Middle East respiratory syndrome coronavirus
Joint Kingdom of Saudi Arabia/WHO mission

Riyadh, 4-9 June 2013

I. Executive summary

Since April 2012 cases and outbreaks of a respiratory disease syndrome have been reported in people who live in or travelled from countries in the Middle East. The fatality rate has been high, at about 60%. The cause has been identified as a coronavirus, subsequently named Middle East respiratory syndrome coronavirus (MERS-CoV).

In May 2013 the Kingdom of Saudi Arabia (KSA) requested WHO to organize a joint mission to improve understanding of the MERS-CoV situation in KSA and to provide guidance.

a. Joint mission

International experts were invited by WHO to join an international team, which visited Riyadh 4-9 June 2013. The joint Saudi/WHO team comprised officials from the Ministry of Health (MoH) of the Kingdom of Saudi Arabia and experts from the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and public health institutions and hospitals in Canada, China (Hong Kong), France, Singapore, the United Kingdom of Great Britain and Northern Ireland (UK), the United States of America (USA), and the WHO country office in Saudi Arabia, the WHO Eastern Mediterranean Regional Office and WHO staff from headquarters.

The aim of the mission was assess the MERS-CoV situation in KSA and provide recommendations for prevention, control and further research.

The joint team met in small groups focused on specific areas and in plenary. Specific areas of discussion included epidemiology of outbreaks in the community and healthcare facilities; infection control and prevention of transmission; clinical features; laboratory issues; and the animal, human and environmental interface and food safety.

b. Responses of the Kingdom of Saudi Arabia

After the report of the first case in September 2012, the MoH responded by setting a case definition and circulating it to all healthcare workers, and introducing active surveillance and notification requirements. It invited experts from WHO, the US Centers for Disease Control and Prevention, and academic and nongovernmental organizations to assist. Samples from patients are being tested outside the country and isolated viruses are being sequenced.

In response to an outbreak in a healthcare facility, the health ministry sent an emergency team, followed the procedures required by the International Health Regulations (2005), and activated the national Infectious Diseases Committee.

Many interventions were put in place, including stringent infection control measures, restrictions on admissions to the hospital concerned, information and education of healthcare workers and vigorous disinfection and cleaning.

c. Epidemiology

By 6 June 2012, 55 laboratory-confirmed cases, including 31 deaths, had been reported from France, Germany, Italy, Jordan, Qatar, Saudi Arabia, Tunisia, United Arab Emirates (UAE) and the United Kingdom of Great Britain and Northern Ireland (UK). In Saudi Arabia, 40 cases and 25 deaths had been reported. All 55 cases were either residents of Jordan, Qatar, Saudi Arabia, or UAE or had a history of travel or direct contact with travellers to these countries.

At the time of this mission, most cases had been in older men and in people with underlying conditions. Sporadic cases and small family clusters of cases have been reported in different parts of KSA, but outbreaks have also occurred in healthcare facilities where person-to-person transmission was established. Both types of clusters and outbreaks were investigated closely by KSA. Application of intensive infection-control measures was successful in minimizing the transmission of MERS-CoV to healthcare workers. The continuing occurrence of cases indicates that there is ongoing transmission but that surveillance is effective in detecting new cases.

To date, there is no evidence indicating transmission of MERS-CoV from asymptomatic infected individuals or ongoing, low-prevalence, mildly symptomatic illness in the community. Nevertheless, close ongoing surveillance is critical.

The joint team identified several key questions and gaps in knowledge. Issues of particular importance are the epidemiology of the infection, including geographic scope of infections, the ways in which people are becoming infected, the potential for person-to-person transmission of MERS-CoV, and the spectrum of severity of MERS-CoV infection.

d. Clinical features

The clinical features of MERS-CoV disease bear some resemblance to those seen in the severe acute respiratory syndrome (SARS). In MERS-CoV disease, fever, cough and dyspnoea are the major presenting symptoms of patients admitted to hospital. Other common presenting symptoms include chills, rigor, headache, myalgia and malaise. Respiratory failure is the major complication. Mild disease and atypical presentation with diarrhoea have also been reported. More than half the cases in KSA have had underlying conditions. More than half the patients with confirmed disease have died.

There is no vaccine and no specific antiviral agents have been found to be effective. Supportive therapy is indicated for management.

e. Laboratory issues

Gene sequencing of a small number of MERS-CoV genomes shows that it is most closely related to a virus found in bats. However, no MERS-CoV has been isolated from bats and no epidemiological studies have established a connection between cases and exposure to bats. Diagnostic tests for viral RNA have been established, with gene targets for polymerase chain reaction testing (PCR) identified and proven to be valid. Serological tests have been developed but their sensitivity and specificity have not been characterized as extensively as for PCR. Sera are being collected and stored for future testing.

Important questions remain about the best types of samples to use for diagnostic testing, as well as methodological details of PCR testing and serological tests. More needs to be known about viral kinetics, shedding and the timing of sampling.

f. Human-animal interface

The virus has not been isolated from any animal and there is at present no indication that infection with MERS-CoV causes disease in animals. The case reporting form currently used to collect data on human cases does not capture sufficient information to allow thorough investigation of potential sources of exposure to MERS-CoV, and the low number of human cases has limited the data upon which to build a strong hypothesis for the potential source of exposure.

The source of exposure for sporadic cases occurring in the community has not been identified in any of the countries affected, and little is known about the environmental or occupational risk factors for infection with MERS-CoV. Outstanding questions include the source of exposure acquired outside healthcare facilities, and the animal reservoir of the virus.

g. Recommendations

The joint team proposed a series of high-level recommendations, with supporting expanded detailed recommendations for action.

Recommendations for epidemiological investigations included detailed study of all confirmed cases with a common protocol and international coordination, case-control studies, and serological testing of patients as well as seroepidemiological surveys. International networks of intensive care specialists should conduct diagnostic (PCR) and serological testing of patients with severe respiratory illness. Countries should implement MERS-CoV surveillance at a level depending on the presence of cases of MERS-CoV infection in their country and on their risk assessment.

For healthcare facilities, recommendations include: adhere to current WHO guidelines for infection prevention and control; enhance case finding, with collaboration between health authorities and hospital staff; health authorities and facilities should wait at least 28 days after the last potential healthcare exposure before declaring an outbreak over.

Clinical recommendations include: clinicians dealing with patients with MERS-CoV infections should participate in the WHO Clinical Network and related teleconferences; collect clinical data with an agreed instrument (of which there are two examples); take serial samples from upper and/or lower tract airways in affected patients; avoid use of corticosteroids for managing illness.

Investigations of human cases need to elicit sufficient information to help identify potential sources of exposure to MERS-CoV. Investigation of cases requires cooperation across ministries and sectors. Careful planning is needed for further surveillance and investigation of potential animal reservoirs.

There are no restrictions placed on travellers to or from countries in the Middle East, although people who develop a fever and persistent cough after such travel should consult a doctor.

II. Introduction

In the middle of 2012, a case of fatal respiratory disease in a previously healthy 60-year-old man was reported from the Kingdom of Saudi Arabia (KSA). The cause was subsequently identified as a new coronavirus that has been named Middle East respiratory syndrome coronavirus (MERS-CoV).[1] Retrospective investigations then revealed that the first cases of the disease had occurred previously in a cluster of hospital-associated cases in Jordan in April 2012.

Since then, additional cases of MERS-CoV infection have been documented in both Jordan and KSA and some other countries in the Middle East (Qatar, United Arab Emirates). Travel-associated cases have been identified in both Europe (France, Germany, Italy and United Kingdom) and North Africa (Tunisia). In some of these travel-related cases there has been secondary transmission. The continuing detection of MERS-CoV cases, the likelihood of further cases and the potential for international spread of this infection have raised global concerns.

In response, KSA urgently initiated several control measure and investigations, including multiple collaborations with multiple international partners (see section V). In May 2013, the KSA MoH requested WHO to organize a joint mission to improve understanding of the MERS-CoV situation and to provide guidance.

III. Terms of reference of the Joint Mission

The aims of the joint mission were

- to identify key questions and information needed for formulation of recommendations and strategies for prevention and control;
- to identify what information is known and to determine gaps in our knowledge;
- to provide guidance, including future actions and areas for further research;
- to issue its report publicly as soon as possible after the conclusion of its work.

