

Middle East Respiratory Syndrome Republic of Korea/World Health Organization Joint Mission

9–13 June 2015

EXECUTIVE SUMMARY

On 20 May 2015, the National International Health Regulations (IHR) Focal Point of the Republic of Korea officially notified the World Health Organization (WHO) that a resident had developed a laboratory-confirmed case of Middle East respiratory syndrome (MERS). Domestically and internationally, there has been anxiety as to whether this outbreak was caused by a newly adapted virus strain and whether the outbreak will continue to spread, including to other countries. The Government of the Republic of Korea and WHO agreed to conduct a joint mission with domestic experts to assess the outbreak and the country's response, and to make recommendations to strengthen the response and outbreak preparedness. The joint mission consisted of domestic and international experts in a variety of disciplines, including several with extensive experience with MERS, and was co-led by Dr Jong-Koo Lee and Dr Keiji Fukuda.

The joint mission found that several factors appear to have contributed to the initial spread of the virus:

- Since MERS is a new infection in the Republic of Korea, physicians and public health authorities did not expect it. In some instances, a travel history was not collected from cases, contributing to a time lag in diagnosis and isolation of cases.
- In some hospitals, infection prevention and control measures were not optimal. Before the index case was diagnosed, he had contact with many people leading to spread of infection in three health-care facilities.
- Certain social patterns and customs contributed to the spread of infection among several hospitals. For example, the practice of “doctor shopping” allowed infected patients to come in contact with more people than if they had stayed with one facility. The custom of having many friends and family members accompany or visit patients in emergency departments or in hospital also exposed more contacts to infection.

The joint mission made the following initial observations:

- There is no evidence to suggest that the MERS viruses in the Republic of Korea are significantly different genetically from recent viruses in the Middle East.
- This outbreak appears similar to hospital-associated outbreaks that have occurred in the Middle East and does not appear to have new epidemiological features that would suggest a shift in how the virus is transmitted. There is no evidence of ongoing community transmission of MERS.
- While the spread of MERS from the Republic of Korea to other countries remains possible, extensive efforts using a variety of approaches are being made to identify symptomatic and

asymptomatic individuals. Such efforts, including mandatory quarantine of close contacts, and restriction of international travel of all cases and contacts, are impressive and appear to be having an effect since incident cases are declining.

The joint mission's recommendations to the Government were shared and discussed with the Minister for Health and Welfare and his staff on 13 June as follows:

- 1) Infection prevention and control measures may be immediately strengthened in all health-care facilities in the Republic of Korea.
- 2) All patients presenting with fever or respiratory symptoms may be asked about: contact with a MERS patient; visits to a health-care facility where a MERS patient has been treated; and history of travel to the Middle East 14 days before symptom onset. Any patient with positive responses should be promptly reported to public health authorities and managed as a suspected case while the diagnosis is being confirmed.
- 3) Close contacts of MERS cases should not travel during the period when they are being monitored for the development of symptoms.
- 4) Strong consideration may be given to reopening schools, as schools have not been linked to transmission of MERS in the Republic of Korea or elsewhere.
- 5) Continued implementation of basic public health measures by all health authorities will contribute to stopping further cases. These measures include:
 - a. early and complete identification and investigation of all contacts;
 - b. robust quarantine/isolation and monitoring of all contacts and suspected cases;
 - c. full implementation of infection prevention and control measures; and
 - d. prevention of travel, especially internationally, of infected people and contacts.
- 6) Local governments must be fully engaged and mobilized in this national emergency.
- 7) In parallel with disease prevention and control measures, it is important to strengthen domestic and international confidence. This includes improving risk communications. The Ministry of Health and Welfare may provide regular updates (in Korean and English) on the epidemiological situation, investigations and disease control measures.
- 8) Additional staff (for surge capacity) are urgently required for the response and to provide relief for staff working on the outbreak.
- 9) Selected hospitals may be designated for safe triage and assessment of suspected MERS cases. This will require trained personnel, facility management and communication with the public.
- 10) Comprehensive research studies designed to close critical gaps in knowledge, including sero-epidemiological studies, may be completed and the results widely communicated as quickly as possible.
- 11) The Republic of Korea may ensure that it is able to optimally respond to future outbreaks. This includes strengthening medical facilities to deal with serious infectious diseases (including increased numbers of negative-pressure isolation rooms), considering how to reduce the practice of “doctor shopping”, training more infection prevention and control specialists, infectious disease experts, laboratory scientists, epidemiologists, and risk communication experts, and investing in strengthening public health capacities and leadership, including at the Korea Centers for Disease Control and Prevention (KCDC).

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1. INTRODUCTION

On 20 May 2015, the National International Health Regulations (IHR) Focal Point (Korea Centers for Disease Control and Prevention, (KCDC)) of the Republic of Korea officially notified WHO that a resident had developed a laboratory-confirmed case of Middle East respiratory syndrome (MERS). The index case had recently travelled to Saudi Arabia, Qatar, the United Arab Emirates and Bahrain but had not been ill during travel.

This was the first introduction of MERS into the Republic of Korea and has resulted in the largest outbreak of this infection outside the Middle East. As of 13 June 2015, there were 138 laboratory-confirmed cases (including 14 deaths), all of whom appear epidemiologically linked to the index case or subsequent secondary cases. As of 13 June, more than 60 health-care facilities had cared for a case of MERS, among which six hospitals have had documented nosocomial transmission. One case travelled from the Republic of Korea to China by transiting through Hong Kong SAR (China). Information on this case was first reported by the Republic of Korea through the IHR (2005) mechanism. The case was then detected and reported by China.

Within the Republic of Korea and internationally, there has been anxiety as to whether this outbreak was caused by a newly adapted virus strain and whether this outbreak will continue to spread, including to other countries.

The Government of the Republic of Korea and WHO agreed to conduct a joint mission with domestic experts to assess the outbreak and the Republic of Korea's response, and to make recommendations to strengthen the response and outbreak preparedness. The joint mission consisted of domestic and international experts in a variety of disciplines, including several with extensive experience with MERS. The mission was co-led by Dr Jong-Koo Lee and Dr Keiji Fukuda. The missions members are listed in Annex 1.

2. TERMS OF REFERENCE

The joint mission travelled to the Republic of Korea:

- to jointly review the current situation of the MERS outbreak in the Republic of Korea, including epidemiological patterns, virus characteristics, clinical features and public health response;
- to provide technical recommendations on response measures to control the outbreak; and
- to share experiences between the Republic of Korea and the international community in responding to the first significant outbreak of MERS occurring outside the Middle East.

