Seroepidemiological investigation of non-health care worker contacts of Middle East respiratory syndrome coronavirus (MERS-CoV) infected patients

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Seroepidemiological investigation of non-health care contacts of Middle East respiratory syndrome coronavirus (MERS-CoV) infected patients

PROTOCOL SUMMARY

A seroepidemiological investigation encompassing a comprehensive assessment of all non-health care worker contacts of confirmed MERS-CoV infected patient, including household, familial, social, and occupational contacts, visitors of confirmed MERS patients and other patients in close proximity to confirmed MERS patients while in hospital, is necessary to determine the extent and spectrum of illness, as well as risk factors associated with infection, to guide efforts for prevention of further human-to-human transmission of MERS-CoV.

This protocol specifically focuses on non-health care contacts and outlines how to find and test all non-health care contacts of laboratory-confirmed MERS-CoV infected patients, and the methods required to assess risk factors for MERS-CoV infection. This investigation will provide data to evaluate some of the key clinical, epidemiological and serologic characteristics of MERS-CoV cases and their contacts to inform national and international public health responses and update guidance to reduce further infection.

Comprehensive investigations of health care personnel who may have been exposed to patients infected with MERS-CoV, diagnosed either prospectively or retrospectively, are described in a separate protocol:

- Assessment of potential risk factors of infection of MERS-CoV among health care personnel in a health care setting

Other MERS-CoV investigation protocols currently available include:

- Cross-sectional seroprevalence study of MERS-CoV infection in presumed high risk populations
- Case-control study to assess potential risk factors related to human illness caused by MERS-CoV

All protocols are available on the WHO website:

COMMENT: In the event of an outbreak of a novel respiratory pathogen, this protocol could be adapted to assess risk factors for infection of the novel respiratory pathogen among contacts of confirmed cases. In this context, the biological specimens, exposure questions and laboratory methods would need to be adapted to reflect the characteristics of the novel respiratory pathogen.

Using a standardized protocol such as the protocol described below, epidemiological exposure data and biological samples can be systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analyzed across many different settings globally. This is particularly important in the context of a rare novel high threat respiratory pathogen.

Comments for the user’s consideration are provided in purple text throughout the document as the user may need to modify methods slightly because of the local context in which this study will be carried out.
DEVELOPMENT OF PROTOCOL

The World Health Organization (WHO), together with technical partners (see Acknowledgements at the end for individual reviewers), was adapted from a protocol developed by the Consortium for the Standardization for Influenza Seroepidemiology (CONSISE), a global partnership aiming to develop influenza investigation protocols and standardize seroepidemiology to inform public health policy for pandemic, zoonotic and seasonal influenza. This international partnership was created out of a need, identified during the 2009 H1N1 pandemic, for better (standardized, validated) seroepidemiological data to estimate infection attack rates and severity of the pandemic virus and to inform policy decisions.

The initial draft of the protocol was released in 2013. This update takes into account recent advances in knowledge of animal-to-human and human-to-human transmission of MERS-CoV, laboratory methods and infection measures to prevent MERS-CoV infection.

More information on the CONSISE network can be found on their website: www(CONSISE.tghn.org

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1.0 SCIENTIFIC BACKGROUND & RATIONALE FOR INVESTIGATION

As of January 2019 more than 2279 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO [1]. Infections have largely been reported from countries across the Arabian Peninsula, with occasional importations and associated clusters in other regions of the world.

MERS-CoV is zoonotic in origin and dromedary camels are the main animal reservoir and the only known source of transmission from animals to humans, although the exact route(s) of transmission remains unclear. The clinical spectrum of MERS-CoV infection ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and other life-threatening complications. Mild symptoms are non-specific and can include headache, tiredness, fever, mild cough, sore throat, and runny nose. Some patients may present with gastrointestinal symptoms such as mild diarrhoea.

While MERS-CoV appears to be inefficient at transmitting between humans in the general community, approximately half of the reported MERS-CoV infections have occurred in health care settings when infection, prevention and control measures have been inadequate. Health care associated human-to-human transmission of MERS-CoV, France, Jordan, the Republic of Health Saudi Arabia, United Arab Emirates, the Republic of Korea and the United Kingdom which has on occasion resulted in significantly large outbreaks [2-6]. Secondary human-to-human transmission has occurred during unprotected contact between patients, from patients to health care workers, and from patients to visitors of the hospital [1-6].

MERS-CoV surveillance initially focused on patients with severe disease, and, as such, the full spectrum of the disease, including the extent of mild or asymptomatic forms of infection is not clear. Since 2015, WHO has updated its guidance for contact tracing, and, as a result, more asymptomatic or mild forms of the disease have been reported [7-11]. However, the extent of infection among contacts in a patient’s family, and other social and non-health care worker groups, and exposures and activities that result in infection in these settings remain unknown. In addition, the role of asymptomatic or subclinical infections in human-to-human transmission of MERS-CoV is not well understood, but there is evidence that laboratory confirmed cases of MERS-CoV infection who are reported as asymptomatic may transmit to other individuals [10].

A comprehensive assessment of known contacts within the household, family, social groups and/or occupational settings, non-health care worker contacts in health care settings (including visitors of confirmed MERS patients and other patients in close proximity to confirmed MERS patients while in hospital) of confirmed MERS-CoV infected individual can help to determine the extent of MERS-CoV infections, identify potential dromedary and non-dromedary source(s) of infection to understand transmission dynamics, and to guide public health prevention and control efforts to reduce human-to-human transmission of MERS-CoV. This investigation will provide data to evaluate some of the key clinical and epidemiological characteristics of cases and their contacts to inform revised national and international policies to reduce the spread of MERS-CoV infection.