IV. Method of work

The joint team comprised officials from the MoH of the Kingdom of Saudi Arabia as well as experts from the Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (OIE) and public health institutions and hospitals in Canada, China (Hong Kong), France, Singapore, the United Kingdom of Great Britain and Northern Ireland (UK), the United States of America (USA), and the WHO country office in Saudi Arabia, the WHO Eastern Mediterranean Regional Office and WHO staff from headquarters (see Annex 1 for list of participants).

Before the international members of the joint team arrived, WHO submitted a list of preliminary questions to the KSA MoH for consideration and as a basis for discussion (Annex 2). The questions were refined in the course of the mission and the MoH provided answers to all questions that were asked. The topics covered areas such as clinical features and course of disease, transmissibility, epidemiology, including exposure and possible sources of infection, results of testing, and virology.

The joint team was based in Riyadh. Saudi and international team members were divided into groups based on their expertise and experience. Each team focused selectively on the following areas: epidemiology of outbreaks in the community and healthcare facilities; infection control and prevention of transmission; clinical aspects; laboratory issues; and the animal, human and environmental interface and food safety.

Broader discussions were then held in daily plenary sessions. For the discussions, additional information and insights were provided by experts in the host country from public health institutions, including the Saudi Food and Drug Administration, hospital clinicians, veterinarians from the Ministry of Agriculture, and specialists from the Saudi Wildlife Authority. Further input was provided in a teleconference held during the mission with experts from other countries. The content of the report is based on the information provided from all these sources but especially the small group discussions and the MoH.

V. Responses of the Kingdom of Saudi Arabia

a. Interventions applied by the Ministry of Health

After the first case of infection with human MERS-CoV infection was reported at the end of September 2012, a case definition of MERS was devised and circulated to all healthcare workers across KSA. Active surveillance was introduced, and all patients admitted to hospitals with bilateral pneumonia were screened for MERS-CoV infection. The MoH issued a requirement that all cases of MERS-CoV infection must be immediately notified to it. All cases were reported to WHO within 24 hours and information placed by KSA authorities on ProMED.

After the first case was reported officially, experts were invited from the WHO Eastern Mediterranean Regional Office and headquarters, the Centers for Disease Control and Prevention, Atlanta, Georgia, USA, EcoHealth Alliance and Columbia University, New York, USA. In April 2013, experts from EcoHealth Alliance and Columbia University were again invited, and visited KSA to collect more animal samples.

b. Response to the cluster of cases in Al-Ahsa

Health Directorate for Public Health visited the hospital in Al-Ahsa where cases had been reported and analysed the information available. Monthly mortality rates were found not to differ significantly from those in previous months. Causes of death shifted with time from chronic co-morbidities to pneumonia and respiratory failure. No significant influenza activity was reported. As a consequence, people began to consider the possibility that MERS-CoV might be involved.

The MoH sent an emergency team to the region. The Regional Director for the Eastern Mediterranean Region was notified by telephone by the National IHR Focal Point immediately after the first case was confirmed by laboratory testing on 24 April 2013. At the same time, an urgent call was made to the national Infectious Diseases Committee.

The following interventions were put in place.

- Infection control interventions were applied in full force at the healthcare facilities concerned.
- The affected hospital was closed to new admissions.

- Patients in affected areas of the hospital were separated and isolated.
- Information (including interim infection-control guidelines, definitions, sample collection methods, and healthcare worker contact tracing) was disseminated.
- Droplet and contact precautions were reinforced.
- Airborne precautions were mandated for aerosol-generating procedures.
- The nurse/patient ratio was increased in affected hospitals.
- Environmental cleaning was enhanced and area-disinfection techniques (vaporised hydrogen peroxide) applied.

c. Pending laboratory work and collaboration

Samples from contacts of infected patients are being tested serologically in the USA. The genome sequences of four MERS-CoV were subsequently posted in the GenBank database.

Further details of the country's responses are given in Annex 3.

VI. Situation assessment

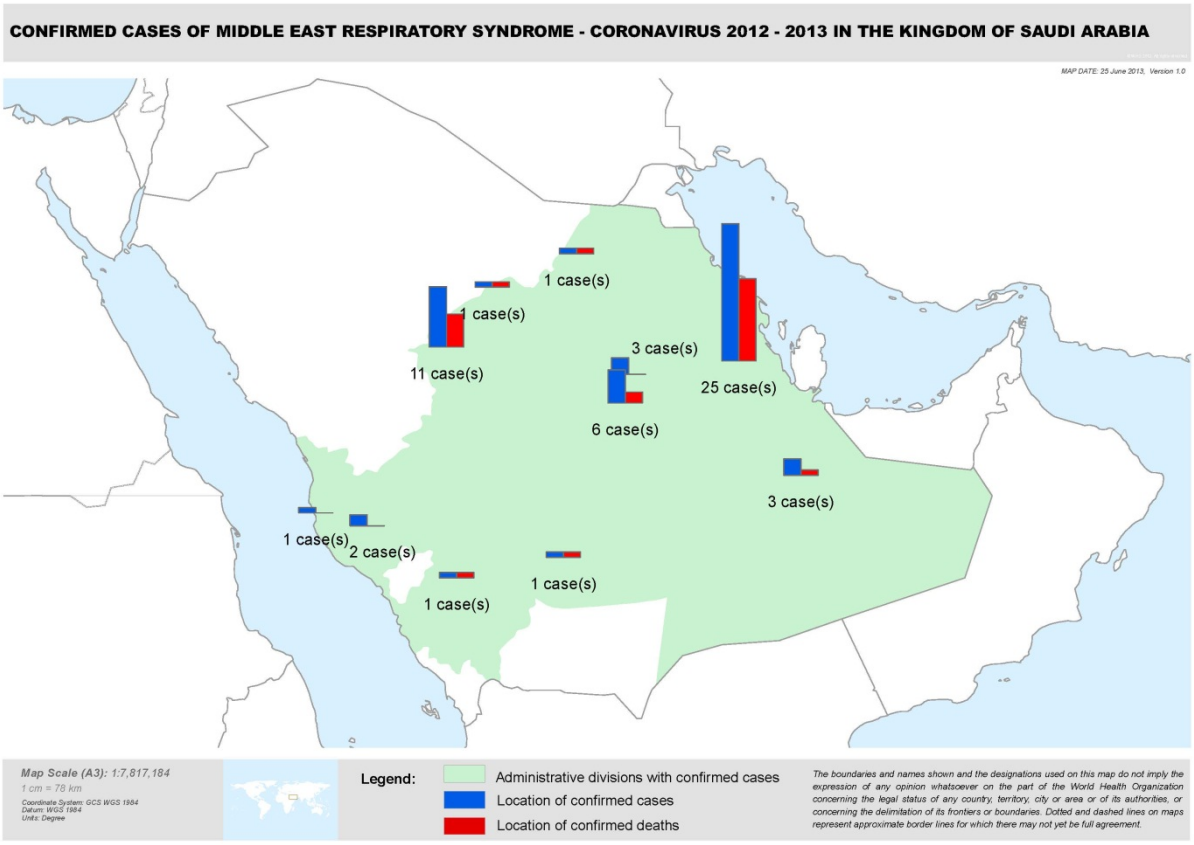
a. Epidemiology and infection control

Findings

The first known outbreak of MERS-CoV infections occurred in April 2012 at a public hospital in Zarqa, Jordan. As of 6 June 2013, there have been 55 laboratory-confirmed cases with 31 deaths reported from France, Germany, Italy, Jordan, Qatar, Saudi Arabia, Tunisia, United Arab Emirates (UAE) and the United Kingdom of Great Britain and Northern Ireland (UK). All cases have either been in residents of Jordan, Qatar, Saudi Arabia, and UAE or have a history of travel or direct contact with travellers to these countries.

The first case of MERS-CoV infection in KSA occurred in June 2012. As of 3 June 2013, a total of 1939 specimens from suspected cases and contacts have been processed by the MoH. As of 6 June 2013, laboratory test results have confirmed 40 cases of MERS-CoV infection (Figure). Evaluation of the case information reveals the following: a mean age of 58 years (range 14–94 years), 30 (75%) are male, 55% have at least two underlying conditions, and most (67%) have occurred in the Al-Ahsa region of the Eastern Province (Figure). Of the 40 patients, 25 (63%) have died. The experience with MERS-CoV in KSA can be characterized into two investigative periods: before and after recognition of person-to-person transmission in healthcare facilities in April 2013.

