

# Seroepidemiological Investigation of Contacts of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Patients

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## PROTOCOL SUMMARY

A cohort study design encompassing a comprehensive assessment of all contacts of confirmed and probable MERS-CoV cases, including household, familial, social, occupational and health care-associated contacts, is necessary to determine the spectrum of illness and risk factors associated with infection, routes and risk of transmission, and to guide efforts for prevention of transmission of the MERS-CoV virus. This protocol outlines 1) how to find and test all contacts of laboratory-confirmed and probable MERS-CoV patients, and 2) methods to assess risk factors for MERS-CoV infection.

Health care personnel contacts can be investigated using a different protocol (see WHO website: [http://www.who.int/csr/disease/coronavirus\\_infections/en/](http://www.who.int/csr/disease/coronavirus_infections/en/)).

This investigation will provide data to evaluate some of the key clinical, epidemiological and serological characteristics of MERS-CoV cases and their contacts to inform national and international policy, and improve guidance to reduce the spread of infection. This investigation will also provide data to evaluate risk factors for infection.

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.

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## 1.0 SCIENTIFIC BACKGROUND AND RATIONALE

As of 3 October 2013, more than 139 laboratory-confirmed cases of human infection with novel coronavirus (MERS-CoV) have been reported to WHO[1]. It is suspected that MERS-CoV is a zoonotic virus, but information on exposures is limited and an animal reservoir is still unknown. Limited human-to-human transmission has occurred in several clusters in health-care facilities, households and in one work setting [1-6]. At this stage, however, as surveillance targets patients with severe disease, the total spectrum of disease and proportion of infections that may be mild or asymptomatic is unclear. In addition, the attack rate in family, and other social groups, and exposures and activities that result in infection in these settings is unknown.

A comprehensive assessment of known contacts – household, familial, social and occupational – of confirmed and probable MERS-CoV cases can help to determine the extent of MERS-CoV infections, identify potential viral source(s), 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 the development of national and international policy to reduce the spread of MERS-CoV infection. This protocol outlines how to 1) identify and test ALL contacts (not limited to close contacts) for MERS-CoV infection using virologic and serologic testing and 2) provides methods to compare the exposures of infected and non-infected individuals to evaluate risk factors for infection.

A separate protocol specifically for assessment of health-care personnel is available on the WHO MERS-CoV website.

## 1.1 OBJECTIVES

The data collected from this study will be used to characterize the key epidemiological transmission features of MERS-CoV virus, 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.

The primary objectives of this study are to:

- Estimate frequency of MERS-CoV infections (as measured by virologic and serologic tests) in relation to human and other exposures (i.e. evaluate determinants/risk factors [including sources] for infection) among contacts of confirmed MERS-CoV cases
- Evaluate (modifiable) risk factors (e.g. exposures, behaviours, practices) for human MERS-CoV infection
- Evaluate the extent of MERS-CoV transmission among contacts of confirmed and probable MERS-CoV patients
- Describe the presentation and clinical course of disease with MERS-CoV infection

- Quantify the proportion of asymptomatic/sub-clinical MERS-CoV infections

COMMENT: Comprehensive study investigations such as the one described below can provide rich data to assess a number of secondary outcomes. Many other secondary objectives can be investigated in terms of epidemiological, immunological, clinical, virological, economic, genetic, behavioural, environmental, and animal factors associated with risk of MERS-CoV infection or outcome of infection. These are not discussed in detail in this protocol.

## 2.0 STUDY PROCEDURES

### 2.1 STUDY METHODOLOGY

The first stage of this investigation focuses on finding and testing (virologically and serologically) all contacts of laboratory-confirmed MERS-CoV patients. The cases and contacts identified during this investigation will make up the study cohort. The second stage of the study will be to conduct a nested case-control study among cases (virologically and serologically positive study subjects) and controls (serologically negative study subjects) found within your study cohort to evaluate risk factors for infection.

