Investigation of cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV)

Interim guidance

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1. Introduction

Coronaviruses are a large family of viruses that can cause a range of illnesses in humans, from the common cold to severe acute respiratory syndrome (SARS). These viruses also cause disease in a wide variety of animal species.

In late 2012, a novel coronavirus that had not previously been seen in humans was identified for the first time in a resident of the Middle East. The virus, now known as the Middle East respiratory syndrome coronavirus (MERS-CoV),[1] has (as of 4 May 2018) caused more than 2,206 laboratory-confirmed cases of human infection. Thus far, all patients infected with MERS-CoV have had a direct or indirect link to the Middle East, however, local non-sustained human-to-human transmission has occurred in other countries, from people who had recently travelled to the Middle East.

Most MERS-CoV patients have primarily had respiratory disease, although a number of secondary complications have also been reported, including acute renal failure, multi-organ failure, acute respiratory distress syndrome (ARDS), and consumptive coagulopathy. In addition, some patients have also reported gastrointestinal symptoms, including diarrhoea. To date, approximately 36% of infected patients have died. The majority of laboratory confirmed cases have had at least one comorbid condition, but many have also been in previous good health. As of 4 May 2018, the median age of reported laboratory-confirmed cases is 52 years (Range <1–99 years) and majority (67%) are males.[2] Updates of the latest cases and situation can be found on the WHO MERS website (http://www.who.int/emergencies/mers-cov/en/).

Our current understanding of MERS-CoV is that it is a zoonotic virus, which has entered the human populations in the Arabian Peninsula on multiple occasions from direct or indirect contact with infected dromedary camels or camel-related products. Several studies have shown that MERS-CoV specific antibodies are widespread in dromedary camel populations in the Middle East and Africa. The evidence from animal seroepidemiologic surveys suggests that MERS-CoV has been circulating in camels for decades. However, the reason(s) human cases first appeared in 2012 are unknown and the specific exposures resulting in and modes of transmission from animals to humans have not been fully elucidated[3].

Human-to-human transmission has been observed to a limited extent in households. However, the majority of human cases reported to date have resulted from human-to-human transmission in health care settings. Failures in infection prevention and control in health care settings have resulted in sometimes-large numbers of secondary cases, as was seen in KSA in April-May of 2014 and Republic of Korea in May-July 2015. To date, there is no evidence of sustained human-to-human transmission.

Background information on MERS can be found in this free Introductory Course on MERS available at: https://openwho.org/courses/introduction-to-mers.

2. Purpose and scope of the document

This document provides a standardized approach for public health authorities and investigators at all levels to plan for and conduct investigations around confirmed and probable cases of MERS-CoV infection. It should be read in conjunction with other detailed guidance referenced throughout the text, such as current laboratory testing guidelines and study protocols. It will be updated as necessary to reflect increased understanding of MERS-CoV transmission and control.

Most of the advice given in this document will apply primarily to countries in which infection is presumed to have originated from an animal (dromedary camel) or environmental source, and the exposures that result in infection remain the critical questions. In countries that have secondary transmission related to imported cases, however, the recommendations for finding secondary cases and observing subsequent community transmission are still valid, though on a more limited scale. As with nearly all recent emerging novel pathogens, most of the early cases of MERS were detected by astute clinicians rather than through established indicator or sentinel surveillance systems. Therefore, the most effective tool in detection will be awareness among the health care providers. An effective detection system will also need to include a readily available channel by which clinicians can report suspect cases, and an effective response mechanism. The WHO Regional Office for the Western Pacific has published a guide for event surveillance[4].