Figure: MERS-CoV cases in KSA, June 2012-June 2013.



In the first investigative period, nine cases occurred in residents of central and western Saudi Arabia (Bisha, Al-Qassim and Riyadh).[2] In general, these cases were predominantly male (89%), occurred sporadically, and included two small family clusters in Riyadh. In the first family cluster, the index case resided in an extended household of 28 males and females, including nine children.4 Secondary cases occurred among two sons who had prolonged contact while providing care to the index patient during his hospitalization; a grandson also became infected. No other MERS-CoV case or respiratory illness among family members was reported; results of serological tests on cases and contacts are pending. The household attack rate for this cluster is 11%; however, it is not clear whether transmission of infection from the index case to the two sons occurred in the home or during his stay in hospital. The second cluster involved two brothers; no other cases among eight contacts were identified and serological testing is pending. [3] The attack rate for this cluster is 13%. During the first investigative period, no illness among healthcare workers was identified, and no significant animal exposures were reported. Collection of specimens from animals was performed; results are pending.

In the second investigative period, almost all cases (30 of 31) occurred in the Eastern Province. Most cases appear to be associated with transmission in healthcare facilities, including three cases among family contacts and two cases among healthcare workers.[4] Transmission occurred in medical wards, intensive care units, and specialized care units of a community hospital. Patient transfers and re-admissions resulted in cases and transmission in both a nearby healthcare facility and a more distant referral centre.

In this outbreak the median incubation period was estimated to be 5.2 days, with 95% of patients estimated to have symptom onset within 12.4 days. The estimated serial interval was 7.6 days. Measures to prevent and control transmission in the first hospital included: staff education, increased auditing of hand hygiene, implementing droplet and contact precautions for all febrile patients, testing patients with fever for MERS-CoV, masking all dialysis patients and increasing the number of dialysis shifts in order to increase the space between patients, dialysing case and symptomatic contacts in separate rooms, enhancing environmental cleaning, excluding visitors and non-essential staff, and closure of some wards. The most recent case acquired at this hospital had onset on 8 May 2013. Although two incubation periods (28 days) have passed since the most recent case, there is an unavoidable gap between case onset, identification and laboratory confirmation and intensive surveillance continues.

The current state of the outbreak in the other healthcare facilities is not clear, in particular with regard to the timing of recently announced cases. The continuing occurrence of cases raises the concern that prolonged application of intensive infection-control measures will be required in order to ensure that there is not an ongoing threat.

In a family cluster in the UK, among 20 household and 13 non-household close contacts there were two cases of confirmed MERS-CoV infection (one with severe illness and the other with mild illness). Accordingly, the attack rate was 6%. It is noteworthy that in this cluster there was no case of MERS-CoV infection among 59 healthcare workers who had not been wearing full personal protective equipment while they had been in contact with the index case.

Data are not available in the East Mediterranean Region to assess any changes in the incidence of hospitalizations or mortality due to pneumonia. However, surveillance for severe acute respiratory illness is ongoing across Saudi Arabia.

Overall, there is as yet an absence of evidence throughout the East Mediterranean Region to support the possibility of ongoing, low-level transmission of virus resulting in mild illness in the community. From available information, the secondary attack rate for MERS-CoV appears to be lower than that of the SARS coronavirus; however, data are limited.

Key questions and gaps in our knowledge

Several key questions remain about the fundamental epidemiology of MERS-CoV. These include understanding where this new virus originated, how index cases are getting infected, and whether there is continuing unrecognized transmission in the community.

Specifically:

a. What is the epidemiology of the infection and how are people getting infected?
   - What does the age and gender distribution of cases tell us?
   - What are the characteristics of index cases globally and what, if any, are the common exposures for MERS-CoV infection?
   - Is there a seasonality to infections?
   - What are the household, community, and hospital attack rates?
   - Is there evidence of prior or ongoing transmission in the community?
   - What is the likely exposure source for sporadic cases?

b. What is the potential for person-to-person transmission of MERS-CoV?
   - What is the incubation period for household/community and healthcare-associated cases?
   - Are there super-spreaders?
   - How long do individuals shed the virus and from which sites?

c. What is the spectrum of severity of MERS-CoV infection?
   - What is the best specimen for identification of cases?
   - What proportion of cases are severe, mild, or asymptomatic?

Recommendations for healthcare facilities

Health authorities and facilities should adhere to current WHO guidelines for infection prevention and control during care of probable or confirmed cases of MERS-CoV infections (available at: www.who.int/csr/disease/coronavirus_infections/IPCnCoVguidance_06May13.pdf).

Additional recommendations for the prevention and control of MERS-CoV infection in healthcare settings are provided at: www.who.int/csr/disease/coronavirus_infections/IPCnCoVguidance_06May13.pdf

Important features of control measures include:

a. Healthcare facilities should ensure strict adherence to standard infection control precautions, including hand hygiene, use of appropriate personal protective equipment, and environmental cleaning.

b. Health authorities and hospital staff must collaborate to effectively implement enhanced case finding and to ensure early isolation of suspected cases. MERS-CoV-infected patients should be managed with droplet and contact precautions. Airborne, droplet and contact precautions are recommended during aerosol-generating procedures.

c. Health authorities and facilities should not declare an outbreak over without a minimum of 28 days (two incubation periods) of continued active case finding after the last potential healthcare exposure.

d. Health authorities and facilities should have system-wide communication and case-finding strategies in place in order to mitigate the risk that patients and visitors exposed in one hospital may not be promptly recognized as infected with MERS-CoV if they attend other healthcare providers.

The following recommendations for epidemiological investigations were made (see Annex 4 for expanded recommendations):

a. There should be an in-depth case investigation on all confirmed MERS-CoV cases, including use of a common international protocol when possible. Case-control investigations should be performed to identify potential exposures. These should be based on standardized international case-control instruments when possible.

b. Serological testing should be conducted among cases and contacts to further characterize the attack rate of infection, and seroprevalence surveys from blood banks or similar sources should be conducted to characterize the extent of infection in the community.

c. International networks of intensive care specialists should conduct diagnostic (polymerase chain reaction [PCR]) and serological testing of patients with severe respiratory illness (without association with travel to or from the Middle East) to characterize the clinical spectrum and geographical distribution of MERS-CoV, using internationally agreed protocols.

d. Countries should implement MERS-CoV surveillance at a level that depends on the presence of cases of MERS-CoV infection in their country and on their risk assessment.

b. Clinical aspects

Key questions and gaps in our knowledge

The key questions can be grouped into the following general topic areas:

1. Transmission and risk factors
2. Natural history of infection and clinical course
3. Validation of serological tests
4. Management and treatment
5. Prevention and control

Questions within these areas include the following.

Transmission: What are the modes of infection? What is the incubation period? Are there any risk factors?

Natural history of infection and clinical course: What are the underlying medical conditions of the cases? What are the initial signs and symptoms? What is the natural history of infection? Are there age differences? What are the rates of co-infection and the co-infecting organisms?

How many cases are mild and what clinical syndrome or disease spectrum did they manifest? What efforts are underway to identify milder cases of infection? What have been the complications (e.g. renal failure, disseminated intravascular coagulation, multi-organ system failure) and how frequently do they occur? What are the predictors of severity?

Management and treatment: What proportion of infected patients require intensive care, invasive or non-invasive ventilation, extracorporeal membrane oxygenation, and like measures? What specific treatment was used (e.g. steroids, ribavirin or intravenous immunoglobulin) and how effective was it? Is there any therapeutic role for convalescent plasma and other immunomodulating agents? Which antiviral agents might be useful in treatment? Are there any data on the viral load kinetics?