Note that for the purposes of monitoring for the appearance of disease in persons at very high risk of infection, it is generally recommended to observe individuals with very close physical contact with a case for a period of up to 14 days after exposure. However, the goal of this study is different. Therefore, for the purposes of this study, it is presumed that individuals in the social sphere of the known case may have had other exposures, similar to those of the case, that could have resulted in primary infection from the source. Therefore, the approach used in this study is to follow 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, all of the workers on the farm should be included for study as “contacts” regardless of whether they had close physical contact with the known case. One might also include office colleagues, classmates, persons belonging to a social group that the case attends, etc., as additional cohorts of contacts, regardless of the degree of contact with the known case.

### 2.2 ETHICAL CONSIDERATIONS

Ethical approval will be sought in accordance with local, regional and national authorities.

COMMENT: It is strongly recommended that ethical approval be obtained in advance from relevant ethical or institutional review boards (e.g. national Ministries of Health, Agriculture, etc.) using a generic protocol such as this one before an outbreak occurs. Once an outbreak occurs, the study design, questionnaires, sampling and consent forms can be modified rapidly to the actual situation. This may still have to be resubmitted for ethical approval, but as the generic protocol including this final step has already been approved, this could be a very rapid process, without substantial delay to the start of the investigations.

## 2.3 STUDY POPULATION: CASE AND CONTACT DEFINITIONS

### 2.3.1 CASE DEFINITIONS

Case definitions for reporting are provided by WHO and are subject to change as more information becomes available. On 3 July 2013 revised case definitions were published by WHO.

COMMENT: Check for the most recent case definition at [http://www.who.int/csr/disease/coronavirus\\_infections/case\\_definition/en/index.html](http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html).

#### 2.3.1.1 PROBABLE CASE

COMMENT: The definition of a probable case may vary depending on the volume of cases in the local population. Currently, the definition of a probable case is narrow and intended to maximize contact tracing of laboratory-confirmed cases. During the course of the study, it is possible that the definition of a probable case will change.

As of 3 July, three combinations of clinical, epidemiological and laboratory criteria can define a probable case:

- A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome)  
**AND**  
Testing for MERS-CoV is unavailable or negative on a single inadequate specimen<sup>1</sup>  
**AND**  
The patient has a direct epidemiologic-link with a confirmed MERS-CoV case<sup>2</sup>.
- A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome)  
**AND**  
An inconclusive MERS-CoV laboratory test (that is, a positive screening test without confirmation)<sup>3</sup>  
**AND**  
A resident of, or traveller to Middle Eastern countries where MERS-CoV virus is believed to be circulating in the 14 days before onset of illness.
- A person with an acute febrile respiratory illness of any severity  
**AND**  
An inconclusive MERS-CoV laboratory test (that is, a positive screening test without confirmation)<sup>3</sup>  
**AND**  
The patient has a direct epidemiologic-link with a confirmed MERS-CoV case.<sup>2</sup>

## Notes

<sup>1</sup>An inadequate specimen would include a nasopharyngeal swab without an accompanying lower respiratory specimen, a specimen that has had improper handling, is judged to be of poor quality by the testing laboratory, or was taken too late in the course of illness.

<sup>2</sup>A direct epidemiological link may include:

- Close physical contact
- Working together in close proximity or sharing the same classroom environment
- Traveling together in any kind of conveyance
- Living in the same household
- The epidemiological link may have occurred within a 14-day period before or after the onset of illness in the case under consideration.

<sup>3</sup>Inconclusive tests may include:

- A positive screening test without further confirmation, such as testing positive on a single PCR target
- A serological assay considered positive by the testing laboratory.

<sup>4</sup>Currently, confirmatory testing requires molecular diagnostics, including either a positive PCR on at least two specific genomic targets or a single positive target with sequencing on a second. However, the interim recommendations for laboratory testing for MERS-CoV should be consulted for the most recent standard for laboratory confirmation

([http://www.who.int/csr/disease/coronavirus\\_infections/en/](http://www.who.int/csr/disease/coronavirus_infections/en/)). See also notes on asymptomatic cases in this document.

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### 2.3.1.2 CONFIRMED CASE

The most recent case definitions are available from WHO at

[http://www.who.int/csr/disease/coronavirus\\_infections/case\\_definition/en/index.html](http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html).

A confirmed case of MERS-CoV is a person with laboratory confirmation of infection with MERS-CoV, either through direct detection of the virus (by viral isolation) or viral RNA (by molecular methods such as RT-PCR) in clinical specimens.