This document addresses two general categories of activities that need to be undertaken to deal with newly identified cases:

1. The first involves further/active case finding, case description, and surveillance enhancements in the area(s) where the case is(are) discovered. The primary purpose of these activities is for early

[1] WHO. Naming of the Novel Coronavirus. Available at http://www.who.int/csr/disease/coronavirus_infections/NamingCoV_28May13.pdf

[2] WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) website. Available at http://www.who.int/emergencies/mers-cov/en/

[3] WHO. Weekly Epidemiological Record (WER). 15 May 2015, vol. 90, 20 (pp. 217-252). Available at http://www.who.int/wer/2015/wer9020/en/

[4] WHO Regional Office for the Western Pacific. *A Guide to Establishing Event-based Surveillance.* Manila, 2008. Available at http://www.wpro.who.int/emerging_diseases/documents/eventbasedsurv/en/

detection of cases for timely isolation and management, to fully describe the epidemiology of the cases, identify and monitor close contacts of the cases and determine the extent of spread of the virus in the area (sections 3 and 4).

2. The second group of activities describe a number of specific studies aimed at answering critical public health questions related to MERS (section 5).

Part I. Further/Active Case Finding, Case Description and Surveillance Enhancements

3. Key steps for an investigation

3.1 Objectives

When setting up an investigation, it is critical to clearly define the objectives of the investigation and use a standardized approach that addresses each of the objectives.

These objectives might be to:

- Prevention and Public Health Objectives
  - Identify other cases and quickly detect any human-to-human transmission.
  - Reduce onward transmission, morbidity and mortality through rapid identification, isolation, (symptomatic) treatment and clinical management of cases and follow-up of contacts.
  - Prevent future cases through identification of potential human, animal, and/or environmental sources of exposure, risk factors for infection, and implementation of appropriate prevention and control measures.
- Knowledge Objectives
  - Determine the size of geographic area where the virus is transmitting.
  - Determine key epidemiological, clinical, and virological characteristics for cases including clinical presentation and natural history, the mode(s) of transmission and disease diagnosis, incubation period, period of transmissibility, and best practices for treatment.
  - Determine if the efficiency of human-to-human transmission of the virus has changed or increased.

3.2 Case identification and interview

Laboratory-confirmation of a MERS-CoV case is an immediate trigger to launch a thorough investigation. However, because collection, shipment, and testing of specimens may require several days or longer, the investigation may need to begin before laboratory test results are available for suspected cases. Even if laboratory-confirmation is not possible, an investigation should still be launched if a patient is strongly suspected to have MERS (e.g., a patient with severe acute respiratory infection [SARI] who has a history of travel to Middle East, has been in contact with cases who have died, or was in contact with infected dromedary camels).

The patient and/or family members (if the patient is too ill to be interviewed or has died) should be interviewed within the first 24–48 hours of the investigation to collect basic demographic, clinical, and epidemiological information. A sample questionnaire for the initial interview can be found here[5] but should be adapted and augmented with questions about practices and exposures in the local community.

The interviews should be carried out by trained health professionals in a systematic manner.

3.3 Preparation

A multi-disciplinary team should be assembled. Team members should have experience in field epidemiology, clinical assessment, laboratory specimen collection, infection prevention and control, and social mobilization and risk communication. Animal health specialists are also a critical part of the team. Additional team members may include logisticians, laboratory experts, data managers, and environmental health specialists. The size and composition of the initial investigation team may vary depending in part on the size and complexity of the anticipated investigation. Designation of a team leader and attribution of roles and responsibilities is critical to the success of the investigation.

Before deploying, the team should gather preliminary background information, assemble the necessary materials and supplies (e.g. personal protective equipment, specimen collection and transport materials) and inform relevant local public health and animal health authorities.

3.3.1 Essential information

Basic Information and Demographics

The following basic information should be collected, including:

- Patient ID number/cluster number (if applicable).
- Relationship between the person answering questions on behalf of the case patient (in the case that the patient is too ill for interview or has died).
- Date of symptom onset (by symptom, if possible).
- Date of initial admission/ visit to health care facility(ies).
- Date of isolation.
- Patient contact details (e.g. name, home address, home/mobile telephone numbers).
- Demographic information (e.g. date of birth/age, sex).
- Occupation (including specific classification such as healthcare worker, laboratory worker, and farm worker etc.).
- Date of sample collection, laboratory testing and specimen type (e.g. nasopharyngeal swab, sputum, etc.).
- Name of laboratory testing specimen.