Findings

Based on published reports describing outbreaks affecting small numbers of patients (up to four) and clinical experience of managing patients with illness due to MERS-CoV, it is evident that the clinical features of MERS-CoV disease bear some resemblance to those seen in the severe acute respiratory syndrome (SARS), which was caused by the SARS

coronavirus (SARS-CoV). In MERS-CoV disease, fever, cough and dyspnoea are the major symptoms of patients admitted to hospital. Other common presenting symptoms include chills, rigor, headache, myalgia and malaise. Respiratory failure is the major complication. Mild disease and atypical presentation with diarrhoea have been reported in both conditions.[5] Common laboratory features observed on admission to hospital include infiltrates on chest radiographs and lymphopenia, whereas thrombocytopenia, elevated lactate dehydrogenase, alanine aminotransferase and creatine kinase levels have been noted in some cases.4 The clinical and epidemiological features of SARS-CoV and MERS-CoV are compared in Annex 5.

A high proportion of patients among the 39 confirmed cases of MERS in Saudi Arabia have been reported to have co-morbidities. The predisposing factors for infection and the predictive factors for poor outcome remain unknown and need further investigation.

Systemic corticosteroids have been used in the treatment of severe cases of MERS-CoV disease, but with no clear survival benefit4 and the potential for serious side effects. In vitro data have shown that interferon with or without ribavirin,[6] and cyclosporin[7] can inhibit MERS-CoV, but treatment late in the course of disease with interferon for 36 h in a 39-year-old man with MERS-CoV disease in the UK was unsuccessful (personal communication; WHO teleconference).

The lessons learnt from experience of SARS and of MERS so far as set out in Annex 6.

Guidance and recommendations

No specific antiviral therapy currently exists. Avoid the use of high-dose systemic corticosteroids.

In view of uncertainty of the availability of any effective antiviral therapy and the increasing number of confirmed human cases, consider establishment of a MERS-CoV convalescent plasma centre in Saudi Arabia. WHO can help link the national focal point with technical agencies.

Collect clinical data using an instrument similar to the case reporting form of the International Severe Acute Respiratory and Emerging Infections Consortium[8] in order to better understand the clinical features, clinical course, complications, risk factors that may predict poor outcome, and treatment response.

While information about viral shedding is insufficient, undertake serial sampling from upper and/or lower airways for real-time reverse transcriptase PCR (RT-PCR) and viral isolation in order to improve our understanding of the viral kinetics, clinical course and response to treatment.

Recommend that clinicians dealing with MERS-CoV infections join the WHO Clinical Network and participate in teleconferences related to clinical management of MERS-CoV.

Revise WHO guidance as needed.

A series of recommended research priorities is listed in Annex 4.

c. Laboratory issues

Findings

Analyses of the genome size, organization and sequence of MERS-CoV indicate that it is most closely related to bat coronaviruses,[9] but that the major difference is found in the region between the spike and the envelope genes.

As of 3 June 2013, 1939 respiratory tract samples have been tested for the presence of MERS-CoV. As of 6 June 2013, 40 were positive. These positive samples all came from symptomatic patients whose condition matched the case definition available at the time. Diagnostic tests were run in parallel in (1) MoH laboratories in Saudi Arabia, targeting the upE gene - the screening target recommended by researchers at the University of the Bonn Medical Centre, Germany (described by Corman et al.)[10] and (2) the Health Protection Agency (now Public Health England) in the UK until April 2013 using upE for screening and the ORF1b and N genes for confirmatory testing.

Because testing for ORF1a is more sensitive than for ORF1b [11], now both upE for screening and ORF1a for confirmation are targeted in assays in Saudi Arabia.

Sera were taken from some patients with confirmed cases of infection. Serum has been systematically collected since April 2013.

The family members (about 450 in total) of confirmed cases were sampled (upper respiratory tract swabs) and tests were run in KSA for the detection of the upE gene. None was positive for MERS-CoV. Sera were taken at the same time.

Swabs and sera were taken from healthcare workers (HCWs) who were contacts of confirmed cases and tested. Screening for the upE was done in KSA on the swabs and all were negative.

All sera were archived for later studies.

Until end of April 2013, testing in KSA was done in a decentralized manner involving the Riyadh Regional Laboratory of Microbiology and the Reference Laboratory in Jeddah. Since early May 2013, the assays have been centralized in the latter.

All samples taken for diagnostic purposes and sent to Public Health England (formerly the Health Protection Agency) were also tested for the presence of the 15 most common respiratory viruses. No co-infection was observed.

RNA extraction was performed in KSA in an automatic manner with different robots.

So far no attempt has been made to isolate the virus in the country.

The **key questions** are:

- how frequent are false-negative and false-positive PCR results?
- what is the detection threshold?
- what is the best type of sample?
- what is the current state of serological testing?

The current **gaps in our knowledge** are:

- What is the excretion pattern of the virus and when is the best time for sampling?

- How reliable are a negative test results on specimens collected from the upper respiratory tract mean in symptomatic or asymptomatic patients?

d. Animal-human interface

Findings

The virus has not been isolated from any animal and there is at present no indication that infection with MERS-CoV causes disease in animals. Although there has been limited investigative sampling and testing for the virus in some species, there is no surveillance for the presence of this virus in animals. To date, there is no information available to use as the basis for designing more targeted animal and environmental sampling.

The case reporting form currently used to report data on human cases does not capture sufficient information to allow thorough investigation of potential sources of exposure to MERS-CoV. Additionally, the relatively low number of human cases means that it has not been possible to establish a strong hypothesis on the potential source of exposure.

MERS-CoV is a novel betacoronavirus. Detailed phylogenetic analysis revealed its close relationship to European bat coronaviruses circulating among bat species of the Vespertilionidae family. Molecular analysis of the two viral isolates from the two first recorded human infections in June and September 2012 showed that these betacoronaviruses share a much earlier common ancestor, suggesting that the diversity of the human isolates is the result of multiple zoonotic events.[12]

In KSA, responsibilities for animals and food are divided among several ministries and agencies. The Ministry of Agriculture is responsible for livestock; municipalities are responsible for activities within their city boundaries, including those related to domestic, companion or stray animals, and slaughterhouses; there are authorities charged with wildlife management (the Saudi Wildlife Authority); the Ministry of Health deals with zoonoses; and the Ministry of the Environment also is involved. The Saudi Food and Drug Authority covers food safety. At the ministerial level, there is intersectoral coordination on the current MERS-CoV event. At the local level, multisectoral collaboration takes place.

KSA has expertise on the geographical distribution of the different bat species present in the country,[13] and has links with international networks of bat experts (e.g. EUROBAT).

In the countries affected in the region, there is as yet little evidence of multisectoral investigations of human infections with MERS-CoV.

Gaps in our knowledge and key questions

By the end of the mission the source of exposure in the community still had not been identified in any of the countries affected. Thus, for instance, pets, rodents, birds and other peri-domestic animals, livestock, live animal markets, wild animals, contaminated food and drink, and contaminated environments could all still be considered as potential sources of exposure to MERS-CoV. Similarly, little is known about the environmental or occupational risk factors for infection. In KSA, contact with animals was reported in only 22% of cases but, because other data are lacking, nothing could be inferred from this figure. More needs to be known about the characteristics and daily lives of people infected with MERS-CoV and their more detailed exposure history in order to identify the source of exposure. Finding that

source might provide the basis for formulating prevention and control measures to prevent future infection and disease.

The **key questions** are:

- What is the source of exposure of human cases of MERS-CoV infection acquired outside healthcare facilities?
- What is the animal reservoir of MERS-CoV?

VII. Discussion and conclusion

The emergence of the MERS-CoV has created a difficult situation for affected countries as well as the global community at large. On the one hand, the number of affected countries, especially those with community-acquired cases, is limited. On the other hand, this infection is associated with a high case fatality rate, has demonstrated its ability to persist over time, has caused community acquired diseases in multiple locations, and can be transmitted from person to person in certain circumstances.

The situation is beset by major uncertainties. In terms of prevention and control measures, the most important question is, how are people becoming infected? In some settings, especially in families and healthcare facilities, certain cases are clearly associated with person-to-person transmission. However, how people are acquiring infection in communities remains unknown despite intensive efforts by KSA authorities, including case investigations and attempts to identify potential animal sources. In terms of the epidemiology of this emerging infection, another crucial question is whether significant numbers of people with MERS-CoV infection remain unidentified. Understanding the scope of infections in communities and other defined settings could provide the insight needed to point the way as to how people are getting infected. At the global level, the overarching concern is whether this virus will spread further internationally and extend its geographical scope. The most immediate international concerns are likely related to travel.