3. ACTIVITIES

On the first day of the mission, the WHO team was greeted by the Minister and Vice-Minister of Health and Welfare. The joint team established a working base at KCDC and met daily and received presentations from Korean experts and responders and discussed critical questions, findings and issues. These presentations and discussions were open to all members of the mission team. Topics included viral characteristics based on international laboratory testing results, clinical management,

epidemiological trends, outbreak investigations, public concerns and risk communications strategies, disease prevention and control measures including contact tracing, monitoring and travel restrictions, information gaps requiring further study, and data management. Topics were discussed in plenary and then often in more detail in smaller subgroups of experts. Some mission members visited Samsung Medical Center and the Emergency Operating Center at the Ministry of Health and Welfare and attended a meeting convened by the Acting Prime Minister. The mission co-leads also met with Her Excellency President Park.

During the last two days of the mission, a briefing was given to the Minister of Health and Welfare and a press conference was held. The agenda of the joint mission is included as Annex 4.

4. FINDINGS

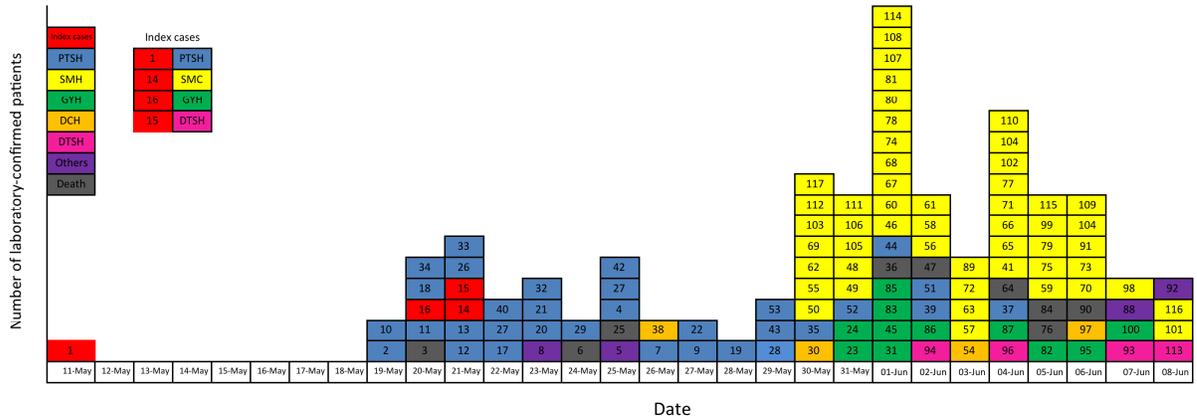
4.1 Epidemiological findings

At the time of the mission, active investigation of cases and their source of infection and contact tracing were ongoing. All known cases were either: health-care workers caring for confirmed cases; patients being cared for at the same health-care facilities as confirmed patients; or family members, friends or others who had visited a confirmed patient or who had visited the same room or facility housing a confirmed case.

Within the overall outbreak, three large clustering events were identified. These involved nosocomial transmission in Hospital B (Pyungtaek St Mary's Hospital) and Hospital D (Samsung Medical Center), and one situation where exposure to a case (case #16) resulted in two smaller clusters in hospitals E and F (KonYang University Hospital and Dae Cheong Hospital). Knowledge of the factors associated with these outbreaks is increasing as more investigations are carried out but many details about transmission are not well understood and will require further investigation.

Among the people who were infected in the Republic of Korea one had travelled to China, first by plane to Hong Kong SAR (China), and then by bus to Guangdong. That person was symptomatic while travelling. On the basis of information provided by the Republic of Korea under IHR 2005, Chinese authorities were able to rapidly locate, provide care for and isolate this person. The Chinese authorities were also able to identify contacts in China. The contacts have been placed in quarantine and are being followed and tested for MERS. No additional cases have been identified among contacts in Hong Kong SAR (China) (n=28) or in China (n=75). This is the first MERS case reported in China.

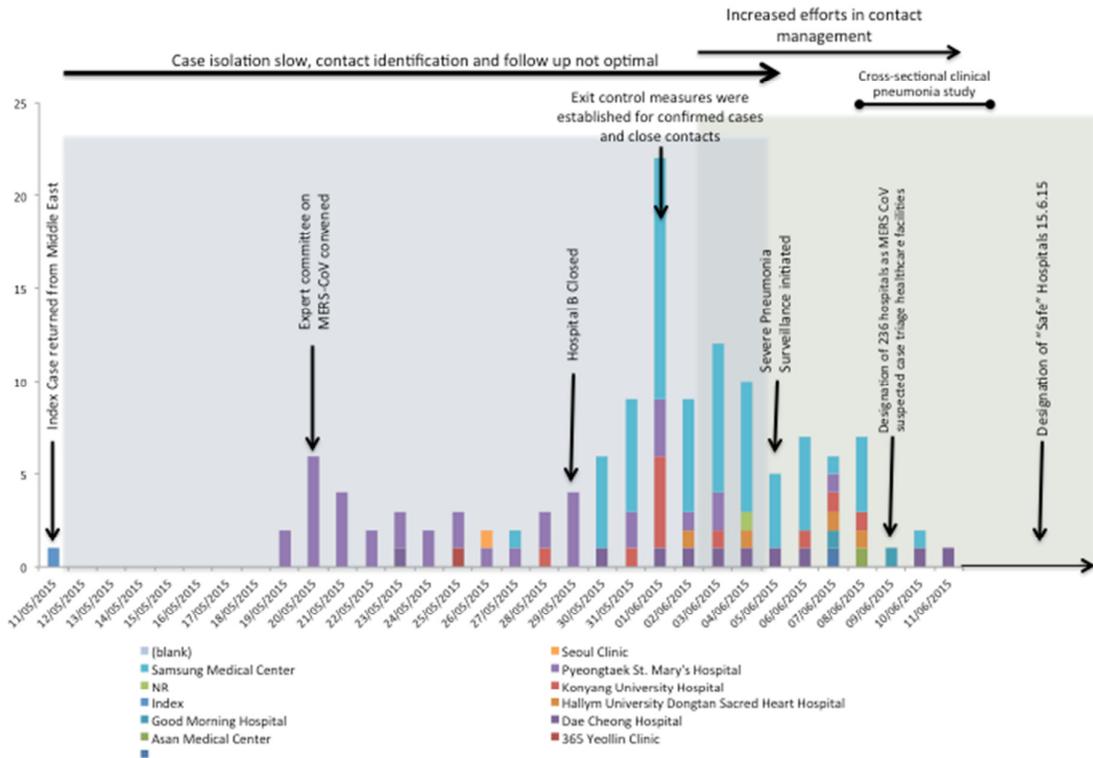
Figure 1. Daily epidemic curve of MERS cases reported by the Republic of Korea and China by date of symptom onset and hospital



*Date as of 13 June 2015; case #10 travelled to China

Efforts to control the outbreak and prevent further spread are being intensified; a timeline of events is shown in Figure 2.