Exposure Information and travel history

Possible exposures in the 14 days[6] before the onset of symptoms should be thoroughly explored and described, with special focus on:

[5] MERS-CoV initial interview questionnaire of cases
Interim Case Summary Form for rapid reporting of probable and confirmed cases of MERS-CoV infection to WHO

[6] The incubation period of MERS is 2-14 days, median of approximately 5.5-6.5 days.

- Animal exposures
  - Presence of animals, especially dromedary camels, in or around household area where the case patient lives or works (e.g. pets, rats, other rodents, bats, camels, birds, etc.).
  - Activities that result in animal exposures and type of camels exposed to (e.g. keeping livestock, visiting farms, visiting live animal markets racetracks, or practicing falconry, participating in the slaughter or sacrifice of animals etc.).
  - Exposures to animal, especially camel, products or products potentially contaminated by animal excreta or body fluids.
  - Consumption of raw camel meat or products (including milk or urine).
- Human exposures:
  - Recent contact with individuals MERS or with respiratory illness and/or gastrointestinal symptoms, including people who have been severely ill or have died (indicate the type(s) of contact, frequency, and duration of exposure, and location).
  - Recent admission or visit to a hospital or other health care facility.
  - Recent visit to traditional healer.
- Travel history
  - Dates, all destinations and details mode of transport for travel (local and international) in the 14 days since symptom onset
  - Activities during the period of travel (including information on camel, human and food exposures as listed above).

Clinical Information

Data on the presentation of illness, pre-existing medical conditions, clinical course of illness, and occurrence of complications are critical for refining case definitions and informing clinical management recommendations. As such, detailed clinical data should be collected on each confirmed case and systematically summarized. A clinical collection form has been developed by WHO/ISARIC[7]; see section 5.6 for more information).

- Clinical data:
  - Signs and symptoms at initial presentation.
  - Time course of illness including time from illness onset to: care-seeking, first hospital admission, deterioration requiring advanced clinical management, and final outcome.
  - Presence of pneumonia and progression to respiratory failure, development of the acute respiratory distress syndrome (ARDS).
  - Occurrence of other complications such as renal failure or other organ system compromise, coagulopathies, secondary infections, sepsis, etc.
  - Presence of pre-existing chronic conditions (immunosuppression, cancer, renal insufficiency, hemoglobinopathies, liver disease, neurological disease, endocrine and metabolic disorders, etc.).
  - Dates and results of any ancillary tests performed (X-Ray, CT scan, etc.).
  - Use of respiratory support (supplemental oxygen and FiO2; non-invasive and invasive mechanical ventilation, prone positioning, use of inhaled nitric oxide, oscillatory ventilation, Extra Corporeal Membrane Oxygenation [ECMO]).
  - Use of other organ support modalities (renal replacement therapy, vasopressors, etc.).
  - Use of antibiotics, corticosteroids, other medical therapies.
  - Documentation of co-infections (viral, bacterial, fungal).
  - Clinical outcomes (recovered, ill, critically ill, duration of intensive care unit admission, duration of hospitalization, deceased).
  - Virological outcomes (if available), including duration of MER-CoV shedding in respiratory tract specimens, and extrapulmonary clinical specimens.
- Infection control related
  - Where and when patient was located in health care facility. Which other places (e.g. radiology) may have been visited.
  - Infection control precautions that were used in relation to patient including type of masks, etc.

Laboratory Information

- Laboratory data (haematology, biochemistry, and virology)
  - Date specimen taken.
  - Type of test, type of specimen.
  - Test results and date of results.
  - Name of laboratory performing test.
  - Name of national laboratory.
  - Name of reference laboratory (if applicable).

3.4 Case finding

3.4.1 Develop a case definition

An additional first step in the investigation is to identify other cases among contacts of the known case and in the community. To do this, the investigation team must first identify the types of clinical presentations or syndromes that will be sought as part of the case finding activity. WHO has developed surveillance case definitions for classification and reporting of human cases globally (http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/) but these are not designed for case finding around newly discovered cases. Definitions for additional case finding must be developed locally and may be shaped by information obtained from the interview with the first case/s.