In this context, KSA faces a particularly complex and difficult situation. The country has confirmed the greatest number of cases. They include a complex mix of infections acquired in community settings in geographically distant locations (Figure), as well as secondary cases resulting from person-to-person transmission within families and in healthcare facilities. Although the number of new cases in Al-Ahsa has declined significantly, new cases are being reported in other parts of the Eastern Province.

In response to MERS-CoV, health authorities in KSA have (1) mounted an extensive communications campaign to raise awareness in the population; (2) created a multisectoral management group to improve collaboration and coordination among government agencies and sectors; (3) invited a range of groups to provide guidance (see Annex 3); (4) initiated enhanced infection control measures in the two healthcare facilities with nosocomial cases; and (5) initiated a range of investigations, including studies to identify potential animal reservoirs and to identify risk factors and routes of transmission. In addition, sequences from four viruses were subsequently posted in the GenBank database. Serum specimens from cases and other persons have been collected and stored in KSA.

The overall scope of the response mounted by the health authorities in KSA has been extensive, covering all major areas. Further understanding of the situation will be improved

by the timely testing of available specimens, especially serological specimens, further analysis of epidemiological data and ongoing investigations and surveillance.

VIII. Recommendations

For detailed guidance and recommendations in support of these general recommendations see Annex 4.

IX. Acknowledgements

We acknowledge the logistical assistance and cooperation of the Government of the Kingdom of Saudi Arabia in facilitating and hosting the meetings, providing data and ensuring the participation of experts from different sectors of government.

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Riyadh, 4-9 June 2013

ANNEXES

Annex 1

List of participants

Kingdom of Saudi Arabia

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Annex 2

List of preliminary questions to the Ministry of Health in the Kingdom of Saudi Arabia for consideration and as a basis for discussion

Preliminary Questions for Joint KSA-WHO MERS CoV Assessment Team to address

3 June 2013

There are very basic issues to be addressed -- for example:

- What is the true severity spectrum of MERS-CoV infection? From the data available now, it appears that secondary cases are likely to be less severe than index cases. Is this a severity-linked case ascertainment bias? How often do severe outcomes occur?
- What is the epidemiology of the infection and how are people getting infected? What is the person-to-person transmission potential of MERS-CoV? What is the potential impact of infection control measures? How does transmissibility vary in different settings (healthcare setting, household, community)? What is the potential effectiveness of public health control and infection control measures (case isolation, quarantine of contacts, enhanced hospital infection control etc).
- What research – modeling can be done to assess control options under a range of scenarios?
- What recommendations should WHO make?

There are basic data requirements to help answer these questions

- A formal line list of suspect and confirmed cases, with outcomes for each case (from public sources; we can't link outcomes to specific cases in a number of instances right now, as they're commonly reported at different times), dates of onset, admission, diagnosis, discharge/death, and more detailed information on co-morbidities.
- Data on contacts (family and other) investigated, who was tested, outcomes of tests (not just numbers testing positive), co-morbidities/health conditions.
- For specific clusters of cases, data on investigation/intervention timelines – when different intervention measures were implemented/enhanced.
- Extent of routine testing across KSA now – are all ILI cases being tested, or all SARI (I know the boundary is fuzzy), or only SARI with a suspected epi-link? Again, denominators (numbers tested per week) would be very useful.
- Sequences – who is doing sequencing, when will results be made available widely for other researchers
- Serosurvey data – of recovered cases (for calibration), contacts of cases, and preferably random population surveys.

Clinical questions

- What are the underlying medical conditions of the cases?
- What was the natural history of infection?
    - What were the initial signs and symptoms?
    - What were the rates of co-infection and the organisms?
    - How many cases were mild and what clinical syndrome did they manifest?
    - What have been the complications and their rates? (e.g. renal failure, DIC, multi-organ system failure)
    - What portion required ICU, ventilation, ECMO, etc. Were there age differences?
    - What treatment was used and how effective was it?

Transmissibility questions

- What is the extent of infection among contacts of cases (secondary attack rate)? Were certain types of contacts greater risk?
- What is the period of transmissibility?
- What is the incubation period?
- What kind of monitoring and surveillance is being done (and planned) to detect cases and assess contacts? (e.g. ILI, SARI, sero-surveys, healthcare worker absenteeism)
- Which clinical specimens are the most useful to detect the virus? With which tests?
- What is the relative sensitivity of testing of nasopharyngeal vs. lower respiratory specimens?
- What other body fluids has the virus been found in?

Risk factors and transmission questions

- What is the geographic distribution of cases?
- What are the potential sources of infection in the community that have been identified? E.g.,
    - Pets, rodents, birds, other peri-domestic animals?, Livestock? Live animal markets? Wild animals?
    - Food and drink? Fresh and dried foods (e.g. dates)? Fruits, raw juices and grains? Processed, unprocessed, unpasteurized products?
    - Occupational exposures? (e.g. farms)
    - Herbal or other traditional remedies?
    - Common links, specific physical location?
    - What are the results of animal testing?
- Human exposures in health care facilities:

- Were procedures performed that might have resulted in transmission (e.g. intubation, bronchoscopy, etc.)?
- Were certain types of healthcare workers or wards more at risk?
- What were the potential routes of transmission?
- What infection control measures were thought to be more useful than others?

- Human exposures in the household: what kinds of interactions resulted in transmission?
- What ethnic or other kinds of groups (e.g. nationality, socioeconomic strata) are involved?
- Have any common exposures been identified among case patients relating to activities in family, social, religious, occupational, or other settings?

Virus questions

- Has genetic variation been noted amongst the isolates? In what ways have they differed?

Annex 3

Kingdom of Saudi Arabia:

responses to outbreaks - human and animal investigations

International collaboration and expert teams invited

In early October 2012, experts from the following institutions responded to KSA's invitation to work with the Saudi Arabian team on the response to MERS-COV cases: (1) the WHO Eastern Mediterranean Regional Office and headquarters (4-10 October); (2) the Centers for Disease Control and Prevention, Atlanta, Georgia, USA (4-10 October 2012); (3) EcoHealth Alliance (6-10 October); (4) Columbia University (New York, USA, 6-10 October).

In April 2013, experts from EcoHealth Alliance and Columbia University visited the Kingdom of Saudi Arabia for a second time in order to collect more animal samples, with visits to: Unizah, Al-Qassim (5-8 April); Riyadh (10-12 April); and Bisha (1-3 April).

In response to the Al-Ahsa outbreak consultative teams were invited from: WHO (Eastern Mediterranean Regional Office and headquarters); Toronto University (Canada); Johns Hopkins Hospital (USA); University of Colorado, Denver (USA), University College London (UK)and Wellcome Trust Sanger Institute (UK).

Pending laboratory work and collaboration

Samples of contacts for serology are being assessed by collaborators at the National Institutes of Health's Rocky Mountain laboratory and the National Institutes of Health Bethesda/Center for Infection and Immunity at Columbia University.

Genome sequences for all MERS-CoV isolates have been submitted to the Wellcome Trust Sanger Institute and four sequences are ready to be posted in the GenBank database in the next few days. The remaining sequences are being augmented and will take some more time to be finalized but will be posted once available.

Animal samples collected on first visit

During the first visit (in October 2012) of international experts, samples were collected at the following locations: Bisha, Naqi and Old Naqi (greater Bisha area). Bats species examined were *Rhinopoma hardwickii* (*n* = 37), *Eptesicus bottae* (1), *Pipistrellus kuhlii* (1), *Eidolon helvum* (25), *Rousettus aegyptiacus* (3), and *Taphozous perforatus* (29). The types of samples taken were: oral, rectal and urogenital swabs, and serum from individual animals. Faeces were collected from the *Rhinopoma*, *Eptesicus* and *Pipistrellus* (mixed roost), and *Taphozous* roosting sites and tested.

Second field trip

During the second field trip (31 March - 13 April 2013), the locations visited were: the Greater Bisha area (Bisha, Naqi, Taballah), Unaizah, and the Greater Riyadh area (Wadi Hanifah). Bat samples collected were faecal pellets from roosts previously sourced in Bisha as well as new sites in all three locations. Multiple roosts were investigated for *Rhinopoma*

(Bisha) and *Pipistrellus* (Riyadh, Unaizah) and a single roost for *Taphozous* (Bisha). Altogether 677 tubes were used, each with 3-5 faecal pellets.