Figure 2. Timeline of control efforts in the Republic of Korea



4.2 Clinical features of cases

Among laboratory-confirmed cases in the Republic of Korea, the clinical spectrum of illness has ranged from mild illness to severe disease and death. Among the first 87 cases, the most common

symptoms were fever (97%), cough (43%), myalgia (30%), and sputum production (24%). Dyspnoea, nausea/vomiting, and diarrhoea were reported less often, at 5.7%, 5.7%, and 9.2%, respectively.

The median age was 55 years (range 16–83); 49 are male (56.3%); and 45 (51.7%) had underlying diseases. The mean incubation period has been estimated at 6.5 (SD 3.2) days. The case-fatality rate at the time of presentation was 7.9% (10 deaths among 126 confirmed cases); all fatal cases thus far had comorbid illness. As of 11 June, five cases were intubated.

An early investigation of the first 58 cases showed that chest radiographs were normal on presentation in 27 (46.5%), or showed bilateral infiltrates or unilateral infiltrates in 16 (27.5%) and 13 (22.4%) cases, respectively. Hypoalbuminemia (< 3.5 g/dL), leukopaenia, thrombocytopenia, and elevated liver enzymes (AST/ALT) were found in less than 50% of cases.

4.3 Case/contact identification and management

Both active and passive methods are being used to find cases of MERS infection and contacts.

Methods to find contacts of laboratory-confirmed cases included interviews of cases and their family members, review of closed-circuit television (CCTV) video surveillance in health-care facilities and use of global positioning system (GPS) tracking of mobile phones to identify the location of contacts. Such activities are not done routinely but have been used because of the urgent need to stop the outbreak.¹

All contacts are recorded in a database maintained by the MERS Task Force in the Ministry of Health and Welfare. Once a contact is identified, a staff member (usually an epidemic intelligence service (EIS) officer) visits and interviews the contact and on that basis, classifies the contact as either “casual” (anyone who has visited a health-care facility where a confirmed case was treated or a person who was in the same household or hospital) or as “close” (a person who was in close proximity to confirmed case but was not wearing personal protective equipment, a person who was within a two-metre distance, a person who had direct contact with respiratory secretions, or passengers, or cabin crew sitting around a confirmed or suspected case).

During the potential incubation period of 14 days, each contact is called twice daily by government officials to check for the development of symptoms. Initially, monitoring focused upon the development of fever but from approximately 9–10 June, fever and respiratory symptoms have been monitored. As of 2 June, quarantine at home for close contacts has been mandatory for 14 days after exposure to a confirmed case. If a close contact does not follow quarantine conditions, the contact is physically brought back to his or her home by government officials wearing protective gear. For casual contacts, quarantine at home is recommended for 14 days after exposure to a confirmed MERS case. During quarantine, any contact who develops symptoms (respiratory or fever) is transported by ambulance to one of 19 referral health-care facilities designated for MERS patients and placed in isolation and a specimen (usually sputum) is collected for laboratory testing.

After 14 days from the time of exposure to a case, a symptomatic contact is released from isolation if polymerase chain reaction (PCR) test results are negative on two different specimens collected 48 hours apart and if the contact has no symptoms. A symptomatic contact who tests positive for MERS by PCR is considered a laboratory-confirmed case and is provided treatment in isolation. Confirmed

¹ These measures were taken in accordance with the Personal Information Protection Act and the Infectious Disease Control and Prevention Act in the Republic of Korea.

cases are released after two samples, collected 24 hours apart, have tested negative by PCR and if the case has no symptoms for more than 48 hours.

In the initial stages of the outbreak, laboratory testing and confirmation were centralized at the Korean National Institutes of Health (KNIH). However, testing is now conducted by many more laboratories. The KNIH laboratory was using standard WHO-recommended molecular diagnostic methods for testing and confirmation and had previously taken part in a WHO external quality control programme with excellent results.

4.3.1 Active case finding

In addition to reporting of cases by health facilities, the Government has implemented two additional surveillance programmes to identify cases.

On 5 June 2015, KCDC began testing patients with severe pneumonia in four geographic areas (Seoul Metropolitan City, Gyeonggi province, Chungnam province, and Daejeon Metropolitan City) for MERS. During 5–10 June, 237 severe pneumonia patients were identified, from which 139 sputum specimens were collected and tested for MERS. One sample tested positive (case #121). This sample came from a patient who had already been identified as a contact and who, after developing symptoms, had already been placed in isolation.

On 9 June, a cross-sectional survey was started to test all people who were hospitalized with pneumonia, who were 15 years or older and who had an epidemiological link to a confirmed case or to a health-care facility where any MERS patient was treated or reported for MERS. This survey will cover hospitals across the Republic of Korea and was to run for one week. As of 12 June, 1064 hospitals had started and thus far, 11 hospitals have identified 13 pneumonia cases that meet the criteria. Among these 13, five were already isolated and on the contact list, while eight were not. None of the 13 tested positive for MERS.

4.3.2 Passive case finding

The Government has made public announcements (at press conferences, through the MERS hotline, and online) requesting that people, who suspect they have symptoms compatible with MERS or who have visited a health-care facility where MERS patients were treated, go to one of 256 designated hospitals for evaluation.

4.4 Outbreak response operations

Before the current outbreak, an overarching national plan for the prevention and control of emerging infectious diseases, including a specific plan for response to MERS, was in place.

The national plan, which includes four phases of response, was adapted for the current outbreak and covered the establishment of a situation monitoring system (24 hours a day/7 days a week), expanded laboratory testing capacities, and stockpiling of personal protective equipment.

The MERS Response Center coordinates the overall health response, especially planning, field response, resource management and communication.

In early June, response measures were significantly intensified (Annex 2). These measures included new policies and emergency measures, implementation of an information system to manage all cases and contacts, a contact location tracking system, a government subsidy for close contacts under quarantine, hospital infection prevention and control, patient management and risk communication activities.

During the mission, operational challenges included maintaining adequate staffing for the outbreak response for a prolonged period; vertical coordination among government, Ministry of Health and Welfare, KCDC, and Field Operations; managing a large and growing number of contacts; coordinating a growing amounts of data from different sources; translating knowledge into clear and balanced risk communication messages; and handling sensitive issues such as risk communications, quarantine policy and school closures.