These definitions are used to identify patients in the community who should be tested for MERS-CoV and should incorporate time periods, localities, illness characteristics, exposure and other information. The criteria used should those that clinicians will find simple, easily understandable, and memorable. The case definition should be sensitive enough during the initial stages of the investigation to capture the majority of cases. An example of a case definition to use for this purpose might include features such as:

- Location: the local community where the case occurred. This will be defined according to the local situation but

[7] Available at http://prognosis.org/isaric/documents/WHO_SARI_NewOutbreak_case_record_form_v2.pdf

should include an area that incorporates other individuals who may have exposures to the same source of virus to which the patient was exposed. As the relevant exposures are currently unknown, they should include the population area that generally includes local markets, places of worship, and health care facilities that the case may have recently visited.

- Time frame: some retrospective case finding should be conducted and therefore the time period should cover at least two weeks before the onset of symptoms of the case.
- Patients' characteristics may include the following, but should be modified according to the latest clinical data on cases:
  - A patient with SARI[8] who presents with fever and cough, requires admission to hospital, and whose disease is not completely explained by another pathogen.
  - A patient with SARI whose clinical course is unexpectedly severe even if another pathogen was initially identified and the patient did not respond to appropriate treatment.
  - A patient with SARI with recent exposure to animals.
  - An immunocompromised patient who presents with an acute illness that is not fully explained by another pathogen.

3.4.2 Contact monitoring

Close contacts of confirmed or probable cases should be identified and monitored for the appearance of respiratory symptoms for 14 days after last exposure to the confirmed or suspected case, while the case was symptomatic. Any contact that becomes symptomatic in that period of time should be tested for MERS-CoV. If feasible, all contacts especially health care workers and other inpatient hospital contacts, regardless of the development of symptoms should be identified and tested for MERS-CoV.

A line-listing of all contacts and co-exposed persons that records demographic information, date of first and last common exposure or date of contact with the confirmed or probable case, and date of onset if fever or respiratory symptoms develop should be maintained. The common exposures and type of contact with the confirmed or probable should be thoroughly documented for any contacts that become infected with MERS-CoV.

Initiate active monitoring (e.g. daily visits or telephone calls) for the development of fever and acute respiratory illness or any other symptoms in close contacts for 14 days after the last exposure to the initial case. Contacts should also be advised to contact health care workers as soon as they develop above symptoms. If any of the contacts are confirmed to have MERS-CoV infection, their close contacts should also be monitored.

Collect appropriate clinical specimens (see section 3.5.1) on any close contacts with an acute respiratory illness regardless of severity, and test for MERS-CoV. While under investigation, symptomatic contacts should limit their contact with well individuals and practice good respiratory hygiene to prevent onward transmission. Current advice on preventing transmission both in the household and in health care facilities can be found on the WHO MERS website. The decision of whether to admit symptomatic cases or contacts should be based on clinical judgment and concerns about further transmission. If symptomatic individuals are managed at home, they should be monitored closely for progression of their illness. Currently, it is not possible to predict the course of illness of an individual patient.

Serological investigation of contacts: In addition to monitoring close contacts for the appearance of acute illness and testing with PCR, it is strongly advised that sera be collected on all close contacts, including health care workers. This will assist in demonstrating the presence of mild and asymptomatic MERS-CoV infections and help in defining common exposures in the environment or exposures to the case that might result in infection. Investigators should collect acute sera on all close contacts immediately after the confirmed or probable case is identified. Sera collection should be repeated in close contacts 3–4 weeks later, regardless of whether contacts have developed symptoms. Symptomatic contacts should also have appropriate respiratory specimens collected for PCR testing (see section 3.5). If the index case was ill more than 3–4 weeks before the investigation is undertaken, only a single serum specimen needs to be collected from contacts. In addition to the second serum specimen, for each contact collect information regarding:

- Any illness that may have occurred during the intervening time period, including all signs and symptoms, and their severity.
- Specific exposures to the confirmed or suspected case including providing care, exposure to body fluids and other physical contact, duration and proximity of exposure, eating with and sleeping in the same room as the case.
- Exposures to camels, unprocessed food and beverages, and other social and environmental contacts.