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### 2.3.2 CONTACTS OF A CONFIRMED HUMAN MERS-COV CASE

The first stage of this investigation will be to identify all contacts of confirmed and probable MERS-CoV patients.

For the purposes of this study, contacts of a confirmed or probable human MERS-CoV case 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, neighbours, colleagues, teachers, classmates, co-workers, servants, members of a social group, or others, and do not have to have had close personal contact with the case. 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.

COMMENT: Identification of contacts should be the first stage of your investigation.

COMMENT: The user of this protocol will need to undertake some preliminary investigations to understand who could be a potential contact of the case(s). The nature and number of contacts will depend 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, farm, etc.

COMMENT: The definition of a contact for the purposes of this study is different from contacts as defined for identifying probable cases.

COMMENT: Health-care personnel exposed to the case should be investigated using a separate protocol. See WHO MERS-CoV HCP Protocol on the WHO coronavirus website: [http://www.who.int/csr/disease/coronavirus\\_infections/en/](http://www.who.int/csr/disease/coronavirus_infections/en/)

## 2.4 RECRUITMENT AND FOLLOW-UP OF CASES AND CONTACTS

### 2.4.1 SUBJECT RECRUITMENT AND DATA COLLECTION

#### 2.4.1.1 RECRUITMENT OF SUBJECTS

Primary study subjects are all contacts of a confirmed MERS-CoV case who are associated with some sphere of activity of the case. All cases and contacts identified in this study will compose the study population cohort.

All efforts will be made to identify the contact cohort at the initial recruitment, including infants and children, to generate the sampling frame for follow up. Details of the contacts will be kept in a line list by the investigation team (Appendix A). At the time of recruitment, combined nasal and throat swabs for virologic confirmation if individuals are symptomatic, blood for serologic testing, and exposure data will be collected (see Questionnaire in Appendix B). The recommended clinical specimens may change in the future as more information is learned about the optimal specimens and appropriate timing after exposure to detect MERS-CoV infection.

Active follow-up of all contacts will take place ideally through daily face-to-face or telephone interview as soon as possible after identification of a confirmed case to ask about the possible development of illness. Contacts will be monitored daily for 30 days after the onset of illness in the case. A baseline blood sample will be taken at time of first interview and sent to a reference laboratory.

Any contact who is symptomatic (fever and cough) at initial visit or by the end of the study period should be tested virologically according to current standards for laboratory confirmation of MERS-CoV. A second “convalescent” serum sample should be collected from all subjects at least 14-21 days after an acute baseline sample is collected.

All contacts found to have evidence of MERS-CoV infection will be re-classified as confirmed cases and reported as such to WHO. Each newly confirmed MERS-CoV case will initiate a new contact investigation as outlined above.

COMMENT: If feasible, consider serial sera collection of all recruited subjects at baseline, 2-week, 4-week or 6-week intervals, including for the confirmed case. This will allow study of antibody kinetics in infected individuals.

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#### 2.4.2 INFORMED CONSENT

During the site visit, the purpose of the study will be explained to all eligible subjects (all contacts) and their consent obtained by a trained member of the investigation team. Consent for children under the age of 18 years old will be obtained from their parents or guardians. Verbal assent will also be obtained for children under 17 years old.

COMMENT: The age of consent and assent may vary by country. Check with local IRB requirements.

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#### 2.4.3 DATA COLLECTION

After enrolment and informed consent, a standardized baseline data set will be collected with any specimens for MERS-CoV testing (and date of specimen collection). Baseline data to be collected include: age, gender, location, relationship to confirmed case-patient, occupation, signs and symptoms, and underlying conditions. In addition, detailed questions will be asked to evaluate risk factors for human infection with MERS-CoV (Appendix B). These are included in the data collection form in Appendix B under the section for “exposures” and include specific aspects of timing, frequency and duration of exposure(s). The questionnaire should be administered each time sera are collected. The study questionnaire for the use of all cases and contacts can be found in Appendix B.