Other samples were collected from livestock (camels, cows, goats and sheep) in slaughter houses and live animal markets, and cats from the vicinity of one Riyadh case.

Summary of results of animal surveys

About 1100 bat samples from Bisha, Unaizah and Riyadh were tested by PCR; some 18,000 such tests were done, with two rounds of high throughput sequencing. Coronavirus infection was found in high frequency in *Pipistrellus* and *Rhinopoma* bats. One 182-nucleotide fragment of the MERS-CoV gene was found in one *Taphozous* bat, but further research could not be pursued owing to degradation of the sample.

Annex 4

Guidance and recommendations

A. Guidance for infection control in healthcare facilities

Healthcare authorities and facilities should adhere to current WHO guidelines for infection prevention and control during healthcare for probable or confirmed cases of novel coronavirus (nCoV) infections (available at: www.who.int/csr/disease/coronavirus_infections/IPCnCoVguidance_06May13.pdf).

The following additional **recommendations for infection control in healthcare facilities** were made:

If a case occurs in the hospital or healthcare facility

(a) Healthcare workers, patients, families and visitors should be educated, informed and made aware of MERS-CoV in order to prepare for cases.

(b) A surveillance system should be in place for case-finding that covers, at a minimum, the following: influenza-like illness in emergency departments and ambulatory clinics; severe pneumonia in intensive care units; and hospital-acquired pneumonia.

(c) A system should be in place for laboratory testing of suspected cases.

(d) A system should also be in place for detection and isolation using contact and droplet precautions in the event of a case of MERS-CoV infection.

(e) Laboratory and infection control staff should be trained so as to be prepared to handle both patients and specimens and to initiate an appropriate investigation.

(f) A plan should be in place at the hospital level so that the hospital administration (including the corporate communications department) is prepared for the potential detection of the first case.

(g) The indications used to guide testing should be the WHO or national case definition.

When the first confirmed case in a hospital or healthcare facility is detected

(a) The patient should be cared for using droplet and contact precautions, preferably in a single room, and with airborne precautions used during aerosol-generating procedures. Equipment should also be dedicated for the patient. Routine cleaning is adequate; however, facilities should ensure that cleaning and disinfection procedures are followed consistently and correctly. Visitors should be restricted, and permitted visitors should be trained in the use of personal protection equipment and to understand the risks of visiting. Countries are encouraged to develop local recommendations for patient accommodation that take into account the availability of private rooms and the balance between the need to prevent transmission of MERS-Cov and other patient-safety issues.

(b) Patients should be kept in isolation until they have been afebrile for 48 hours ***and*** no longer have respiratory or gastrointestinal symptoms.

(c) Patients who have substantially recovered but have persistent respiratory symptoms or loose stool should be tested on day 14-15 after onset of symptoms and removed from isolation if PCR tests on respiratory samples are negative. Expectorated or induced sputum is the preferred specimen; nasopharyngeal aspirates or swabs are acceptable alternatives.

(d) Based on experience with other respiratory viruses, children with underlying medical conditions may continue to shed virus for a prolonged period of time. Decisions about release of these children from isolation should be made on an individual basis.

(e) Quarantine cannot be justified at present, based on the limited ability of MERS-CoV to be transmitted from person to person.

(f) Infection control and infectious diseases specialists need to be consulted and actively involved in management of the infected patient and their contacts.

(g) Contact with a confirmed patient with MERS-Cov infection is defined as either one of:

a. In households: having close personal contact (e.g. hugging) with or spending more than 1 hour in the same room when the patient is symptomatic and at home;

b. In healthcare settings: present in the same room/space as a symptomatic laboratory-confirmed case for more than 15 minutes or any exposure during aerosol-generating procedures or to respiratory secretions in the absence of adequate personal protective equipment.

(h) Contact tracing needs to be initiated for:

- healthcare workers who were exposed a patient with confirmed MERS-CoV when the healthcare worker was not wearing gloves, gown or mask;
- visitors to the index case who did not wear gloves, gown or mask;
- patients who were in the same ward or in the same treatment area while the index patient was symptomatic and before isolation was initiated;
- contacts should be identified and contacted periodically to check symptoms for 14 days. If they develop fever or respiratory or gastrointestinal symptoms, they should promptly be tested for MERS-CoV and kept away from work or school while waiting for results. If the initial test results are negative and the contact remains symptomatic, testing should be repeated. Contacts who develop fever or any respiratory or gastrointestinal symptoms, these contacts should be managed with contact and droplet precautions.
- Acute and convalescent serology should be done for all contacts and detailed epidemiological data should be collected.

(i) Case-finding should be directed at identifying as many potential cases as possible in order to rapidly isolate new cases to contain the spread within the healthcare facility.

As such, the indications for testing should be broadened in consultation with a multi-disciplinary outbreak management team that includes infection control and infectious disease specialists, microbiologists and public health/preventive medicine experts. Consideration should be given to testing all patients with unexplained fever or respiratory illness. This enhance case-finding should continue until 28 days after adequate precautions have been implemented for the case.

(j) In healthcare systems in which patients are frequently transferred between facilities or admitted/re-admitted to different facilities, there should be systems for communication to ensure that each facility is aware of potential exposures in their patients.

When there is more than one case in a hospital or healthcare facility

(a) An outbreak management team needs to be convened, involving hospital administration, laboratory managers, infection control staff, and infectious disease teams, and public and occupational health staff.

(b) The indications for testing for MERS need to be broadened so as to cover all patients with either a contact history and/or fever or respiratory symptoms. These indications are necessarily broad but the aim is to control the spread of the outbreak in a hospital.

(c) Consideration needs to be taken to closing sections of a hospital to new admissions based on a risk assessment. Patients who may be incubating the virus should not be discharged to other facilities unless such a step is essential.

(d) In view of the reported high mortality associated with the disease, a precautionary approach should be adopted with a low threshold for testing and enhanced precautions and other outbreak control measures.

(e) Continued active surveillance for healthcare-associated cases should continue for a minimum of 28 days (2 incubation periods) after the last exposure in healthcare. Healthcare authorities and facilities should be aware that cases may present in hospital visitors and/or discharged patients, and that there may be a significant period of time between onset of symptoms and presentation to healthcare. A local risk assessment should be conducted to determine the extent to which continued surveillance after 28 days is needed.

Measures to assess the effectiveness of hospital infection control

Standard infection control audits need to be in place and documented, including hand hygiene audits, correct use of personal protective equipment, and audits of adherence to surveillance of hospital-acquired infections. The time from onset of symptoms to detection and institution of isolation precautions should be monitored and tracked.

B. Recommendations for action on epidemiological investigations

Case investigation – There should be an in-depth case investigation on all confirmed MERS-CoV cases, including use of a common protocol in consultation with international partners under the auspices of the MOH.

(a) Data on all confirmed cases of MERS-CoV infection should be collected in a standard format at MoH level and details shared with WHO as per IHR without compromising patient confidentiality. Index cases should have, in addition to a completed standard case investigation form, a detailed interview using exploratory, open-ended questions to identify possible exposures and routes of transmission in order to inform the generation of hypotheses.

(b) Findings from data collection should be regularly reviewed by MoH and KSA regional epidemiologists to improve the data collection forms and findings.

(c) Findings should be shared regularly between hospital and community investigators, and should be communicated to infection control specialists and should inform infection control guidance.

Case-control public health investigations – Case-control investigations should be performed to identify potential exposures. These should be based on standardized case-control instruments in coordination with international partners under the auspices of the MoH.

(a) Case-control investigations should be performed on all confirmed cases of MERS-CoV when possible in a combined cross-jurisdiction collaboration.

(b) The case-control instrument should be based initially on an agreed standard protocol.

(c) The investigation team should include epidemiologists in both human and animal health.

(d) Findings from data collection should be regularly reviewed by epidemiologists within jurisdictions and between jurisdictions to improve the data collection forms and findings.

(e) Data from case-control investigations in all countries should be done in a standard format and discussed between countries without compromising patient confidentiality.

Serological investigations – Serologic testing should be conducted as part of public health investigations and seroprevalence surveys should be conducted to characterize circulation in the community.