A protocol for contact investigation has been developed by WHO and CONSISE and is available at: http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/

3.4.3 Active search for additional cases

Efforts to identify additional cases beyond close contacts are critical for prevention and control of infection, and to determine the total extent of transmission in the community. Active case finding in the area under investigation should focus on:

- Patients currently admitted to health care facilities in the community where the confirmed MERS-CoV case was discovered. Any patients currently in the hospital with unexplained SARI should be considered for testing for MERS-CoV.
- Health care providers in the community; health workers should be interviewed about recent cases of unexplained pneumonia and notified to immediately report any patients who have signs and symptoms that meet the case definition developed for the investigation as described above in section 3.4.1. Patients meeting the case definition should be tested for MERS-CoV.

[8] SARI definition: An acute respiratory infection with history of fever or measured fever of ≥ 38 C^0 and cough, with onset within the last seven days, that requires hospitalisation.

- Patients who recently died of an unexplained illness consistent with the case definition developed for the investigation should be tested for MERS-CoV infection if appropriate clinical specimens are available.

3.4.4 Enhance surveillance

In addition to case finding activities, surveillance in the area under investigation should be enhanced to detect cases that might arise subsequent to the discovery of the index case. 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 the enhanced surveillance will depend on the findings of the investigation and whether there is evidence indicating that sustained transmission may be occurring in the area. A minimum of one month of enhanced surveillance is a reasonable starting point.

Enhancements include:

- Daily reporting, data management and data dissemination to relevant stakeholders
- Introduction of laboratory molecular testing capacity for MERS-CoV testing in the local health care facility, if feasible, or establishment of mechanisms for rapid transfer of specimens to a capable laboratory.
- Inform clinicians in the community of the need for vigilance and the case definition for case finding (section 3.4.1).
- If SARI surveillance is in place, expand to other facilities in the area. If it is not, initiate SARI surveillance at health care facilities in the community of the case. Standards and guidance for SARI surveillance can be found in the 'WHO Global Epidemiological Surveillance Standards for Influenza' available at http://www.who.int/influenza/resources/documents/influenza_surveillance_manual/en/
- Increase the testing for MERS-CoV of SARI cases at local health care facilities in the area under investigation.
- If resources allow, consider some testing of milder cases of influenza-like illness presenting to surveillance sites.

3.5 Biological specimen collection and laboratory testing

3.5.1 Specimen Collection

To confirm the presence of MERS-CoV in suspect cases, collect appropriate clinical specimens for testing:

- Available evidence suggests that lower respiratory tract specimens contain higher virus titres than upper respiratory tract specimens and are more sensitive for detecting the presence of the virus. Lower respiratory tract specimens include:
  - Sputum, induced or non-induced.
  - Endotracheal aspirate for patients on mechanical ventilation.
  - Bronchial alveolar lavage for those in whom it is indicated for patient management.
- Upper respiratory tract specimens such as nasopharyngeal and oropharyngeal swabs should be collected if lower respiratory tract specimens cannot be collected. If initial testing of an upper respiratory specimen is negative in a patient suspected of having MERS-CoV infection, repeat testing should be performed.
- Collect blood for serological testing. For recent cases, an initial blood specimen should be collected and a repeat specimen taken after a period of at least 3 weeks. For cases that had symptom onset more than 3 weeks prior to being investigated, a single blood sample is sufficient.
- MERS-CoV has been identified in other body fluids including blood, urine, and stool of infected patients. However, titres of virus in these body fluids are quite low and they may not be useful for diagnostic testing. The presence of virus in these body fluids could have public health implications and could be part of an ancillary study of a case.

Health care workers collecting clinical specimens should exercise appropriate infection control measures including use of personal protective equipment. Current guidelines for infection control and prevention can be found on the WHO MERS-CoV website at: http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/

3.5.2 Molecular diagnostics

PCR is the most widely used method for detecting the presence of the virus. At least three sites in the virus genome have been identified as suitable targets for such assays, including upE, ORF 1a and ORF 1b, and genome sequences of the necessary primers have been published. To perform these assays, laboratories should order the primers from their usual suppliers. Positive controls for the UpE screening and the ORF 1a confirmation assays are also available.