4.5 International collaboration

The Republic of Korea promptly communicated information on the outbreak to WHO via the IHR (2005) mechanism. The Republic of Korea was also communicating with other governments via the IHR (2005), including information about foreign nationals on the contact list and contacts travelling to other countries before control efforts were intensified.

In addition to sharing information via IHR (2005), the Korean health authorities endeavoured to ensure monitoring of contacts abroad. In particular, contacts of Korean nationality traveling abroad were actively located through Korean embassies, and then were put under quarantine with guidelines to follow until release in close cooperation with health authorities abroad. Recognizing the importance of sharing MERS-related information with the international community as well as foreigners residing in the country, the Republic of Korea provided English-translated press releases, MERS statistics and the list of hospitals with MERS exposures through the nation's MERS portal website (www.mers.go.kr) as well as the Ministry of Health and Welfare website. The Republic of Korea also established the MERS hotline with services in multiple languages including English, Chinese and Japanese.

Virus genetic sequences from one patient in the Republic of Korea have been shared with WHO experts by KNIH. Virus genetic sequence from the patient hospitalized in China was publicly shared via the United States National Center for Biotechnology Information (NCBI) GenBank. This virus genetic information was discussed at a WHO teleconference on 7 June 2015 (see report at: http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-9june2015/en/) and was pivotal in reaching international consensus that genetic mutations did not appear to be a significant concern for this outbreak. Clinical specimens have been shared with the United States Centers for Disease Control and Prevention.

5. ASSESSMENT

5.1 Factors contributing to the initial spread of MERS

This outbreak in the Republic of Korea started with the introduction of a single case of MERS into the country in a traveller who recently returned from visiting Saudi Arabia, Qatar, United Arab Emirates, and Bahrain (18 April–4 May). The spread of infection has been amplified by uncontrolled exposures in health facilities, resulting in a significant number of secondary cases among contacts, primarily in

hospitals. As of 12 June, 126 laboratory-confirmed cases had been identified (including the case who travelled to China).

One difficulty in monitoring the progress of the outbreak, and a source of confusion for the public and others, has been the reporting of cases. The daily counts of cases provided by the Republic of Korea have included newly identified cases whose infection occurred in the past (for example, older cases associated with earlier hospital clusters) and new cases, reflecting recent infection.

This issue is important because, as shown in the epidemic curve, it appears as if the trend in new incident cases is declining; but it is too early to tell whether the trend is firm or whether it represents a reporting lag. This will require another few weeks for a robust assessment but suggests that recent implementation of much stronger disease control measures, such as contact tracing and monitoring and quarantine measures, is working.

Several factors appear to have contributed to the initial spread of this virus:

- Since MERS is a new infection in the Republic of Korea, physicians and public health authorities did not expect it. In some instances, a travel history was not collected from cases, contributing to a time lag in diagnosis and isolation of cases.
- In some hospitals, infection prevention and control measures were not optimal, related in part to crowded emergency rooms and hospitalization of infectious patients and other patients together in multi-bed rooms for extended periods. Before the index case was diagnosed, he had contact with many people leading to spread of infection in three health-care facilities. After diagnosis, he was transferred to the National Medical Center, which was designated by the Government for MERS treatment. He was placed in a negative pressure isolation room. The index case was admitted to Hospital B when he did not yet have a diagnosis. This resulted in 38 new MERS cases. Some of these people were then treated in other health-care facilities before their MERS infection was diagnosed, thus spreading the virus to others.
- Certain social patterns and customs contributed to the spread of infection among hospitals. For example, the practice of “doctor shopping”, in which patients move from one health-care facility to another seeking care, allowed infected patients to come in contact with more people than if they had stayed with one facility. The custom of many friends and family members accompanying or visiting patients in emergency departments or in hospital also exposed more contacts to infection.

5.2 Initial observations

Overall, the pattern of nosocomial infections in the Republic of Korea is similar to nosocomial outbreaks observed in the Middle East (e.g. Saudi Arabia and United Arab Emirates (Annex 3)). Despite the critical role of suboptimal infection prevention and control measures, especially in crowded situations, there are still unanswered questions about the role of other factors and conditions that may make it easier for this virus to spread from person to person. For example, questions remain about changes in viral sequences and structure affecting transmission properties, environmental contamination, suboptimal ventilation or airborne virus transmission and the potential role of asymptomatic/mild cases, particularly in health-care workers, in transmission.

Although definitive conclusions are not yet possible, some initial observations can be made:

- So far, genetic sequences of two viruses from this outbreak in the Republic of Korea (one virus from the Republic of Korea and one virus from the Korean national who travelled to China) appear genetically similar to viruses found in the Middle East. At present, there is no evidence to suggest that the MERS viruses in the Republic of Korea are significantly different genetically from recent viruses in the Middle East.
- This mission team was not able to determine whether environmental contamination or airborne transmission had any role in the spread of this virus. These are complex issues that will require further investigation, including experimental studies. Ongoing consideration of such possibilities is important because the factors affecting transmission remain poorly understood. Nonetheless, this outbreak appears similar to hospital-associated outbreaks that have occurred in the Middle East and does not appear to have new epidemiological features that would suggest a shift in how the virus is transmitted.
- There is no evidence of ongoing community transmission of MERS. All cases, including those among family members, can be linked to probable exposure in a hospital. The issue of community transmission is important to clarify. Because this virus clearly can spread from person to person, it is possible and even likely that examples of person-to-person transmission outside health-care settings might be found. The identification of such sporadic cases would be neither surprising nor particularly important unless it were indicative of ongoing transmission in the community. Sporadic transmission outside health settings, for example, within families, has occurred in other MERS outbreaks in the Middle East without evolving into sustained community spread.
- Transmission of virus in Hospital B (Pyungtaek St Mary's Hospital) and in Hospital D (Samsung Medical Center) resulted in large clusters. The size of these clusters is of concern, but not unprecedented. In 2014, Jeddah and Riyadh, Saudi Arabia, experienced large nosocomial outbreaks ranging from 2 to 180 cases per hospital. In the Republic of Korea, the clusters associated with Pyungtaek St Mary's Hospital (38 cases including one case exported to China) and Samsung Medical Center (approximately 70 cases at the time of the mission) appear to have resulted from many individuals with prolonged exposure to infectious patients in crowded areas and before MERS was suspected. Investigation of all factors related to transmission in such clusters is critical as such studies may improve the understanding of how this virus is spread.