This protocol outlines how to 1) identify and test all contacts for MERS-CoV infection using molecular and serologic testing and 2) compare the exposures of infected and non-infected individuals to evaluate risk factors for infection.
COMMENT: Before submission to a local/national Institutional Review Board (IRB) or ethical review committee, the background and rationale will need to be updated with the most recent research findings and further

COMMENT: This protocol focuses on all known non-health care worker contacts of confirmed MERS-CoV infected patient, including household, familial, social, and occupational contacts, visitors of confirmed MERS patients and other patients in close proximity to confirmed MERS patients while in hospital, of a confirmed case of MERS-CoV infection. A separate protocol specifically for assessment of health-care personnel who have been exposed to MERS-CoV infected patients is available on the WHO website:


Current information on the MERS-CoV and interim guidance on contact tracing and infection prevention and control can be found on the WHO website: http://www.who.int/emergencies/mers-cov/en/

1.1 OBJECTIVES

The data collected from this investigation will be used to characterize the key epidemiological transmission features of MERS-CoV virus among known contacts of confirmed MERS-CoV infection to help understand spread, severity, spectrum of disease, and impact on the community and to inform operational models for implementation of countermeasures such as case isolation, contact tracing and quarantine.

1.1.1 PRIMARY OBJECTIVE

The primary objective of this investigation is to:

- Estimate the extent of infection of MERS-CoV among known contacts of confirmed case of MERS-CoV infection.

1.1.2 SECONDARY OBJECTIVES

Seroepidemiologic investigations, such as the one described below, can provide rich data to assess secondary objectives, including, but not limited to:

- Evaluate determinants/risk factors, including sources for infection, among known contacts of confirmed MERS-CoV infected patients
- Describe the spectrum of illness and clinical course of disease among confirmed contacts with evidence of MERS-CoV infection
- Quantify the proportion of individuals in whom seroconversion occurs in areas in which outbreaks of MERS-CoV have not previously been reported, if possible
- Assess the effectiveness of infection prevention and control measures for known contacts of confirmed MERS-CoV infection, if possible

COMMENT: Little is known about the extent of MERS-CoV infection in the general population or about antibody kinetics over time. Only one seroepidemiologic study of MERS-CoV has been conducted to date in the general population. This study, of more than 10 000 people in the general population in Saudi Arabia, found less than 1% of samples collected in 2012 from the population had evidence of seroconversion [12]. Antibody kinetics have been evaluated by a small number of studies. For example, one study conducted on 42 MERS-CoV infected from the outbreak in the Republic of Korea and found
that although all surviving patients were seroconverted, none had detectable antibodies 10 months after infection [13]. These considerations should be accounted for when assessing the ability of the study to capture evidence of seroconversion as a secondary objective of this study.

COMMENT: This protocol addresses risk factors for transmission specifically among known contacts of confirmed MERS-CoV cases. Other protocols available or under development include:

- Assessment of potential risk factors of infection of MERS-CoV among health care personnel in a health care setting
- Cross-sectional seroprevalence study of MERS-CoV infection in presumed high risk populations
- Case-control study to assess potential risk factors related to human illness caused by MERS-CoV

These protocols can be found on the WHO website:

2.0 STUDY PROCEDURES

2.1 STUDY DESIGN

The first stage of this investigation focuses on finding and testing (using molecular and serologic methods) of all non-health care worker contacts of laboratory-confirmed MERS-CoV patients. The cases and contacts identified during this investigation will make up the study population.

The second stage of the investigation is to conduct a nested case-control study among cases with molecular or serologic evidence of MERS-CoV infection and controls (participants with negative serologic results) identified within the study cohort to evaluate risk factors for infection (see 3.2.2).

COMMENT: The timing of this investigation is critical. Ideally, this investigation should be initiated as soon a patient with MERS-CoV (the index case) is identified. Note that it will take 14-21 days for MERS-CoV specific antibodies to develop among contacts, if infected – see 2.5.

2.2 SELECTION OF PARTICIPANTS

For the purposes of monitoring for the appearance of MERS-CoV infection in persons at high risk of infection, it is generally recommended to observe individuals with close physical contact with a confirmed case of MERS-CoV infection for a period of up to 14 days after last contact.

However, the goal of this investigation is different. It is presumed that individuals in the social sphere of the known case of MERS-CoV infection may have had other exposures, similar to those of the case, that could have resulted in primary infection from the source (e.g., contact with dromedary camels). Therefore, the approach used in this study is to identify the larger social sphere of contacts, including those with relatively limited contact with the case but who might have been exposed to the same environment. For example, if the case owns a farm with dromedary camels, all of the workers on the farm should be included in the investigation as contacts, regardless of whether they had close physical contact with the known case.

The same applies for household, family, social groups and/or occupational setting contacts as well as visitors of confirmed MERS patients and other patients in close proximity to confirmed MERS patients while in hospital, irrespective of the degree of direct contact with the known case of MERS-CoV infection. Every effort should be made to include all known contacts within the social sphere of the confirmed case of MERS-CoV infection.

2.3 CASE DEFINITIONS

MERS-CoV case definitions for reporting are provided by WHO and are subject to change as more information becomes available. As of July 2018, the revised case definitions are as follows:

COMMENT: Any further revisions to the MERS-CoV case definitions will be published on the WHO website:
Please consult the website and use the latest WHO Case definitions for MERS-CoV infection.
2.3.1 CONFIRMED CASE

A person with laboratory confirmation (see 2.9) of MERS-CoV infection, irrespective of clinical signs and symptoms.