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#### 2.4.4 PREVENTION OF MERS-COV TRANSMISSION IN FRONT-LINE STAFF

Before study implementation, front-line staff, including all study personnel, will be trained in infection control procedures (standard, contact, droplet or airborne precautions), including 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 patients during home visits and elsewhere, but also to minimize the risk of staff becoming a vector of MERS-CoV transmission between subjects or households.

## 2.5 SPECIMEN COLLECTION AND LABORATORY EVALUATIONS

### 2.5.1 SPECIMEN COLLECTION, TRANSPORTATION

There is now increasing evidence that lower respiratory tract specimens such as bronchoalveolar lavage, sputum and tracheal aspirates contain the highest viral loads and these should be collected when possible. However, published case series also demonstrate the importance of upper respiratory tract specimens such as nasopharyngeal/oropharyngeal swabs for detecting the virus. It is recommended that both upper and lower respiratory tract specimens be collected whenever possible.

To increase the likelihood of detecting the virus, multiple samples from multiple sites should be collected over the course of the illness. Even after the initial detection of the virus, continued sampling and testing will add to current knowledge about the duration of virus shedding and is strongly encouraged. Virus has been detected in blood, urine and faeces but at levels below those found in the lower respiratory tract.

Serum samples should be collected. Paired samples are preferred but single samples are also of value. Paired serum samples should be collected 14-21 days apart, with the first being taken during the first week of illness. If only a single sample is to be collected, it should be done at least 14 days after onset of symptoms.

Specimens should reach the laboratory as soon as possible after collection. The importance of proper handling during transportation cannot be overemphasized. When there is likely to be a delay in the laboratory receiving respiratory tract specimens, it is strongly recommended that the specimens be frozen, preferably to -80°C, and shipped on dry ice. It is, however, important to avoid repeated freezing and thawing of specimens. 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. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations.

Transport of specimens within national borders should comply with applicable national regulations. International transport of MERS-CoV specimens should follow applicable international regulations as described in the WHO Guidance on Regulations for the Transport of Infectious Substances 2013-2014 available at: [http://www.who.int/ihr/publications/who\\_hse\\_ihr\\_20100801/en/index.html](http://www.who.int/ihr/publications/who_hse_ihr_20100801/en/index.html).

Additional records should be kept for each biological sample, including the time of collection, the conditions for transportation, personnel involved in collection and transport, and the time of arrival at the study laboratory.

**COMMENT:** You may consider that specimens will be aliquotted 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.

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## 2.5.2 LABORATORY PROCEDURES

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### 2.5.2.1 VIROLOGIC TESTING

MERS-CoV case definitions are described above and can be found at:

[http://www.who.int/csr/disease/coronavirus\\_infections/case\\_definition/en/index.html](http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html)

As of 6 June, to consider a case as laboratory-confirmed, one of the following conditions must be met:

- 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. Member States are requested to immediately notify WHO of any confirmed or probable case.

Full details for virologic laboratory testing of MERS-CoV can be found here:

[http://www.who.int/csr/disease/coronavirus\\_infections/LaboratoryTestingNovelCoronavirus\\_21Dec12.pdf](http://www.who.int/csr/disease/coronavirus_infections/LaboratoryTestingNovelCoronavirus_21Dec12.pdf).

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### 2.5.2.2 SEROLOGIC METHODS

COMMENT: Several serological assays are currently available, having been developed by different laboratories using different platforms, including fluorescent antibodies, enzyme-linked immunosorbent assays, luciferase immunoprecipitation systems, and virus neutralisation. The assays each have advantages and disadvantages but appear to have similar utility. Until their interoperability and comparability are better understood, more than one assay should be performed for each serum sample. An algorithm will be needed to decide the combinations of results considered “positive” for the purpose of comparative analysis.

COMMENT: Only 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 possible. Collaboration is at the discretion of Member States carrying out the investigation, but WHO strongly supports such collaboration and would willingly facilitate collaboration and possible shipment elsewhere for testing.

## 3.0 STUDY ENDPOINTS AND STATISTICAL ANALYSES

The following section discusses the endpoints – that is, what will be measured and calculated using the data that are collected in this study – for the primary objectives, including statistical advice.