5.3 Risk of spread to other countries

While the spread of MERS from the Republic of Korea to other countries remains possible, extensive efforts using a variety of approaches are being made to identify both symptomatic and asymptomatic individuals who are presumably at elevated risk of incubating MERS infection. Such efforts, including multiple approaches to detect cases and identify contacts, mandatory quarantine of close contacts, and restriction of international travel of all cases and contacts, are impressive and appear to be having an effect since incident cases are declining. The combination of these efforts, which are aimed at identifying symptomatic and asymptomatic infections, is likely to be more effective than screening measures at borders.

6. RECOMMENDATIONS TO THE GOVERNMENT OF THE REPUBLIC OF KOREA

The following high-level recommendations were shared and discussed with the Minister for Health and Welfare and his staff on 13 June:

- 1) Infection prevention and control measures may be immediately strengthened in all health-care facilities in the Republic of Korea.
- 2) All patients presenting with fever or respiratory symptoms may be asked about: contact with a MERS patient; visits to a health-care facility where a MERS patient has been treated; and history of travel to the Middle East 14 days before symptom onset. Any patient with positive responses should be promptly reported to public health authorities and managed as a suspected case while the diagnosis is being confirmed.
- 3) Close contacts of MERS cases should not travel during the period when they are being monitored for the development of symptoms.
- 4) Strong consideration may be given to reopening schools, as schools have not been linked to transmission of MERS in the Republic of Korea or elsewhere.
- 5) Continued implementation of basic public health measures by all health authorities will contribute to stopping further cases. These measures include:
 - a. early and complete identification and investigation of all contacts;
 - b. robust quarantine/isolation and monitoring of all contacts and suspected cases;
 - c. full implementation of infection prevention and control measures; and
 - d. prevention of travel, especially internationally, of infected people and contacts.
- 6) Local governments must be fully engaged and mobilized in this national emergency.
- 7) In parallel with disease prevention and control measures, it is important to strengthen domestic and international confidence. This includes improving risk communications. The Ministry of Health and Welfare may provide regular updates (in Korean and English) on the epidemiological situation, investigations and disease control measures.
- 8) Additional staff (for surge capacity) are urgently required for the response and to provide relief for staff working on the outbreak.
- 9) Selected hospitals may be designated for safe triage and assessment of suspected MERS cases. This will require trained personnel, facility management and communication with the public.
- 10) Comprehensive research studies designed to close critical gaps in knowledge, including sero-epidemiological studies, may be completed and the results widely communicated as quickly as possible.
- 11) The Republic of Korea may ensure that it is able to optimally respond to future outbreaks. This includes strengthening medical facilities to deal with serious infectious diseases (including increased numbers of negative-pressure isolation rooms), considering how to reduce the practice of “doctor shopping”, training more infection prevention and control specialists, infectious disease experts, laboratory scientists, epidemiologists, and risk communication experts, and investing in strengthening public health capacities and leadership, including at the Korea Centers for Disease Control and Prevention (KCDC).

In addition to these high-level recommendations, the joint mission team made technical recommendations, which can be applicable in the Republic of Korea and other countries when combating a MERS outbreak. These are available in Annex 5.

ANNEX 1. MEMBERS OF THE JOINT MISSION

From the Republic of Korea

Dr LEE Jongkoo, Director of JW Lee Centre for Global Medicine, College of Medicine, Seoul National University, former Director of Korea Centers for Disease Control and Prevention (KCDC) (Team Lead)

Dr JEE Youngmee, MERS Response Taskforce, KCDC

Dr PARK Ok, MERS Response Task Force, KCDC

Dr CHEONG Hae-Kwan, Professor in Social and Preventive Medicine, School of Medicine, Sungkyunkwan University

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Dr LEE Moo-Sik, Professor in Preventive Medicine, College of Medicine, Konyang University

Dr OH Hyang Soon, Professor in Nursing, Woosong University

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From the World Health Organization (WHO) and other agencies

Dr FUKUDA Keiji, Assistant Director-General, Health Security and Emergencies, WHO headquarters (Team Lead)

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Ms MCLELLAN Faith, Information Manager, Health Security and Emergencies, WHO headquarters (Rapporteur)

ANNEX 2. LIST OF KEY ACTIONS TAKEN BY THE REPUBLIC OF KOREA TO ADDRESS MERS

Date	Actions
20 May	<p>First imported case of MERS confirmed. MERS alert level was elevated from ATTENTION (BLUE) to CAUTION (YELLOW).</p> <ul style="list-style-type: none"> • MERS Response Unit (led by Chief of Infection Control Centre, KCDC) was expanded to National MERS Response Centre (led by Assistant Minister and Director of KCDC) • Strengthened border quarantine measures against returning travellers from Middle East from self-declaration to thermal screening system
21 May	<p>KCDC convened an expert advisory committee on MERS following the identification of two additional infected cases – (1) spouse of index case (case #2), and (2) a patient (case #3) who admitted at same hospital room when the index case was admitted at hospital B from 15 to 17 May 2015. The committee advised while keeping the alert level at YELLOW to intensify public health measures including isolation of 64 close contacts (family members and healthcare workers) and active monitoring for 14 days after last contact</p>
26 May	<p>KCDC revised the definition of suspected cases by lowering temperature threshold from 38 degree Celsius to 37.5 degree Celsius following the identification of additional infected case – daughter of case #3 (case #4) and two suspected cases among healthcare worker close contacts.</p>
29 May	<p>MOHW urgently convened two meetings – (1) the Expert Committee on Infectious Disease Crisis Management and (2) a meeting with concerned ministries and provincial government. These meeting occurred after the travel incident of a suspected case to China. While keeping the alert level at YELLOW, the response system was further strengthened as follows:</p> <ul style="list-style-type: none"> • To establish the MERS response task force in MOHW under the leadership of Vice-Minister • To conduct contact identification exercise again • To examine the readiness of designated isolation facilities nationwide • To strengthen the monitoring of returning travellers from Middle East
31 May	<p>The Minister of Health and Welfare announced the establishment Government-Civil joint MERS task force co-chaired by Vice-Minister of Health and Welfare, and the President of Korean Society of Infectious Disease.</p>
2 June	<p>Followed by an urgent meeting of concerned Ministers on MERS outbreaks convened by acting Prime Minister, the Minister of Health and Welfare announced further strengthened response system as follows:</p> <ul style="list-style-type: none"> • Elevate MOHW MERS response task force level from Vice-Minister to Minister • Intensify contact tracing and management • Conduct nationwide cross-sectional pneumonia survey • Expand the MERS CoV testing laboratories
5 June	<p>Minister of Health and Welfare announce that MOHW will carry out a joint mission on MERS with WHO.</p>
7 June	<p>The Ministry of Health and Welfare decided to disclose of the name of hospitals that MERS cases had visited before diagnosis.</p>
9 June	<p>The Minister of Health and Welfare designated 256 hospitals as MERS suspected- case triage healthcare facilities.</p>
10 June	<p>The nationwide cross-sectional pneumonia survey was initiated. The joint mission on MERS provided initial recommendations to the Ministry of Health.</p>
13 June	<p>The joint mission on MERS concluded with press conference.</p>

ANNEX 3. GLOBAL SITUATION AND CONTEXT

Global situation

As of 12 June 2015, 1285 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS) had been reported to WHO since 2012, including at least 442 deaths. Overall, 65% of cases (n=838) are male and the median age is 50 years (range 9 months to 99 years).