2.3.2 PROBABLE CASE

Definition 1:

- A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome); and
- Direct epidemiologic link with a laboratory-confirmed MERS-CoV case; and
- Testing for MERS-CoV is unavailable, negative on a single inadequate specimen, or inconclusive

Definition 2:

- A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) that cannot be explained fully by any other etiology; and
- The person resides or travelled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred; and
- Testing for MERS-CoV is inconclusive

Definition 3:

- An acute febrile respiratory illness of any severity; and
- Direct epidemiologic link with a confirmed MERS-CoV case; and
- Testing for MERS-CoV is inconclusive

2.4 CONTACT DEFINITION

For the purposes of this study we will define contacts as higher risk and lower risk contacts.

A higher risk contact is defined as:

- Health care associated exposure, including family members or social contacts (non-health care worker) providing direct care for MERS-CoV patients, visiting patients or staying in the same close environment of a MERS-CoV patient
- Working together in close proximity or sharing the same environment with a with MERS-CoV patient
- Traveling together with MERS-CoV patient in any kind of conveyance
- Living in the same household as a MERS-CoV patient

A lower risk contact is defined as:

- As above without direct contact with a confirmed patient

COMMENT: Identification of contacts should be the first stage of the investigation. Before implementing this investigation, some preliminary investigations will need to be conducted in order
to understand potential social spheres of contacts for each MERS-CoV individual. The nature and number of contacts will likely vary, depending on the context of the situation. Contacts should be grouped according to the social sphere of the case in which they belong, e.g. household, workplace, social group, etc.

COMMENT: For the purposes of this investigation, note that the definition of a contact is different from that used for identifying probable cases of MERS-CoV infection.

Each group of contacts will form a separate, though sometimes overlapping, cohort of contacts. For example, one cohort may include all of the schoolmates who sit in the same classroom as the case if the case is a student, or office colleague of an office worker, even if they have not had recent close contact with the case. Alternatively, if the case owns a farm, or works on a farm, all of the workers on that farm could be included as contacts regardless of whether or not they had close physical contact with the case. The goal is to include a broad range of people with different types of exposures who have been part of the same environments as the case in order to be able to link type of exposure to evidence of infection. A data collection form to help identify all possible contacts is provided in Appendix A.

Comment: If the case occurs in a high risk population, such as a dromedary camel worker, a separate protocol is available on the WHO website:
- Cross-sectional seroepidemiologic study of MERS-CoV infection in high-risk populations in contact with dromedary camels

2.5 ELIGIBILITY CRITERIA

Every effort should be made to include all known contacts of the confirmed of MERS-CoV infection. Contacts of a confirmed case of MERS-CoV infection are defined as all individuals who are associated with some sphere of activity of the case and who may have similar environmental or other exposures as the case. Contacts can include household members, other family contacts, visitors, neighbors, colleagues, teachers, classmates, co-workers, servants, members of a social group, or others, and do not necessarily have to have had direct personal contact with the MERS-CoV infected individual.

Inclusion criteria: All known non-health worker care contacts within the social sphere (household, family, social group and/or occupational setting) of a confirmed MERS-CoV infected individual.

Exclusion criteria: Any contact for whom venipuncture is contraindicated or who is unable to give informed consent.

COMMENT: This protocol is designed to assess the extent of infection among known contacts of confirmed MERS-CoV infection. It does not include health care personnel or staff at health care facility who may have provided care or had contact with a MERS-CoV infected patient at the health care facility. A protocol that looks specifically at risk factors for infection among health care personnel is available on the WHO website:

2.6 CONTACT FOLLOW-UP AND SPECIMEN COLLECTION

After potential participants have been identified and listed from the social sphere of a confirmed MERS-CoV infection, informed consent from all participants will be obtained (see 2.8.1). Details of the contacts will be kept in a line list by the investigation team (see Appendix A). At the time of recruitment, and if identified within 14 days of last exposures of a patient, combined nasopharyngeal and oropharyngeal swabs will be collected from all participants for molecular testing, a blood sample from all contacts for serology will be collected 14-21 days after first contact and a questionnaire will be administered to all participants (Appendix B).

Table 1: Type and timing of specimen collection for MERS-CoV investigation of known contacts of a confirmed MERS-CoV infected patient

<table>
<thead>
<tr>
<th>Specimen collection</th>
<th>Timing of collection</th>
<th>References for methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal and oropharyngeal swabs</td>
<td>Sample collection within 14 days from last contact with MERS-CoV patient / point of exposure</td>
<td>MERS-CoV RT-PCR assay on RNA [14]</td>
</tr>
<tr>
<td>Single serum sample</td>
<td>Sample collection &gt;14-21 days from last contact with MERS-CoV patient / point of exposure</td>
<td>Laboratory confirmation methods [15-19]</td>
</tr>
<tr>
<td>Paired serum (from same individual)</td>
<td>Sample collection:</td>
<td>Paired serum guidance [20]</td>
</tr>
<tr>
<td></td>
<td>• First sample: as soon as possible after contact with MERS-CoV patient / point of exposure</td>
<td>Antibody kinetics [13,21]</td>
</tr>
<tr>
<td></td>
<td>• Second sample: ≥21 days after first sample</td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>Administer questionnaire at the point of data collection. If paired sample collection, two questionnaires should be administered</td>
<td>See Appendix B</td>
</tr>
</tbody>
</table>

COMMENT: The recommended clinical specimens are subject to change as more is learned about MERS-CoV infection. Further revisions to clinical specimens to collect will be published on the WHO website: http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-surveillance/en/ Please consult the website and use the latest WHO recommendations for clinical specimen collection for MERS-CoV infection.

All contacts will be monitored daily for symptoms for 14 days after last contact with the confirmed MERS-CoV infected patient / point of last exposure. The collection of a blood sample will be repeated at least 21 days after the first specimen collection for all participants.
COMMENT: Little is currently known about MERS-CoV antibody kinetics, and the implementation of this investigation provides the opportunity to further understanding of antibody kinetics, depending on feasibility.