(a) Until more is known about the circulation of MERS-CoV in humans, collect sera of cases and their contacts to further characterize the attack rate of infection;

(b) Conduct unlinked anonymous seroprevalence studies using blood banks or other sources of available human sera to characterize the extent of infection in the community.

Global networks to aid detection – International networks of intensive care specialists should conduct diagnostic (PCR) and serologic testing of patients with severe acute respiratory illness (without association with travel to and from the Middle East) to characterize the clinical spectrum and geographical distribution of MERS-CoV using internationally agreed protocols.

Surveillance approaches – Countries should implement MERS-CoV surveillance at a level depending on the presence of cases of MERS-CoV in their country and on their risk assessment. Countries may choose to implement any of the following measures at a lower threshold according to their own risk assessment.

(a) if there are no cases in a country or if the primary cases are epidemiologically linked to exposures within countries in the Middle East, follow the WHO protocol to detect initial cases and to identify contacts and secondary cases

(b) if there are secondary cases from a primary case linked to a Middle Eastern country,

- follow the actions above,
- monitor for changing levels of influenza-like illnesses in the community,
- collect acute and convalescent sera from cases and contacts
- based on risk assessment, consider using a lower threshold for testing patients for MERS-CoV (e.g. testing patients with febrile respiratory illness who do not meet the WHO case definition)

(c) if the index case arises in country,

- conduct MERS-CoV testing in all patients with severe acute respiratory illness meeting the WHO case definition
- in areas where cases have been identified, use a lower threshold for testing patients for MERS-CoV (e.g. testing patients with febrile respiratory illness who do not meet the WHO case definition)
- collect acute and convalescent sera from cases and contacts
- until more is known about the circulation of MERS-CoV in humans, conduct seroprevalence evaluations using available sera from blood banks or other sources to characterize the whether MERS-CoV circulation has occurred in the community
- conduct monitoring of influenza-like illness in the community through outpatient sentinel networks or emergency departments. Collect specimens from a sample of patients with influenza-like illness for MERS-CoV testing to enhance identification of unrecognized community transmission of MERS-CoV.

C. Recommendations on clinical aspects

- The following major research priorities were identified:
- study of viral kinetics related to infection with MERS-CoV in order to help to determine the optimal timing of any treatment measure
- the therapeutic role and timing of administration of convalescent plasma
- the potential of any antiviral therapy, such as ribavirin with interferon, in combination with immunomodulating agents, such as intravenous *N*-acetylcysteine
- determine the full spectrum of clinical disease
- identification of predictors of poor clinical outcome
- ventilatory strategies and the role of extracorporeal membrane oxygenation as rescue therapy
- inflammatory and cytokine responses to MERS-CoV
- seroprevalence studies in the community and among healthcare workers
- comparisons of the severity of the index case and the secondary cases.

D. Guidance and recommendations on laboratory issues

Revise the WHO interim recommendations for "Laboratory testing for novel coronavirus" to incorporate modifications such as:

- greater emphasis on the collection and transport of samples, avoiding freezing until the specimens reach the destination laboratory
- greater emphasis on the collection of lower respiratory tract samples for diagnostic testing
- RT-PCR assays to detect upE and ORF1a targets could be run in parallel instead of sequentially
- A patient in whom the diagnosis is highly suspected but who has tested negative once should be retested at least one more time:
    - on a new sample from the lower respiratory tract
    - or, if it is not possible to obtain a new lower respiratory tract sample, on a new extraction using a manual protocol
- In the result report, laboratories should include an interpretative comment indicating that a negative test result does not exclude infection; clinical correlation is required.
- RT-PCR should systematically include the standard controls (for instance, inhibition of RT-PCR and sample quality)
- attempts at virus isolation should be made as close as possible to the diagnostic laboratories if it is safe to do so.
- Appropriate biosafety and biosecurity measures must be applied according to the current WHO recommendations www.who.int/csr/disease/coronavirus_infections/NovelCoronavirus_InterimRecommendationsLaboratoryBiorisk_190213/en/index.html
- Clinical specimen transportation must follow current rules and regulations (for air transport see www.iata.org)
- As crucial data required on shedding kinetics and compartments are very limited, until these are available, research is encouraged based on the serial collection of serum and the testing of urine, rectal samples and EDTA blood.

It might be useful to adapt real-time RT-PCR protocols and serological assays developed for humans for application in domestic animal species and possibly wildlife species.

E. Guidance and recommendations on the animal-human interface

In order to answer the two key questions (what is the source of exposure of human cases of MERS-CoV infection acquired outside healthcare facilities, and what is the animal reservoir of MERS-CoV), the following investigations are needed: those to establish a potential source of exposure for human cases, which may inform public health interventions, and research studies to establish the original animal source(s) of the virus and subsequent virus evolution in human cases, which may inform public health interventions, and research studies to establish the original animal source(s) of the virus and subsequent virus evolution.

Investigations should be defined accordingly to further understanding and control of MERS-CoV infection.

1. Investigations into source of exposure

- Interview, where possible, each patient with MERS-CoV infection (both confirmed and probable cases linked to a confirmed case) as well as their family members and contacts using an expanded questionnaire specific to potential exposure sources for MERS, for example, enquiring about animal contacts, food and environment (see http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_investigation_guideline_Jul13.pdf).

- Undertake case-control studies in order to test different hypotheses with open-ended questionnaires (see http://www.who.int/csr/disease/coronavirus_infections/MERSCoVCaseControlStudyPotentialRiskFactors_03Jul13.pdf).

- Investigations into the source of exposure should be designed and conducted in a multisectoral manner that involves agencies, including ministries responsible for health, agriculture, food safety, environment and wildlife.

- Animal investigations to identify the source of exposure to MERS-CoV should be designed on the basis of evidence provided by epidemiological investigations of human cases and the results of case-control studies, or from other on-going sampling and testing of animal samples.

- Analyse results from epidemiological investigations to identify potential common exposures (food, animal, or environmental) among community cases.

- Any additional cases detected through serological studies in humans should be considered for inclusion in the investigation into potential source exposure.

2. Animal investigations and research into a reservoir

Investigations into an animal reservoir should only be initiated once there are indications that a particular potential source has been identified through the activities listed above.

Supporting activities

To support the investigations listed above, it would be useful to collect additional information in the following areas:

- past, ongoing and planned animal studies (what studies have been done so far on sampling and testing of animals in the region, with what results)
- ongoing work on evaluation and/or validation of diagnostic tests for MERS-CoV in different animal species in international veterinary reference laboratories
- review the literature on coronaviruses in animals and sequence analyses from coronavirus deposited in publicly available databases.

- review the literature on persistence of coronaviruses in the environment and in animal excreta and secretions
- collect population and trade data on animals (including exotic species), in order to detect any recent changes within the past 1.5 to 3 years
- register and share information on any recent changes in the patterns of animal diseases or on unusual events
- ecological and/or environmental changes involving the human-animal-environment interface (e.g. farming and irrigation patterns).

Annex 5

Comparison of the clinical and epidemiological features of SARS-CoV and MERS-CoV

The appearance of human disease due to a novel coronavirus less than 10 years after the emergence of SARS-CoV inevitably results in a desire to understand how similar the clinical features and epidemiology of these two diseases are. The relatively small (n = 58) number of cases of MERS-CoV identified to date limits the certainty about both clinical presentation and epidemiology, it is already apparent that there are both similarities and differences between SARS-CoV and MERS-CoV.

The table below highlights some of these similarities and differences, by comparing available data from MERS-CoV (categorized as cases reported by KSA and cases reported by other countries), and data from cohorts of SARS cases reported from Canada (Toronto), China (Beijing, Hong Kong and Taiwan), and Singapore.

As shown in the table, there is considerable variability between cohorts of SARS reported from different countries. There are as yet too few cases of MERS-CoV infection to assess the extent to which there will be similar variability. Compared with SARS-CoV, patients with MERS-CoV to date are more likely to be men, are significantly older, especially index and sporadic cases, and are more likely to have co-morbid conditions. They appear somewhat less likely to present with fever, but may be more likely to have cough than patients with SARS. The case fatality rate is significantly higher, although, as shown in the table, a substantial fraction of the difference in the case fatality rate may be due to surveillance bias or to the fact that patients with MERS-CoV are older, more likely to be male, and more likely to have diabetes mellitus and other co-morbid conditions, all factors known to increase the case fatality rate in SARS. In addition, the denominator of MERS CoV infections is not known, which could significantly lower estimated mortality rates.