### 3.1 STUDY OUTCOME MEASURES

#### 3.1.1 PRIMARY OUTCOMES

The following will be assessed as study endpoints corresponding to the study's primary objectives:

1. Evaluate source(s), risk exposures, and (modifiable) risk factors for human infection with MERS-CoV
2. Estimate the age-specific frequency of MERS-CoV infection (as measured by virologic and serologic tests) in relation to human and other exposures
3. Describe the full spectrum of clinical disease associated with MERS-CoV infection
4. Quantify proportion of asymptomatic/sub-clinical; mild illness; and severe illness (hospitalization/ICU/death) with MERS-CoV infection.

### 3.2 STATISTICAL ANALYSES

#### 3.2.1 FOR PRIMARY OBJECTIVE 1

##### RISK FACTORS FOR HUMAN INFECTION

One way to measure risk factors for infection is to compare the characteristics and exposures (behaviours and practices) of infected individuals (i.e. laboratory-confirmed and sero-positive individuals) versus non-infected (i.e. sero-negative contacts).

**To assess risk factors for transmission:** To evaluate human-to-human transmission, a comparison of human exposures of infected (seropositive and laboratory-confirmed patients) vs non-infected (seronegative contacts) will be made.

The reported practices among cases and (possibly matched, see above) contacts should be compared using appropriate statistical tests, e.g. bivariate associations between risk factors and (asymptomatic) infection will be determined by chi-square statistics or 2-sided Fisher's exact test and expressed as odds ratios with 95% confidence intervals. Multivariable logistic regression will be used to further analyse the associations.

**COMMENT:** Univariate statistical analysis by use of logistic regression for a case-control study could be used to test the significance of each predictor on the outcome of infection. Multivariable logistic regression can be used to identify 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. If matched analysis is to be performed, variables to be assessed as risk factors will have to be identified in the beginning of the study so these variables can be used as matching variables.

#### ATTACK RATES

The attack rate is defined as the proportion of a well-defined population that develops illness (e.g. signs and symptoms) over a particular period of time.

List all forms of attack rates that may be estimated: clinical illness attack rates, infection attack rates, attack rate among children, subject type, etc., secondary attack rates.

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. *Note that it may be very difficult to distinguish common exposure from secondary transmission.*

One may also calculate infection attack rate (IFR) using serologic results and can calculate attack rates by subject type (e.g. household contacts, occupational contacts) or by age, location (e.g. school, workplace, institutional setting [military, long-term care facility, etc.]).

#### 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:

$$P \text{ MERS-CoV}_{\text{serologic confirmation}} = \frac{\text{(number of cases that test seropositive/ sample size of study population [all contacts recruited and tested])} \times 100\%}{1}$$

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.

#### CLINICAL PRESENTATION AND COURSE OF DISEASE

The proportion of symptoms of subjects with evidence of infection (individuals with virologic confirmation per WHO guidelines or serologic positive results) should be calculated.

#### QUANTIFY PROPORTION OF ASYMPTOMATIC/SUB-CLINICAL INFECTION

Individuals in the study survey found to have serological evidence of acute MERS-CoV infection who do not recall having any defined symptoms during the period of the investigation period will be counted as probable asymptomatic infections. The lowest limit of asymptomatic infections is:

The asymptomatic infection proportion =  $\frac{\text{number of contacts who tested seropositive and had no history of symptoms}}{\text{total number of contacts testing seropositive}}$