To date, 25 countries have reported cases, including countries in the Middle East: Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen; in Africa: Algeria, and Tunisia; in Europe: Austria, France, Germany, Greece, Italy, the Netherlands, Turkey and the United Kingdom; in Asia: China, the Republic of Korea, Malaysia and the Philippines; and in North America: the United States of America (USA). The majority of cases (more than 85%) have been reported from Saudi Arabia. Since May 2015 two new countries have been affected (China and the Republic of Korea).

Situation in Saudi Arabia

The first report of MERS described a patient who died from a severe respiratory illness in a hospital in Jeddah, Saudi Arabia, in June 2012.

MERS cases have continued to be reported in countries in or near the Arabian Peninsula, with more than 85% of cases reported from Saudi Arabia. A camel (*Camelus dromedarius*) reservoir is suspected based on case investigations, serologic studies, and the isolation of live infectious MERS from camels. Limited human-to-human transmission has been documented in households and in health-care facilities, but no sustained community transmission has been documented. Although shedding of MERS RNA from the upper respiratory tract of cases with mild symptoms (typically health-care workers) is well documented, the potential role in transmission of mildly ill cases is not well defined.

Outbreaks of MERS continue to be reported in the Arabian Peninsula, highlighting the ongoing risk of transmission of this emerging respiratory virus. Although the risk factors for transmission have not been thoroughly described, limited human-to-human transmission has been documented through contact investigations in households and in health-care facilities. In Jeddah in 2014, secondary transmission (often without clearly defined links) accounted for 97% of assessed cases, including in health-care workers, patients and visitors to health-care facilities.

Multi-facility outbreaks in Al-Hassa and Taif in 2013 and 2014 and, more recently, in Hofuf, Eastern Province, in 2015, highlight the explosive nature and high morbidity and mortality of MERS in health-care settings.

Factors that led to outbreaks in health-care settings in Saudi Arabia included crowding in emergency rooms, inadequate triage and delayed recognition. The Saudi Ministry of Health established a command centre to respond to MERS infection. It oversees infection control, clinical operation, risk communication, laboratory capacity, and interministerial and public health response to MERS. In Saudi Arabia, each health-care facility had to establish a triage system in the emergency room for patients with suspected respiratory infections. The Ministry of Health carried out extensive training throughout the country of health-care personnel on early recognition of suspected MERS patients and the proper use of personal protective equipment. A large number of negative-pressure rooms were added to existing facilities. Although every health-care facility must be ready to manage suspected cases of MERS, certain hospitals were prepared and designated to manage confirmed cases. Experts in infection control were hired, and additional resources are being acquired.

Fortunately, no MERS cases were associated with the 2013 and 2014 Hajj pilgrimages.

ANNEX 4. AGENDA OF THE JOINT MISSION

Date/time	Activities	Note
Day 1 (Tuesday, 9 June 2015)		
09:00	Courtesy visit to Minister of Health and Welfare	Minister's Office
10:00	Technical Briefing to Mission Team <ul style="list-style-type: none"> • Clinical Management • Lab test and virus characteristics 	Joint Mission Office at KCDC
12:00	Lunch break	
14:00	Technical Briefing to Mission Team (continued) <ul style="list-style-type: none"> • Outbreak Investigation • Public response measures 	Joint Mission Office at KCDC
Day 2 (Wednesday, 10 June 2015)		
09:00	Small group discussions	Joint Mission Office at KCDC
10:30	Site visit to health-care facility outbreak cluster	Samsung Medical Centre
12:00	Lunch break	
14:00	Small group discussions	Joint Mission Office at KCDC
17:00	Site visit to Emergency Operation Centre	MOHW
Day 3 (Thursday, 11 June 2015)		
09:00	Small group discussions	Joint Mission Office at KCDC
11:00	Technical Briefing to Mission Team <ul style="list-style-type: none"> • Environmental study at Pyungtaek St Mary's Hospital 	Joint Mission Office at KCDC
12:00	Lunch break	
12:30	Meeting with Foreign Business Community hosted by Acting Prime Minister	Press Centre, Seoul
14:00	Small group discussions	Joint Mission Office at KCDC
14:30	Meeting with the President of the Republic of Korea and local public health workers	Paldal Public Health Centre, Suwon City
17:00	Technical Briefing to Mission Team (continued) <ul style="list-style-type: none"> • Environmental study at Pyungtaek St Mary's Hospital 	Joint Mission Office at KCDC
Day 4 (Friday, 12 June 2015)		
09:00	Small group discussions	Joint Mission Office at KCDC
12:00	Lunch break	
14:00	Small group discussions	Joint Mission Office at KCDC
19:30	Debriefing to the Minister for Health and Welfare	Minister's Office
Day 5 (Saturday, 13 June 2015)		
11:00	Press Conference	MOHW

ANNEX 5. TECHNICAL RECOMMENDATIONS

The following technical recommendations are made to the Republic of Korea and for the consideration of other governments in managing MERS outbreaks.

A1. Response strategy and measures

The main goals of the response should be to stop the outbreak in the country, prevent spread internationally and decrease public anxiety. All actions should be guided by ongoing risk assessments.

- 1) Mobilize and prioritize resources needed to ensure implementation of key control measures, including hospital infection prevention and control, a system for early detection of suspected cases and contact management, patient management and risk communications.
- 2) Expand epidemiological analytic capability and data visualization: create clear daily situation reports of key indicators for decision-makers.
- 3) Capitalize on the opportunity the outbreak creates to generate important knowledge about MERS epidemics by creating a dedicated scientific studies team within the response structure.
- 4) Consider a back-up team comprising people removed from operational responsibilities whose purpose is to consider broad issues, detect unusual patterns, monitor and evaluate response metrics for course correction, and anticipate the need for strategic changes.
- 5) Enhance risk communication skills.
- 6) Continue timely communication and sharing of information with the international community, including control measures.
- 7) Revise the national response plan to include new scenarios for nosocomial and health-care facility outbreaks.
- 8) Consider creating an interim action evaluation and after-action report.
- 9) Prepare for future outbreak responses through increased investment in public health surveillance and response systems, especially a field epidemiology training programme, as required under IHR (2005).