A confirmed case should either have positive test results for at least two different sites in the virus genome, or a positive result for a single site plus sequencing of a different, appropriate site that shows close similarity to known sequences of the virus. Testing should be carried out in laboratories that are experienced in performing these procedures. Specimens should be sent to a reference laboratory for confirmation.

A BSL2 facility including use of a microbiological safety cabinet (class 1, 2, or 3) is required for the handling of specimens thought to contain MERS-CoV when performing RNA extraction for PCR. Recommendations on the laboratory biorisk management for MERS-CoV have been prepared.

WHO guidance on laboratory testing for MERS-CoV is available at http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-laboratory/en/

3.5.3 Serological testing

Several MERS-CoV specific serologic assays have been developed and are now available and work on further serological assays is continuing in several laboratories around the world. Collection of sera from patients being investigated for infection with MERS-CoV will greatly aid in the validation of assays currently under development and may be useful for confirmation of infection once the validation process is complete.

See WHO guidance on laboratory testing for MERS-CoV for more information on serologic testing of MERS-CoV:

http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-laboratory/en/

3.5.4 Viral culture

The MERS-CoV virus has been shown to grow in a number of different commonly available cell lines. However, culture of this virus should not be attempted outside of specialised laboratories with appropriate biosecurity level 3 capabilities.

3.5.5 Genetic sequencing

Specimens testing positive for MERS-CoV should be genetically sequenced, and the data uploaded to publicly accessible databases. If the laboratory doing the initial test does not have the capacity for genetic sequencing, an aliquot of the specimen should be forwarded to a reference centre. Such centres should attempt to isolate viruses from all cases so that whole genome sequencing can be performed, either in the national or international reference laboratory. Both partial and whole genome sequencing provides crucial information as to the origin and source of exposure to MERS-CoV.

3.6 Infection control

Many of the standard prevention and control measures to reduce opportunities for further transmission of nosocomial infections have been noted previously and are listed below.

- Strict infection control, the use of personal protection equipment during the delivery of care and isolation of confirmed and probable cases
- Strict infection control and use of personal protection equipment during collection, transportation and testing of laboratory specimens in patients suspected of having infection with MERS-CoV.

If symptomatic contacts or cases with milder symptoms are cared for at home, infection control measures should be used if. However, because of rapid progression to acute respiratory distress syndrome (ARDS) and other severe life-threatening complications, even otherwise healthy, symptomatic contacts or probable cases should be considered for close observation in a medical facility. Guidance is available on the WHO website at http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/.

4. Data Analysis

The analysis plan will depend on the objectives of the investigation.

At a minimum, descriptive analysis of cases should be performed in terms of person, place, and time. For investigations that yield multiple cases, graphical and/or tabular descriptions of cases by date of onset (i.e. epidemic curve), geographical location (e.g. maps of the locale, case patients' homes), relationship(s) (i.e. transmission or family trees), and demographic characteristics (e.g. distribution by age and sex) should be developed. Key epidemiological (e.g. estimation of an incubation period, description of transmission patterns, attack rates by age, occupation, exposure history etc.) and clinical (e.g. spectrum of illness severity, proportion of cases who develop pneumonia, require hospitalization, die) parameters should be characterized to enhance understanding of the spectrum and dynamics of disease associated with MERS-CoV infection.

Part II. Specific studies aimed at answering critical public health questions related to MERS

5. Studies and specific investigations

Many of the critical questions regarding the clinical manifestation and epidemiological characteristics of MERS-CoV infection will be answered only by careful, detailed formal studies around cases. The following provides some guidance on the types of studies that should be considered.

Outbreak investigation protocols have been developed by Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) in consultation with WHO and external partners from numerous organizations can be found on at http://consise.tghn.org/articles/novel-coronavirus-ncov/ and http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/.

This section covers the different epidemiologic study designs and investigations for MERS-CoV, including a brief description of the investigation and the objectives of each.