Paired samples are preferred but single samples are also of value. If only one specimen (single serum sample) can be taken from all contacts, this should be conducted at least 14 days after the last contact with the confirmed MERS-CoV infected patient / point of last exposure, see Table 1. Note that with a single sample, time of infection cannot be determined.

Ideally, two specimens (paired samples) should be taken: one at baseline as soon as the participant has been identified as a contact, and then again at least 14-21 days later, see Table 1. Further investigations could consider sera collection of all recruited subjects at baseline, 2 week, 4 week and 6 week intervals, including for the confirmed case, if feasible.

If symptoms (particularly fever and/or respiratory symptoms) are reported by any contact during the follow-up period, virological testing will be carried out immediately on additional nasopharyngeal and oropharyngeal swabs and, ideally, on specimens taken from the lower respiratory tract (e.g., sputum, aspirate, lavage, as appropriate), if possible, to increase the likelihood of detecting MERS-CoV.

Any contact who shows molecular or serologic evidence of MERS-CoV infection as defined by WHO [22] will be re-classified as a confirmed case of MERS-CoV infection and reported as such to WHO under the International Health Regulations (2005). Each newly confirmed case of MERS-CoV infection will initiate a new contact investigation as outlined above.

2.7 SPECIMEN TRANSPORTATION

All those involved in collection and transporting specimens should be trained in safe handling practices and spill decontamination procedures. Guidance documents on infection control are available at http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/.

When collecting nasopharyngeal and oropharyngeal specimens, swabs specifically designed for collecting specimens for virology must be used. These swab kits should contain virus transport medium. The nasopharyngeal and oropharyngeal swabs should be placed in the same tube to increase the viral load.

For each biological sample collected, the time of collection, the conditions for transportation and the time of arrival at the study laboratory will be recorded. Specimens should reach the laboratory as soon as possible after collection. If the specimen is not likely to reach the laboratory within 72 hours, specimens should be frozen, preferably at -80°C, and shipped on dry ice. It is, however, important to avoid repeated freezing and thawing of specimens. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations. Serum should be separated from whole blood and can be stored and shipped at 4°C or frozen to -20°C or lower and shipped on dry ice.

COMMENT: You may consider that specimens will be aliquoted so that specimens remain in country and only aliquots are sent to a reference lab. Some serologic assays may become available to be done in country.

WHO laboratory guidance on specimen collection and transportation in full can be found at:


### 2.8 DEMOGRAPHIC AND EXPOSURE DATA COLLECTION

At the time of recruitment, a brief questionnaire will be administered to those contacts who have provided written, informed consent. Data to be collected include: age, gender, location, interaction with confirmed MERS-CoV infection, occupation, signs and symptoms, and underlying medical conditions. In addition, further questions will evaluate risk factors for MERS-CoV infection, including frequency and pattern of known exposures or risk factors for infection. A sample questionnaire has been provided in Appendix B and should be administered to all cases and all contacts each time specimens are collected. However, this will need to be adapted based on the local setting, and outbreak characteristics. It will also need to be pilot tested in a small group of participants and revised before being administered to all participants.

### 2.9 ETHICAL CONSIDERATIONS

Ethical approval must be sought in accordance with local, regional and national authorities prior to the implementation of this protocol.

COMMENT: While this generic approval has not been submitted for ethical approval, it has been reviewed by many technical partners and the use and adaptation of a generic protocol, such as this one, to the current outbreak setting may minimize delays to the start of investigations.

#### 2.9.1 INFORMED CONSENT

The purpose of the investigation will be explained to all known contacts of a confirmed MERS-CoV infected patient. Informed consent will be obtained from all cases and contacts willing to participate in the investigation before any procedure is performed as part of the investigation by a trained member of the investigation team. Consent for children under the age of 18 years old will be obtained from a parent or legal guardian. Verbal assent will also be obtained for children under 17 years old. Each participant must be informed that participation in the investigation is voluntary and that s/he is free to withdraw, without justification, from the investigation at any time without consequences and without affecting professional responsibilities.

COMMENT: The age of consent and assent may vary by country. Check the requirements of local, regional or national authorities.

Informed consent will seek approval to collect blood, combined nasopharyngeal and oropharyngeal swabs and possibly lower respiratory tract specimens for the intended purpose of this investigation, that samples may be shipped outside of the home country for additional testing and that samples may be used for future research purposes. Informed consent will also indicate that any suspected or confirmed MERS-CoV infection may be notified to the national health authorities under the requirements of the International Health Regulations (2005).
2.9.2 RISKS AND BENEFITS FOR SUBJECTS

This investigation poses minimal risk to participants, involving the collection of a small amount of blood and upper (and lower) respiratory tract specimens. The direct benefit to the participant is the possibility for early detection of MERS-CoV infection which would allow for appropriate monitoring and treatment. The primary benefit of the study is indirect in that data collected will help improve and guide efforts to understand transmission of MERS-CoV and prevent further spread of MERS-CoV.

2.9.3 CONFIDENTIALITY

Participant confidentiality will be maintained throughout the investigation. All subjects who participate in the investigation will be assigned a study identification number by the investigation team for the labeling of questionnaires and clinical specimens. The link of this identification number to individuals will be maintained by the investigation team and the Ministry of Health (or equivalent) and will not be disclosed elsewhere.

COMMENT: If the data is shared by the implementing organization to WHO or any agency or institution providing support for data analysis, data shared will include only the study identification number and not any personally identifiable information.

2.9.4 PREVENTION OF MERS-CoV INFECTION IN INVESTIGATION PERSONNEL

Before the start of the investigation, all personnel involved in the investigation will be provided training in infection prevention and control procedures (standard contact, droplet or airborne precautions, as determined by national or local guidelines). These procedures should include proper hand hygiene and the correct use of surgical or respiratory face masks, if necessary, not only to minimize their own risk of infection when in close contact with MERS-CoV infected patients, but also to minimize the risk of spread among contacts of MERS-CoV infected patients.