A2. Surveillance

Surveillance should be enhanced to detect new cases who are linked to the hospital outbreaks and, especially, to identify cases that may not be linked to the current chain of transmission. The geographical area targeted will need to be assessed on a case-by-case basis and is defined by the suspected exposures of the case under investigation. The duration of enhanced surveillance will depend on the findings of the case investigations and whether there is evidence to indicate that community transmission may be occurring in the area. A minimum of one month of enhanced surveillance is a reasonable starting point.

- 1) Establish sentinel-based surveillance for severe acute respiratory infections (SARI), irrespective of a history of contact, in provinces where there are laboratory-confirmed cases.²
- 2) It is strongly recommended that the surveillance for pneumonia patients (the severe pneumonia surveillance in four geographic regions and the cross-sectional survey for clinical pneumonia in hospitalized patients described above) include MERS testing for all hospitalized pneumonia cases, regardless of an epidemiologic link to a confirmed case or hospital where cases have been treated.
- 3) All returning travellers from the Middle East, who have had direct or indirect contact with dromedary camels (e.g. visiting a market or racetrack) or have visited a health-care facility and

² WHO. Global Epidemiological Surveillance Standards for Influenza, January 2014
http://www.who.int/influenza/resources/documents/influenza_surveillance_manual/en/

who develop respiratory or gastrointestinal symptoms within 14 days of return should immediately notify their health-care provider.

- 4) To evaluate the extent of infection among close contacts, sero-epidemiology studies may be implemented in cohorts of close contacts (health-care workers, patients) to define risk factors for infection. This may be particularly relevant for the three major case clusters observed so far. WHO has developed sero-epidemiologic investigation protocols for close contacts³, and separately for health-care workers, which could be used in the outbreak⁴.
- 5) As detailed information is being collected from confirmed cases and their contacts, infection rates by exposure type can be stratified (i.e. higher risk activities vs. lower risk activities).

A3. Contact tracing

Contact tracing is a critical part of disease control. The intensified activities of the Government to identify all contacts, rapid and enforced home quarantine among close contacts, follow up for 14 days after the date of exposure, and immediate isolation and testing of contacts with symptoms will have a positive impact on the outbreak. Contact management requires mutual support between the government and the public, especially to ensure that home quarantine does not become an amplifier of infection. Early isolation of suspected MERS cases in emergency departments and hospitals will minimize the likelihood of exposure to other people.

- 1) The number of hospitals individuals should visit if they suspect they have MERS should be reduced. Messages to the public can assist that worried individuals are directed to a smaller number of hospitals, which are prepared to quickly isolate suspect cases while testing is underway.
- 2) The restriction of movement of contacts and the monitoring of contacts for 14 days since their last exposure are essential.
- 3) Close contacts of MERS cases should not travel, especially internationally, when they are being monitored for the development of symptoms.
- 4) At this time, the use of two categories of contacts (close and casual) seems appropriate and cautious. As the epidemic progresses and our understanding improves of increases in infection rates among contacts, the Government may want to consider a third category to try to capture high-, medium-, and low-risk contacts.

A4. Laboratory

- 1) As PCR testing for MERS is now decentralized to provincial, private and hospital laboratories, the testing algorithms and methods may be harmonized. A system for quality assurance and quality control should be implemented to ensure sensitivity and specificity of the laboratory diagnostic system. Aliquots of positive specimens should be submitted to the national laboratory for further investigations (e.g. genetic analysis) where appropriate.
- 2) Explore ways to decrease turnaround times for laboratory diagnostic testing and reporting, to minimize delays in specimen transport and the reporting of results back to clinicians.
- 3) Currently, the primary specimen being used for laboratory diagnosis is sputum. Lower respiratory specimens (e.g. sputum, endotracheal aspirate) can give a higher diagnostic yield than upper respiratory specimens (e.g. nasopharyngeal swab, broncho-alveolar lavage), when considered overall. However, the mucus content of sputa can sometimes pose a challenge for efficient nucleic acid extraction and may contain PCR inhibitors, sometimes leading to false-negative results. Thus, it is recommended that, wherever possible, nasopharyngeal swabs be used in parallel with sputum,

³ WHO. Seroepidemiological Investigation of Contacts of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Patients, 19 November 2013

http://www.who.int/csr/disease/coronavirus_infections/WHO_Contact_Protocol_MERSCoV_19_November_2013.pdf

⁴ WHO. Assessment of potential risk factors of infection of Middle East respiratory syndrome coronavirus (MERS-CoV) among health care personnel in a health care setting Version 1, 27 January 2014

http://www.who.int/csr/disease/coronavirus_infections/Healthcare_MERS_Seroepi_Investigation_27Jan2014.pdf

especially in highly suspected cases and when retesting is done for patients who yield equivocal results on initial testing. Also, repeat testing is advisable before a diagnosis of MERS in highly suspected patients is ruled out.

- 4) Serial sampling for viral load assays should be attempted on selected patients to assess periods of peak infectivity and the impact of commencement of antiviral therapy.
- 5) PCR testing of non-respiratory specimens (faeces, plasma, urine) from representative patients should be carried out to define dissemination of the virus beyond the respiratory tract. Virus isolation should be attempted on any PCR-positive specimens. This would help to assess potential nosocomial risks from body fluids other than respiratory specimens.
- 6) Viral genetic sequencing should be carried out from the direct clinical specimen rather than viral isolates wherever possible from representatives of time and place, for enhancing epidemiological understanding and for genetic characterization to provide monitoring for potential biological changes in circulating viruses.
- 7) Viral isolates should be obtained from representative patient samples for biological characterization for comparison with reference strains. Such biological characterization may involve, but not be limited to, viral replication kinetics in primary human respiratory epithelial cells, differentiated human respiratory epithelial cultures, or in vivo cultures of the human respiratory tract.
- 8) Antibody titres on serial serum samples from selected patients should be carried out to define the antibody kinetics of MERS infections.
- 9) Testing of environmental samples for virus RNA should be considered to assess potential transmission routes. These may include swabs of surfaces in patient-care settings and air sampling. Wherever relevant, virus culture should be attempted from virus RNA-positive samples to differentiate live virus from inactive viral RNA.
- 10) Close and regular networking between laboratory and epidemiology colleagues may be encouraged to facilitate efficient collaboration.
- 11) Obtaining host innate immune response data (e.g. plasma cytokine, chemokine levels) over the course of the disease may help to better understand pathogenesis.
- 12) Handling unexpected epidemics of respiratory viruses requires laboratories to maintain surge capacity. Appropriate resource allocations may be made for staff, equipment, and consumables so that capacity is built and maintained in “peace time”, as it is impossible to ramp up such capacity in times of crisis.
- 13) Participation in the WHO laboratory network is encouraged to share information and novel findings that are relevant to public health and clinical care. These might include sharing of viral genetic sequences, novel virological findings, virological specimens or virus isolates. In particular, collecting sera from confirmed infected patients to contribute to the WHO serum biobank would allow different serological tests to be evaluated and validated in a collaborative manner.