In comparing the epidemiology of SARS-CoV to MERS-CoV infections, the proportion of cases that are in healthcare workers is lower for MERS than for SARS, while the proportion of cases that are health-care associated infections is substantially higher. The incubation period and serial interval are similar, although it should be noted that the confidence limits on estimates of these characteristics for MERS-CoV are still wide because of the small number of cases. The mean number of secondary cases for each case described in MERS appears smaller than that for SARS. This may in part be because of difficulties with diagnosis of less severe illness due to MERS-CoV. The attack rates in household contacts appear to be similar, although for MERS-CoV the number of household investigations is limited, and the confidence limits on estimates wide. As with SARS, there is as yet no evidence that MERS-CoV is transmitted before the onset of symptoms. During SARS, transmission appeared to increase over time after onset of symptoms, with a low risk of transmission (<0.01 transmissions per day) on day 1 and days 3-6, a somewhat higher risk on day 2 (0.03 transmissions per day) then an increasing rate of transmission that peaked at 0.06 per day on day 9. In contrast, to date, although transmission from MERS-CoV patients does appear to have occurred late in illness, many episodes of transmission appear to have occurred on the first day of illness of the index patient.

Table

Comparison of epidemiological and clinical features of SARS-CoV with MERS-CoV infection

	SARS-CoV					MERS-CoV	
	China (Hong Kong)	Canada (Toronto)	China (Beijing)	China (Taiwan)	Singapore	KSA	Else-where*
Median age (years)	NR	45	35	45	21	58	
Percentage male	44%	39%	56%	48%	32%	74%	
Percentage with co-morbidity	20%	28%	4%	30%	NR	95%	-
Percentage with diabetes mellitus		11%			NR	52%	-
Symptoms at presentation	100%	99%	100%		100%	83%	-
Fever	57%	69%	43%		39%	87%	-
Cough	-	42%	-		13%	42%	-
Shortness of breath	20%	23%	7%		7%	22%	-
Diarrhoea	20%	19%	15%		11%	17%	-
Nausea/vomiting					-	32%	-
Gastrointestinal symptoms							
Chest X-ray at presentation					9%		
Normal					61%		
Unilateral infiltrate					30%		
Bilateral/multifocal infiltrate							
Percentage of cases occurring in healthcare workers	23%	77%	16%	18%	42%	6.7%	5%
Percentage of cases that are healthcare-acquired in hospital patients	6.8%	2%	6.3%	7.7%		50%	7%
Case fatality rate							
Overall	17%	6.5%	3.3%	28%	12%	60%	40%
In 51-60 year olds	18%	-	12%	42%		-	-
In 60+ year olds	55%	-	25%	49%		-	-
In persons with co-morbidity	46%	-	14%	40%		-	-
In patients with healthcare -acquired disease	53%	-	0	70%		-	-
Incubation period	4.6 days (95% with onset by 12.9 days)					5.2 days (12.4 days)	NA
Serial interval	8.4 days					7.6 days	NA
Mean number of secondary symptomatic cases per index case before control measures	7 (Singapore) 2.2-3.6 (modelled)					1.5 (outbreak) 0.4 (3/9) (sporadic)	1.0 (8/8)

Household attack rate	Canada, Toronto: 10.2% (6.7-23.5%) Viet Nam: 4.2%, 95% CI 1.5-7 China, Hong Kong: 8% (11% early - 5% late) China, Hong Kong: 7.2%		11% (4/36)	5% (1/20)
Duration of infectiousness	- Not infectious before onset of symptoms - Transmission greater later during severe illness - Viral shedding increases to day 9-12 of illness	-	- No case with evidence of transmission before onset of symptoms in index case - Most transmission on day 1-5 of illness in index case	

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Annex 6

Lessons from the past for present and future strategies

Epidemiology and infection control

(a) A rapid and coordinated global public health response, with transparent sharing of information, is a key lesson from the SARS epidemic.[14]

(b) Rapid genetic sequencing of the virus and communication of results is important for rapid decision-making.

(c) Laboratory testing is important but does not replace appropriate case definitions. Successful outbreak control measures should be implemented for suspect as well as laboratory-confirmed cases of infection.

(d) Vigilance and continued collaborative risk assessment are required.

(e) During the global SARS outbreak, teleconferences for international collaborators were very helpful in sharing epidemiological information and setting country policy for investigations and control measures. A mechanism to facilitate similar collaboration between epidemiologists from different countries may assist in generating hypotheses for case-control studies.

Clinical aspects

Ribavirin monotherapy was ineffective for SARS-CoV and resulted in haemolysis and bradycardia.[15] Although data from non-randomized clinical trials suggest that ribavirin in combination with protease inhibitors (lopinavir/ritonavir) was more effective in improving clinical outcome in SARS-CoV,[16] unpublished data from the Netherlands show that protease inhibitors have no activity against MERS-CoV (personal communication; WHO teleconference).

Serial sampling during SARS-CoV infection showed that viral load peaked on day 10-12 of illness onset.[17] Viral kinetic data for MERS-CoV are currently lacking and knowledge in this area will facilitate planning of infection control and clinical management. Administration of convalescent plasma within 14 days of onset of illness was associated with a higher discharge rate on day 22 of illness than for those who received convalescent plasma late for SARS-CoV or not at all.[18] Use of convalescent plasma and related hyperimmune globulin for patients with severe influenza A(H1N1)pdm09 was associated with improved clinical outcome and faster decline in viral load and cytokines.[19] Convalescent plasma may provide a useful treatment modality for severe MERS-CoV disease.

In an uncontrolled study, use of alpha interferon plus corticosteroids in nine patients with SARS-CoV disease was associated with improved oxygenation and more rapid resolution of pneumonic changes radiologically than 13 other patients who received corticosteroids alone.[20] In contrast to cases of severe viral pneumonitis in which corticosteroids might be harmful, use of systemic corticosteroids for treatment of SARS suggested some therapeutic benefit for a subset of patients with bronchiolitis obliterans organizing pneumonia but it resulted in avascular necrosis and fatal fungal infection in some cases.[7] Use of systemic corticosteroids in acute respiratory distress syndrome due to influenza A(H1N1)pdm09 was

associated with increased risk of mortality and nosocomial infections.[21] Caution is urged in the use of high-dose systemic corticosteroids for severe MERS-CoV illness, except in the setting of refractory septic shock, where low-dose treatment with hydrocortisone (50 mg every 6 hours) is helpful (WHO interim guidance 2013[22]). Based on published case reports, there is no survival benefit from the use of systemic corticosteroids for treatment of severe MERS-CoV disease.

A case summary form for case-based data collection is available on request.

Laboratory aspects

(a) The experience in KSA and a review of the literature show that positive cases were detected using the real-time RT-PCR protocol published by Corman et al. in 2012, modified over time to substitute ORF1a for ORF1b.23 This approach complies with the WHO interim recommendations for "Laboratory testing for novel coronavirus" dated 21 December 2012.

(b) The data accumulated from the cases in KSA indicate that including the N gene as a third target will not further limit the occurrence of false-negative results.

(c) As reported in the literature and observed in KSA, with some exceptions, lower respiratory tract samples (induced sputum, broncho-alveolar lavage and endotracheal aspirates) are far more sensitive than upper respiratory tract samples.

(d) Serology is the key to understanding the natural history of the disease and its epidemiological features. Serological testing could be useful in the future for diagnosis. Seroneutralization is available to laboratories that have access to seed virus. Although some serological assays have been described (Corman et al, 2012b; C. Reusken et al. Eurosurveillance 2013),24, 25 there is no validated assay for epidemiological serosurveys. Validation might be achieved by using sera collected from all countries with documented confirmed cases. In KSA, a collaborative exercise is expected in order to survey the incidence of relevant coronaviruses as a prerequisite for validation.

(e) There is a need to have a carefully designed protocol that is adhered to for handling samples (including an appropriate cold chain but with avoidance of freezing).

Animal-human interface

Previous emerging disease events have shown that investigations of human cases through targeted questionnaires and case-control studies are often necessary to identify the source of exposure and a potential animal reservoir.

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