5.1 Case-control studies

Based on the results of initial interviews with cases regarding exposures, risk factors for infection should be further investigated using case-control studies. The purpose of these studies is to determine whether specific exposures occur more frequently in patients infected with MER-CoV (cases), than they do in persons without MER-CoV infection (controls) of the same age and sex in the community during the same time frame. Cases are compared to randomly selected community controls in terms of their recent exposures to other sick individuals, animals, foods and beverages, and other exposures suspected to be the source of infection.

A study protocol has been developed for this purpose and is available at http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/. The specific line of questioning for the study, however, should be guided by initial interviews with the cases.

5.2 Health care exposures

Several outbreaks of MERS associated with health care facilities have been reported. Human-to-human transmission was observed between health care workers who work in the same institution, between patients, between patients and health care workers and between patients and visitors in health care settings. The mode of transmission, types of exposures that result in infection and the effectiveness of specific infection control measures in preventing transmission, however, are unknown. For cases admitted to hospital, studies of health care workers and other patients exposed to confirmed cases can provide some of this information. Ideally, these studies would be done prospectively as soon as MERS-CoV infection is suspected. The study will examine the occurrence of infection in persons exposed to the case in the health care environment, using both molecular diagnostics and serological testing and attempt to associate infection with specific types of

exposures such as the performance of specific procedures, contact (or not) with body fluids, and proximity of exposure. If performed retrospectively using single sera to reflect probable infection, it is necessary to also use a control group, such as unexposed health care workers as diagnosis of acute infection cannot definitively be made from a single serum sample.

Specific information to be gathered during these investigations include:

- Exposures while performing specific procedures on the patient.
- Use of specific personal protective equipment by the health care worker.
- Time of exposures in relation to illness of patient.
- Duration of exposures.
- Exposure to body fluids, secretions, or excretions.
- Occurrence of illness in the health care worker.
- Exposures that may have taken place outside of the work environment as described in the case-control protocol above.

A protocol for investigations in health care workers has been developed by the CONSISE network in collaboration with WHO:

- Assessment of potential risk factors of infection of MERS-CoV among health care personnel in a health care setting (http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/)

5.3 Investigations of close contacts and at risk populations

Two additional seroepidemiologic studies have been developed for MERS to evaluate risk of infection among close contacts:

- Seroepidemiological Investigation of Contacts of MERS Patients (http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/)
- Cross-sectional seroprevalence study of MERS-CoV infection in presumed high risk populations (http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/)

to baseline (same time period in previous years). Any cases currently in the ICU whose illness is not entirely explained should be tested for MERS-CoV;

c. Review of hospital admission records of local hospitals for evidence of recent increases in numbers of pneumonia. As with patients in ICU, any unexplained pneumonia currently in hospital should be tested for MERS-CoV;
d. Review of records of local outpatient treatment clinics for evidence of recent increases in respiratory disease or influenza-like illness;
e. Review of hospital records and vital statistics data for evidence of recent increases in mortality due to pneumonia.

5.5 Seroprevalence studies

With the appearance of a novel pathogen, often only the most severe cases are detected in the beginning. Seroprevalence studies, which measure the prevalence of antibodies against the novel pathogen in specific populations, can be used to compare relative prevalence of previous infections in different populations, with different types of exposures and to also estimate the incidence of infection in a defined period of time. The first will require samples of individuals from different exposure groups such as market workers, farm workers, health care workers, clerks or business people, etc. The types of activities regularly performed by individuals in each group are compared to the seroprevalence of antibodies to MERS-CoV in each group and to the specific activities that they do. This is then analysed to determine the activities with associated risk of MER-CoV infection.

It should be kept in mind that the likelihood that an individual with a single positive serological test has actually been infected will depend on the specificity of the assay being used. A positive test in a single individual may not represent infection because of cross reactivity with antibodies against other types of coronaviruses. However, the relative differences of prevalence between groups of individuals can be associated with exposures to develop a better understanding of important exposures and the relative risk of infection between different groups. Acute and convalescent titres for individuals recently exposed to sources of infection, however, may be used for specific diagnosis if using an assay which has been validated and for