A5. Clinical management

Good clinical management can result in decreased morbidity and mortality.

- 1) Cases of unexplained pneumonia should be managed with a high suspicion for MERS. Early implementation of infection control measures and MERS testing are essential to prevent outbreaks.
- 2) Although there is no specific treatment for MERS, experimental protocols may be used in a standardized and closely monitored way.
- 3) Understanding the kinetics of MERS will guide initiation of anti-viral agents. Serial sampling of upper and lower respiratory tract specimens (where appropriate) should be done.
- 4) Based on experience with the severe acute respiratory syndrome (SARS) and pandemic influenza, convalescent plasma from patients who have recovered from MERS is likely to be an effective treatment option.

A6. Infection prevention and control

Early recognition of transmissible infections is the cornerstone of the prevention of healthcare-associated outbreaks. Emergency departments and respiratory clinics need to effectively triage patients with potential respiratory infections, especially those with epidemiological links (travel history, contact with MERS cases). Infection prevention and control measures may immediately be strengthened in all facilities across the country.

- 1) The 19 currently designated referral hospitals for MERS patients may be assessed for infection prevention and control practices, and the availability of personal protective equipment and single-bed rooms.
- 2) Patients with suspected or confirmed MERS may require transfer to other facilities. Therefore, a clear protocol to address infection control and risk communication issues is needed.
- 3) Effective communication between health-care facilities regarding the movement of patients with potentially infectious diseases may prevent further spread of MERS. The public health authority may trace individuals on the contact list and alert health-care facilities caring for these individuals. Health-care facilities must inform public health authorities when these patients are being transferred or discharged.
- 4) Adequate human resources are needed to run effective infection control activities. Significant shortages of infection control professionals were noted in one hospital and are likely to be an issue in others.
- 5) Transmission of MERS takes place mainly through droplet and contact routes. Therefore, adequate space between patients (at least one meter) in waiting rooms and clinical areas, especially in emergency rooms and intensive care units, is essential.
- 6) MERS may be aerosolized during certain respiratory procedures. Because jet nebulizers are used in some countries for patients with asthma or chronic obstructive pulmonary disease, and some of these patients may also be infected with MERS, procedures such as nebulization and intubation should be performed in negative-pressure rooms as part of infection prevention and control measures. Where negative-pressure isolation rooms are not available, consider alternative methods to improve ventilation, such as installation of window exhaust fans or portable HEPA filters. The role of jet nebulizers and other respiratory procedures that may generate aerosols (e.g. intubation, sputum suction, bronchoscopy, non-invasive ventilation, tracheostomy) in enhancing disease transmission should be examined in major hospital outbreaks of MERS.
- 7) Knowledge and practice of proper infection control practices requires regular training, auditing and accountability. Training on respiratory protection should be offered now to all health-care workers.
- 8) To ensure maximum protection of health-care workers from aerosolized MERS, high-efficiency respirator fit testing should be performed, especially for those working in critical areas (emergency rooms, intensive care units, respiratory clinics).
- 9) Environmental factors may play a role in transmitting MERS. As part of outbreak investigation, environmental sampling (by real-time reverse polymerase chain reaction (RT-PCR) testing and viral cultures) should be performed and additional environmental decontamination techniques considered for high-risk areas.
- 10) For health-care workers exposed to MERS:
 - a. Examine in depth the events that led to the secondary transmission (time, place and person).
 - b. Establish a screening clinic where temperature and symptoms are evaluated daily during the incubation period.
 - c. Screen health-care workers with high-risk exposures, regardless of the development of symptoms (as described above), to detect asymptomatic carriers (with PCR testing of nasopharyngeal specimens).
 - d. Consider conducting a sero-prevalence study among health-care workers to detect unrecognized or asymptomatic infections.

- e. Develop a guideline to determine when health-care workers can return to their clinical duties.
- 11) To be ready to deal with MERS and other emerging infections, health-care facilities should:
- a. Increase the availability of negative-pressure isolation rooms in emergency rooms, intensive care units and wards.
 - b. Increase the ratio of trained infection control practitioners to hospital beds to meet international standards.
 - c. Restrict visits by family members and friends to patients with suspected or confirmed infectious diseases.
 - d. Enhance contact tracing among health-care workers and patients exposed to MERS and stratify the risk of their exposure.
 - e. Apply infection control principles in radiology and other ancillary medical departments.
 - f. Consider additional environmental decontamination techniques in high-risk areas.

A7. Data management and information sharing

Several databases are being used in this outbreak, i.e. for contact tracing, laboratory testing and case report forms. Each database is critical for individual parts of the investigation. However, linking these databases, for example, by national identification number, would give greater power to the analyses. The command and control centre may coordinate these efforts to enable more rigorous analysis and interpretation.

- 1) The following metrics may be calculated daily for internal assessment of the outbreak and a selection may be reported publicly on the government's website:
 - a. Overall incidence;
 - b. Cases by date of symptom onset and by hospital;
 - c. Number of laboratory-confirmed cases identified from contact lists and specified as "close" or "casual" (i.e. high or low risk);
 - d. Time elapsed between symptom onset and isolation;
 - e. Time elapsed between symptom onset and diagnosis;
 - f. Daily suspected cases under investigation/isolation;
 - g. Number of contacts who are either noncompliant or lost to follow up; and
 - h. Alteration in delivery of health-care services, e.g. postponement of surgical procedures.
- 2) Continue to share viruses and sequence data.
- 3) Encourage continued sharing of information about cases and response measures.
- 4) Participate in global alert, surveillance, clinical and laboratory networks with countries and researchers experienced with MERS to share experiences.

A8. Communications

- 1) Target communications more effectively at community level: identify and use chief influencers (e.g. teachers, religious leaders, mothers' groups).
- 2) Use evidence to develop messaging, such as web and Twitter analytics, impact assessment and sentiment analysis to develop, refine and alter messaging.
- 3) Ensure messaging alignment: engage those likely to be speaking regularly and agree on and provide uniform messaging.
- 4) Use trusted messengers: technical experts and respected community members are more likely to be trusted than political figures.