WHO technical guidance on infection prevention and control specific to MERS-CoV can be found here: http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/

2.10 LABORATORY EVALUATIONS

As of January 2018, a MERS-CoV case may be laboratory confirmed by molecular testing or by serology.

WHO case definitions for MERS-CoV can be found here:


COMMENT: The following laboratory recommendations are subject to further updates as diagnostic tests and approaches become available.

2.10.1 MOLECULAR TESTING

As of July 2018, laboratory-confirmation of MERS-CoV infection requires one of the following conditions:

- positive RT-PCR or other validated molecular assays for at least two different specific targets on the MERS-CoV genome; OR
• one positive RT-PCR assay for a specific target on the MERS-CoV genome and an additional different PCR product sequenced, confirming identity to known sequences of the new virus.

A positive PCR assay for a single specific target without further testing is considered presumptive evidence of MERS-CoV infection. Final classification of cases will depend on clinical and epidemiological information, combined with laboratory data.

WHO Member States are required to immediately notify WHO of any confirmed case of MERS-CoV infection, under the International Health Regulations (2005).

2.10.2 SEROLOGIC TESTING

For serologic testing, it is advised that serum samples are collected from contacts as early as possible after the date of contact with a confirmed MERS-CoV infection and that a second serum sample is collected 2–3 weeks after the last contact. Sera may be tested by a screening serologic test (ELISA or IFA) and any positive screening results need confirmation with neutralization tests. In the event that a participant reports fever and/or respiratory symptoms, lower respiratory tract specimens should also be collected for nucleic acid amplification test (NAAT) testing (see section 2.3).

A number of different technical approaches for confirming MERS-CoV infection using serology have been developed. Details of two immunofluorescence assays to detect antibodies to MERS-CoV have been published [14], and these assays, along with a serum neutralization test, were used in a 2 to 3 stage procedure to screen contacts of a case in Germany and determine population seroprevalence in Saudi Arabia [15,16].

Other approaches include detecting MERS-CoV antibodies using protein microarray technology [17] and a two-stage approach with a screening test using a recombinant nucleocapsid (N) and spike (S) protein-based indirect enzyme-linked immunosorbent (ELISA), followed by a confirmatory microneutralization [18]. Details of a neutralization test based on retroviral pseudoparticles which demonstrates high levels of specificity to MERS-CoV have been published [19].

COMMENT: A limited number of laboratories have the facilities for MERS-CoV serologic testing and therefore collaboration between countries without current capacity and designated reference laboratories is encouraged. Collaboration is up to the discretion of Member States carrying out the investigation, but WHO is able to facilitate this collaboration and possible shipment for testing, if required.

COMMENT: At present, it is not clear if asymptomatic contacts with evidence of seroconversion to MERS-CoV, without molecular evidence of infection, are able to infect others.
3.0 INVESTIGATION ENDPOINT & STATISTICAL ANALYSES

The following section discusses sample size considerations, study endpoints – that is, what can be measured and calculated using the data collected in this study – and the statistical analyses that should be performed to answer the study questions.

3.1 SAMPLE SIZE CONSIDERATIONS

The study-specific sample size will be determined by the number of contacts within each social sphere of the confirmed MERS-CoV infected individual and by assumptions related to secondary MERS-CoV transmission. Every effort should be made to include all contacts of the confirmed MERS-CoV infected individual to maximize the statistical power of the investigation.

3.2 OUTCOME MEASURES

3.2.1 PRIMARY ENDPOINTS

The primary objective of this investigation is to estimate the extent of infection of MERS-CoV among known contacts of confirmed MERS-CoV infection. The primary endpoints will therefore be:

- Virological infection: % of all known contacts of a confirmed MERS-CoV infection included in the investigation who are RT-PCR positive for MERS-CoV
- Immunological infection: % of all known contacts of a confirmed MERS-CoV infection included in the investigation who are seropositive for MERS-CoV

COMMENT: Depending on the sample size of the investigation, these proportions may be reported as overall infection rates or by subgroup (e.g. by social sphere of the MERS-CoV infected individual, by age, gender, etc.).

3.2.2 RISK FACTORS FOR INFECTION

The second stage of the investigation is to conduct a nested case-control study among cases (participants with molecular or serology positive results) and controls (participants with negative serology results) identified within the study cohort to evaluate risk factors for infection (see 3.2.2).

The data collected on exposures (e.g. characteristics, behaviors, practices) of cases and controls can then be compared to identify risk factors for infection. These comparisons should be done using appropriate statistical tests. For example, bivariate associations between risk factors for infection should be determined by chi-square statistics or 2-sided Fisher’s exact test and expressed as odds ratios with 95% confidence intervals. Multivariate logistic regression should be used to further analyze the associations if the sample size permits.

COMMENT: Univariate statistical analysis by logistic regression could be used to test the significance of each predictor on the outcome of infection. Multivariate logistic regression can be used to identify independent risk factors (after adjusting for known or potential confounders) or a combination of risk factors associated with the odds of infection.

COMMENT: Alternatively, Mantel-Haenszel matched-pair analysis (McNemar test) can be used to estimate the strength and statistical significance of associations between exposures and infection.
3.2.3 ATTACK RATES

The attack rate is defined as the proportion of a well-defined population that develops infection over a particular period of time. Attack rates that may be estimated include: clinical illness attack rates, infection attack rates, attack rate among children, secondary attack rates. Infection attack rates use are based on the results of serologic testing. The secondary attack rate is a measure of the frequency of new cases of an illness among the contacts of known index cases in a defined period of time.

COMMENT: It may be very difficult to distinguish common exposure from secondary transmission.