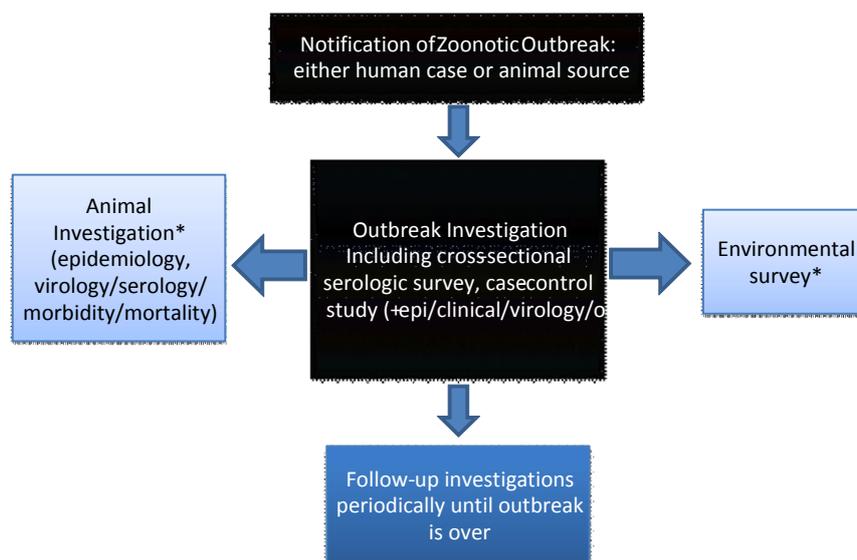
#### 4.0 REPORTING OF FINDINGS

##### 4.1 REPORTING OF FINDINGS

Any deviations from the study methodologies should also be reported to aid in the interpretation of findings.

#### 5.0 COMPLEMENTARY STUDIES

Although not described as part of this investigation, we recommended that in conjunction with this outbreak investigation of familial, social and HCP 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 (Figure 1), particularly if the objective includes identifying a zoonotic source of infection among index cases or contacts of the index case.



**Figure 1. Study Design of Potential Related Activities**

\*in collaboration with relevant bodies/parties

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## REFERENCES

1. WHO, World Health Organization. *Global Alert and Response. Coronavirus Infections*. Available at: [http://www.who.int/csr/disease/coronavirus\\_infections/en/](http://www.who.int/csr/disease/coronavirus_infections/en/). Last accessed 30 July 2013, 2012-2013.
2. Assiri, A., et al., *Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus*. *New England Journal of Medicine*, 2013. **2013 Jun 19**. [Epub ahead of print].
3. Guery, B., et al., *Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission*. *The Lancet*, 2013.
4. Hijawi, B., et al., *Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation*. *Eastern Mediterranean Health Journal*, 2013. **19**(Supplement 1): p. S12-S18.
5. Memish, Z.A., et al., *Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections*. *NEJM*, 2013. **Published 29 May 2013**: p. DOI: 10.1056/NEJMoa1303729.
6. Pebody, R.G., et al., *The United Kingdom public health response to an imported laboratory confirmed case of a novel coronavirus in September 2012*. *Euro Surveill*, 2012. **17**(40): p. pii=20292. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20292>



APPENDIX B DATA COLLECTION FORM

## Questionnaire for Seroepidemiological Investigation of Contacts of MERS-CoV patients

The following questionnaire should be used for all cases and contacts included in the above investigation. This questionnaire is separated into sections: **General Questions, Background Medical History, Exposure (e.g. Travel History, Human, Animal, and Food) Questions**. We encourage the user to keep these sections in the recommended order and to add additional exposure questions that are relevant to your cultures, situation, contexts, and understanding of the situation in your country.

Each subject should be allocated a unique identification number.

COMMENT: Once the questionnaire is finalized, full instructions and skip patterns should be added. Comments throughout the questionnaire are highlighted in purple.

COMMENT: Note that adding multiple choice answers will allow for easier data analysis.

COMMENT: The time period of exposures should be 14 days before symptom onset for cases AND should be the same 14-day period for contacts. If a contact becomes symptomatic and tests positive by PCR, the questionnaire should be re-administered to cover the 14-day period just before symptom onset.

### SECTION 1 GENERAL QUESTIONS

Patient name (First/Given): \_\_\_\_\_ (Last/Family) \_\_\_\_\_

Case identification number: \_\_\_\_\_

Residence (City, Province): \_\_\_\_\_

Subject is a (circle one): Confirmed case Probable case contact

If contact, for which case is the subject a contact (provide identification number of case): \_\_\_\_\_

Person answering questions is: subject relative (specify relationship: \_\_\_\_ ) acquaintance

