDC) recommends that the AIIRs should be single, negative pressure, patient rooms, with a minimum of 12 air changes per hour. CDC also recommends a direct discharge of air from these rooms to the outside, or filtration through a high-efficiency particulate air (HEPA) filter before recirculation. Before the MERS outbreak, the Korean government prepared a total of 119 negative pressure beds. However, many of these did not meet the recommended criteria, and some were not even built as single patient rooms [21]. The resultant shortage of AIIRs meant that not all MERS suspected patients were isolated at the peak of the Korean outbreak. Furthermore, AIIRs and specialized healthcare settings were also disproportionately distributed between public and private hospitals. Thus, as newly built AIIRs were concentrated in public hospitals under local government, most advanced healthcare facilities and critical care personnel were linked to large sized private university hospitals. During the outbreak, many public hospitals had to recruit medical personnel from university and army hospitals, and also volunteer nurses.

3. Donning & doffing; proper training on putting on and take off "Personal Protective Equipment (PPE)"

CDC's PPE recommendation are as follows [22]: "Workers must receive training on and demonstrate an understanding of when to use PPE; what PPE is necessary; how to properly don (put on), use, doff (take off) PPE; how to properly dispose of or disinfect and maintain PPE; and the limitations of PPE. Any reusable PPE must be properly cleaned, decontaminated, and maintained after and between uses." During the Korean MERS epidemic, although doctors and nurses used PPE, some of them were infected with MERS-CoV. Even as the reasons for infection in these healthcare workers were uncertain, some epidemiologic researchers attributed this to inadequate use of PPE.

4. Well-trained healthcare workers to care for patients infected with highly contagious pathogens must be fostered

During the Korean MERS outbreak, only a few doctors and nurses at each healthcare facility were engaged in MERS patients care. The number of infectious diseases specialists was less than 200 for the 50 million Korean people at the time of the 2015 MERS outbreak. This resulted in overworked healthcare professionals, which could be a threat for both the healthcare workers and the patients [23]. The Korean government plans to increase the numbers of infection control and epidemiology professionals, and establish specialized infectious diseases hospitals. However, this seems to be a half successful measure, since the numbers of trained specialists, that existing societies and educational associations could certificate annually, are far from the goal.

5. Crowded and narrow hospital rooms should be converted to visitor controlled larger-spaced hospital rooms

Almost all secondary infected Korean MERS cases were patients, healthcare workers, or visiting family members, who were exposed to source patients in crowded hospital environments such as multiple occupancy rooms and emergency rooms. These close personal contacts may allow easy transmission of MERS-CoV. Therefore, stronger policies need to be in place to initially maintain patients with acute febrile and/or respiratory illness in single patient rooms (preemptive isolation), followed by a move to multiple occupancy room, depending on infectiousness. Moreover, regulations and restrictions on visiting acquaintances in hospital are also needed. Thus, even as visiting sick family members of friends in hospital is a friendly way to express social relationship for Koreans for long time, this culture should be modified to better prevent catastrophic contagious diseases.

Conclusion

Last year, struggling with an unfamiliar syndrome, the Korean healthcare system was unable to find infected cases in time, and to react quickly and accurately as the first imported case was reported. Multiple potential factors were associated with the super-spreading events: misdiagnosis, delayed hospital admission, inter-hospital transfers without accurate information, and also behaviors such as ignoring instructions regarding infection control, and poor environmental conditions. Institutional and healthcare system's preparedness is required to prevent such outbreaks. Efforts to halt transmission of infectious diseases need to be prioritized and should include: reviewing existing recommendations, improved contact tracing policy, improved public hospital facilities for critical care of severe infections, and pre-emptive isolation for unknown acute respiratory infection. These strategies are crucial to prepare for a future MERS-like epidemic in Korea.

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