3.2.3 AGE-SPECIFIC INFECTION RATES

The seroprevalence of MERS-CoV antibodies (P) to the MERS-CoV virus can be determined for overall and if sample size allows, by each age group, or contact type (e.g. household, occupational, social or familial contacts) using MERS-CoV serologic results, as follows:

\[ P_{\text{MERS-CoV serologic confirmation}} = \left( \frac{\text{number of cases that test seropositive}}{\text{sample size of study population [all contacts recruited and tested]}} \right) \times 100 \]

COMMENT: You will not be able to extrapolate the seropositive rate of the study population to the general population as the contacts cannot be assumed to be a representative sample of the general population.

3.2.4 CLINICAL PRESENTATION AND COURSE OF DISEASE

The proportion of symptoms of participants with evidence of infection (molecular testing, see 2.9.1 and/or positive serology results, see 2.9.2) should be calculated and the clinical presentation and course of disease described. The proportions of mild illness and severe illness (hospitalization/ICU/death) should also be reported.

3.2.5 PROPORTION OF ASYMPTOMATIC/ SUB-CLINICAL INFECTIONS

Participants found to have serologic evidence of MERS-CoV infection (see 3.2.2) who do not recall having any symptoms (asymptomatic) or who recall having symptoms that did not require medical consultation (sub-clinical) should be classified as MERS-CoV infections and reported as such to WHO.

The asymptomatic infection proportion = (number of contacts who tested seropositive and had no history of symptoms ÷ total number of contacts testing seropositive)
4.0 REPORTING OF FINDINGS

Reports of the results of this investigation should include the number of contacts recruited and tested and the number of confirmed MERS-CoV infections among contacts, or the number of contacts with serologic evidence of MERS-CoV infection, including the proportion of asymptomatic or sub-clinical infections.

It is also important to fully document the study design, including recruitment methods, eligibility criteria, techniques for determining MERS-CoV infection and the outcome measurements, in order to assist the interpretation of the findings.

COMMENT: The timely dissemination of the results of this study are critical to understanding the transmission of MERS-CoV, in order to update guidance and inform national and international public health responses and infection prevention and control policies.

4.1 COMPLIMENTARY STUDIES

Although not described as part of this investigation, we recommended that in conjunction with this outbreak investigation of familial, social and occupational contacts, environmental sampling, including testing of areas around the infected household, farms, markets and potential contaminated water sources, and retrospective and prospective animal mortality investigations should supplement these activities in collaboration with relevant parties, particularly if the objective includes identifying a zoonotic source of infection among index cases or contacts of the index case.
REFERENCES


ACKNOWLEDGMENTS

We thank the many people who were involved in the creation and revision of this protocol. These include: Maria D Van Kerkhove, Mamun Malik, Amgad Elkholy, Anthony W Mounts, Sergey Eremin, Cota Vallenas, Julia Fitzner, Tim Uyeki, John Wood, Othmar Engelhardt, Jeffery Cutter, Salah Al Awaidi, Susan I Gerber, Pasi Penttinen, Julien Baute and Elizabeth Bancroft, Rebecca Grant and Amy Dighe.
APPENDIX A: LINE LIST OF ALL KNOWN CONTACTS OF CONFIRMED CASES OF MERS-CoV INFECTION

<table>
<thead>
<tr>
<th>Contact ID</th>
<th>Initials</th>
<th>Age</th>
<th>Sex M/F</th>
<th>Location</th>
<th>Place of contact</th>
<th>Date of first questionnaire administration</th>
<th>Date of first specimen collection</th>
<th>Symptoms at first specimen collection</th>
<th>Date of second questionnaire administration</th>
<th>Date of second specimen collection</th>
<th>Symptoms at second specimen collection</th>
<th>Date of follow-up completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Household contacts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Higher risk contacts</td>
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<td>Lower risk contacts</td>
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<tr>
<td><strong>Family contacts</strong></td>
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<td>Higher risk contacts</td>
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<td>Lower risk contacts</td>
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<td><strong>Social contacts</strong></td>
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<td>Higher risk contacts</td>
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<tr>
<td>Lower risk contacts</td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>Occupational contacts</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher risk contacts</td>
<td></td>
</tr>
<tr>
<td>Lower risk contacts</td>
<td></td>
</tr>
</tbody>
</table>

* Include all individuals within the larger social sphere of contacts, including those with relatively limited contact with the case, but who might have been exposed to the same environment.

COMMENT: Add additional categories of contacts or additional lines per category of contacts or as needed.
APPENDIX B: QUESTIONNAIRE ON FREQUENCY AND PATTERN OF EXPOSURE OF KNOWN CONTACTS OF A MERS-CoV INFECTED PATIENT

This questionnaire is designed to gather information about the frequency and patterns of exposure among all known contacts of a confirmed MERS-CoV infection.

This is intended to allow health authorities and public health researchers to better understand potential exposures that may lead to infection among contacts of a confirmed MERS-CoV infection and to develop hypotheses to test in subsequent investigations.

It should be completed by all cases and by all individuals within the larger social sphere of contacts, including those with relatively limited contact with the case, but who might have been exposed to the same environment.

The administration of this questionnaire should be repeated each time biological specimens are collected as part of this investigation.

The time period for questions on exposures should be:

- 14 days before symptom onset for confirmed MERS-CoV infection
- Same 14 day period for all known contacts of a confirmed MERS-CoV infected patient

COMMENT: The questionnaire needs to be modified for the context of the specific study by the researchers carrying out the investigation.

COMMENT: If a contact becomes symptomatic and/or tests positive for acute MERS-CoV infection, the questionnaire should be re-administered to the individual reclassifying him or her as a case, and to all of his or her contacts covering the 14 day period before symptom onset or positive laboratory result if no symptoms are reported.

If you have any questions, please contact:

Name of study investigator: ________________________________

Telephone: ________________________________

COMMENT: Once the questionnaire has been finalized, skip patterns should be added.

Section A: General demographic questions
The following section is a series of general demographic and confirmation as case or contact of a MERS-CoV infected patient.

A.1. Participant name (First name/ Surname): ________________________________

A.2. Investigation identification number: ________________________________

A.3 Name of interviewer: ________________________________

A.4. Date of interview (DD/MM/YYYY): ___/___/_____

A.5. Place of interview: ________________________________
A.6. Gender

☐ Male         ☐ Female

A.7. Age: _______ years

A.8. Date of birth (DD/MM/YYYY): ___/____/______

A.9. Current marital status:

☐ Single       ☐ Married       ☐ Divorced       ☐ Widowed

A.10 In your household (defined as sharing a single kitchen)

A.10.1 How many adults aged 18 years or above live in your household? __________________________

A.10.2 How many children aged under 18 years live in your household? __________________________

A.11 MERS-CoV case or known contact of MERS-CoV infected patient

☐ Confirmed case ☐ Probable case ☐ Contact

A.11.1: Type of contact of MERS-CoV infected patient

☐ Household       ☐ Family

☐ Social         ☐ Occupational

☐ Other, please specify: ________________________________________________________________

Section B: Respiratory symptoms or illness

The following series of questions are focused whether you have had any signs and symptoms of respiratory illness during the last 14 days and if so, details about the medical care you received.

B1. Are you sick today with fever and/or cough?

☐ Yes          ☐ No

B2. Have you experienced any respiratory symptoms or signs of illness during the last 14 days?

☐ Yes          ☐ No          ☐ Unknown

B3. If you answered yes to either B1 or B2, please indicate which symptoms:

<table>
<thead>
<tr>
<th></th>
<th>Today</th>
<th></th>
<th>Last 14 days</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>B3.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry cough</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>B3.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Productive cough</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>B3.3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Phlegm</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>B3.4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Runny nose</td>
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<tr>
<td>B3.5</td>
<td></td>
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<tr>
<td>Sore throat</td>
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<tr>
<td>B3.6</td>
<td></td>
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<tr>
<td>Fever</td>
<td></td>
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<tr>
<td>B3.7</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
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</tbody>
</table>
B3.8 Muscle pain □ □ □ □ □ □ 
B3.9 Diarrhea □ □ □ □ □ □ 
B3.10 Chest Pain □ □ □ □ □ □ 
B3.11 Vomiting □ □ □ □ □ □ 
B3.12 Rashes □ □ □ □ □ □ 

B4. Have you sought/did you seek medical consultation?
☐ Yes  ☐ No  ☐ Unknown

B4.1 If yes, where did you seek medical care (Name and address of medical facility/outpatient center)? ____________________________

B5. Have you been hospitalized during the course of your illness?
☐ Yes  ☐ No  ☐ Unknown

B5.1 If yes, when were you hospitalized (DD/MM/YYYY): ___/___/______

B5.2 If yes, which hospital did you receive treatment(s)? (Name and address of medical facility)
_________________________________________________________

Section C: Medical history

The following series of questions are focused on your health status and current or previous medical conditions.

C1. Do you currently smoke tobacco (ex. cigarettes, cigars, shisha)?
☐ Daily  ☐ A few days a week  ☐ Not at all  ☐ Unknown

C2. Do you share your tobacco (e.g., shisha)?
☐ Yes  ☐ No  ☐ Unknown

C3. Have you smoked tobacco daily in the past?
☐ Yes  ☐ No  ☐ Unknown

C4. Is there any hereditary disease running in your family?
☐ Yes  ☐ No  ☐ Unknown

C4.1 If yes, please specify the disease(s):
________________________________________________________

C5. Do you currently have any chronic illness (e.g. asthma, cancer, diabetes)?
☐ Yes  ☐ No  ☐ Unknown

C5.1. If yes, please specify the disease(s):
________________________________________________________

C6. Have you taken medications regularly in the last six months?
☐ Yes  ☐ No  ☐ Unknown

C6.1 If yes, what medications do you regularly take?
List all: ________________________________

C7. Have you taken any traditional medications in the last six months?
C7. If yes, which traditional medications?
List all: __________________________________________________________

C8. Have you seen a traditional healer in the last six months?
☐ Yes ☐ No ☐ Unknown

C9. If female, were you pregnant in the last six months?
☐ Yes ☐ No ☐ Unknown

Section D: Recent travel history
The following series of questions are focused places you have travelled within the 14 days before the onset of illness (case) or within the last 14 days after last contact with a MERS-CoV patient (contact) and the contact with animals you may have had during these travels.

D1. During the last 14 days have you travelled outside (insert country where investigation is being conducted)?
☐ Yes ☐ No

D1.1 If yes, what countries/regions have you visited?

<table>
<thead>
<tr>
<th>Country</th>
<th>Region/City</th>
<th>Approximate dates</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

D2. Have you attended any mass gatherings (e.g., weddings, festivals or religious pilgrimages) where there were large numbers of people together within the 14 days before the onset of illness (case) or within the last 14 days after last contact with a MERS-CoV patient (contact)?
☐ Yes ☐ No ☐ Unknown

D2.1 If yes, specify event(s) and location:
__________________________________________________________________________________

D3. When you travelled, did you do any of the following?

<table>
<thead>
<tr>
<th>Tick all that apply:</th>
<th>Location of the farm (town, country)</th>
<th>Animals present at venue</th>
<th>Did you have direct contact with any of these animals?</th>
<th>Did you have any direct contact with any animal carcasses, body fluids, secretions, urine or excrement while at this venue?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit a farm with animals</td>
<td>☐</td>
<td>☐ Camel ☐ Goat ☐ Sheep ☐ Horse ☐ Cattle</td>
<td>☐ Yes ☐ No ☐ Unknown</td>
<td>☐ Yes ☐ No ☐ Unknown</td>
</tr>
<tr>
<td>Visit an animal market</td>
<td>☐</td>
<td>☐ Camel ☐ Goat ☐ Sheep</td>
<td>☐ Yes ☐ No ☐ Unknown</td>
<td>☐ Yes ☐ No ☐ No</td>
</tr>
</tbody>
</table>
Section E: Human exposures

The following series of questions are focused on contact you have had with anyone with respiratory illness or diarrhea within the 14 days after the onset of illness (case) or within 14 days after the last contact with the MERS-CoV infected patient (contact). Modify as appropriate.

E1. Have you had contact with anyone with a respiratory illness or diarrhoea within the 14 days before the onset of illness in the MERS-CoV infected patient (case) or within the 14 days after last contact with a MERS-CoV patient (contact)?

- □ Yes  □ No  □ Unknown

E1.1. If yes, what was your relationship to the person?

- □ Close family  □ Extended family  □ Friend  □ Other ____________

E1.2. If yes, when did this person become ill (DD/MM/YYYY)? ____________

E1.3. Did you have close physical contact with this person while they were ill?

Close physical contact: touching the infected person, providing care, sharing same living space or meals etc.

- □ Yes  □ No  □ Unknown

E1.4 If yes, please describe the nature of the contact: __________________________

E1.5. If the person was hospitalized, did you visit him or her at the health care facility?

- □ Yes  □ No

E1.6. If yes, at what hospital (name, region, city, district)

________________________________________________________________________

E1.7. If yes, was he or she on a ventilator at the time?

- □ Yes  □ No  □ Unknown
Section F: Dromedary camel exposures in/around the home where you live

The following series of questions are focused on exposures to dromedary camels in and around the home or place of residence.

F1. Have you had any dromedary camels in or around your home in the last six months?

- Yes
- No
- Unknown

F1.1 Indicate the number of dromedary camels and what they are used for

<table>
<thead>
<tr>
<th>Number of camels</th>
<th>What they used for?</th>
<th>Did you have direct contact (i.e., touch) with these camels?</th>
<th>Any illness affecting camels in the last six months?</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 animals</td>
<td></td>
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<td></td>
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<tr>
<td>≥ 10 animals</td>
<td>income</td>
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<tr>
<td></td>
<td>food</td>
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<td>racing</td>
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<td>pets</td>
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<td>□ Yes</td>
<td>□ Yes</td>
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<td>□ No</td>
<td>□ No</td>
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<tr>
<td></td>
<td></td>
<td>□ Unknown</td>
<td>□ Unknown</td>
</tr>
</tbody>
</table>

F2. In the last six months, did you have any contact with any carcasses, body fluids, secretions, urine or excrement of camels in or around your home?

- Yes
- No
- Unknown

F3. In the last six months, did you have any contact with any camel bedding, stray of feed in or around your home?

- Yes
- No
- Unknown

F4. At your home, in the last six months did you do any of the following activities:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4.1 Feed camels</td>
<td></td>
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<tr>
<td>F4.2 Clean camel housing</td>
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<tr>
<td>F4.3 Slaughter camels</td>
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<tr>
<td>F4.4 Assist with the birth of camels</td>
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<tr>
<td>F4.5 Milk camels</td>
<td></td>
<td></td>
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<tr>
<td>F4.6 Kiss/hug camels</td>
<td></td>
<td></td>
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<tr>
<td>F4.7 Other tasks related to camels</td>
<td>Specify:</td>
<td></td>
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</tr>
</tbody>
</table>

F5. Do others living in your household (e.g., domestic help or relative) frequently visit or work on a farm or market where camels are kept or sold?

- Yes
- No
- Unknown

F5.1 Have others living in your household (e.g. domestic help or relative) visited or worked at a farm or market where camels are kept or sold within the 14 days before the onset of illness (case) or within the last 14 days after last contact with a MERS-CoV patient (contact)?

- Yes
- No
- Unknown

F5.2 Have others living in your household (e.g. domestic help or relative) had direct contact with camels within the 14 days before the onset of illness (case) or within the last 14 days after last contact with a MERS-CoV patient (contact)?

- Yes
- No
- Unknown
Section G: Food medicinal exposures

The following series of questions are focused on regular food exposures and consumption of camel or camel products for medicinal or therapeutic reasons.

G1. Do you regularly eat camel meat or consume other camel products (e.g., milk, urine)?
☐ Yes ☐ No

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1.1 Do you regularly drink raw camel milk?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G1.2 Do you regularly drink boiled camel milk?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G1.3 Do you regularly drink camel urine?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G1.4 Do you regularly eat raw camel meat?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G1.5 Do you regularly eat cooked camel meat?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

G2. Do you believe that camels or camel products have medicinal or therapeutic properties?
☐ Yes ☐ No ☐ Not sure

G3. Do you use camel products for medicinal purposes?
☐ Yes ☐ No

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3.1 Do you drink camel milk for medicinal or therapeutic purposes?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G3.2 Do you drink camel urine for medicinal purposes?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>G3.3 Do you receive or use any traditional medications that contain camel products?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

G4. What illnesses or medical conditions are you treating with camel or camel related products?

________________________________________________________________________

H: Contact

H1. May we contact you again with follow up questions or clarifications?
☐ Yes ☐ No ☐ Unknown

H1.1 If yes, telephone number of participant:

________________________________________________________

Thank you very much for participating in this study.

The information you have provided will help to assess the risk of MERS-CoV infection among contacts of confirmed MERS-CoV infection. It will also help to understand the full extent of infection and transmission of MERS-CoV, which in turn can assist efforts to reduce the further spread of MERS-CoV.