Sex (circle one): Male Female

Date of interview (dd/mm/yyyy): \_\_\_\_/\_\_\_\_/\_\_\_\_

Place of interview (city, province): \_\_\_\_\_

Language used for interview: \_\_\_\_\_

Name of interviewer: \_\_\_\_\_

Institution of interviewer: \_\_\_\_\_

#### 1. General questions

1.1. What is your full name: \_\_\_\_\_

1.2. Place of primary residence (address): \_\_\_\_\_

1.2.1. Do you have homes elsewhere? Y/N

- 1.2.2. If yes, please specify where:
- 1.3. Date of birth: \_\_\_/\_\_\_/\_\_\_\_ (dd/mm/yyyy)
- 1.4. Occupation: \_\_\_\_\_
- 1.4.1. Describe work-related duties: \_\_\_\_\_
- 1.4.2. Where is the work done (city): \_\_\_\_\_
- 1.4.3. How many hours per week:
- 1.4.4. Does work involve animal contact? (If yes, describe: \_\_\_\_\_)
- 1.5. What is your highest level of education? (add multiple choice)
- 1.6. Do you own a car?
- 1.7. What is your approximate household income level (provide ranges and circle best fit)?

### **Personal living situation**

- 1.8. What is your current marital status? (single, married, living with a partner, other)
- 1.9. How many people live in your household with you (one household is defined as sharing a single kitchen)?
- 1.9.1. Children under age 18: \_\_\_\_\_
- 1.9.2. Adults over age 18 years: \_\_\_\_\_
- 1.10. Do you have servants?
- If yes,
- 1.10.1. how many?
- 1.10.2. what kind of service do they provide? Please specify
- 1.10.3. do they live in your house?
- 1.10.4. what nationality are they?
- 1.11. What type of dwelling do you live in?
- Apartment detached house other (please specify: \_\_\_\_\_)
- 1.11.1. Do you have air-conditioning in your house?
- 1.11.2. What is the size of your family living space (square meters):

## **SECTION 2 BACKGROUND MEDICAL HISTORY**

The following questions are addressing your background medical history and other background questions.

### **2. Health**

- 2.1. Do you currently smoke cigarettes: yes no
- 2.1.1. If yes, what do you smoke (circle all that apply)? cigarettes ,HOOKAH, NARGHILE, SHEESHA

- 2.1.2. If yes, for how many years?
- 2.1.3. If yes, how many cigarettes (or other) per day do you smoke?
- 2.2. Did you previously smoke?
- 2.2.1. If yes, for how many years?
- 2.2.2. If yes, what did you smoke? \_\_\_\_\_
- 2.2.3. If yes, how many cigarettes (or other) per day did you used to smoke?
- 2.3. Do you consume alcoholic beverages?
- 2.3.1. if yes: how much and what beverage?: Daily/weekly/monthly?
- 2.4. Is there any hereditary disease running in your family? yes no unknown  
If yes, please specify: \_\_\_\_\_
- 2.5. List any underlying chronic diseases you might have:
- Diabetes: yes no unknown  
If yes, insulin used: yes no unknown
- Emphysema, chronic bronchitis or other chronic lung disease besides asthma: yes no unknown  
If yes, are medications used for treatment? Yes no (if yes, specify: \_\_\_\_\_)
- Asthma: yes no unknown  
If yes, which of the following have been used for treatment in the last month  
(circle all that apply):
- |                   |                                  |
|-------------------|----------------------------------|
| Handheld Inhalers | Oral medications to open airways |
| oral steroids     | Home nebulizer treatment         |
| other (specify):  |                                  |
- Kidney failure: yes no unknown  
If yes, is dialysis needed? Yes no unknown
- Chronic liver disease such as hepatitis: yes no unknown
- Heart disease: yes no unknown  
If yes, please specify
- Deficient immune system? Yes no unknown  
If yes, describe specific condition: \_\_\_\_\_
- History of cancer treatment in the last year? yes no unknown  
If yes, please give name of cancer and time of last treatment: \_\_\_\_\_
- Hematological disorder such as chronic anemia? Yes no unknown  
If yes, describe specific condition: \_\_\_\_\_

- 2.6. Do you have any known allergies (list): \_\_\_\_\_
- 2.7. What medications do you regularly take?: \_\_\_\_\_
- 2.8. What medications do you sporadically take?: \_\_\_\_\_
- 2.9. If female, are you pregnant? Yes no unknown  
If yes, how many weeks?
- 2.10. If female, have you recently had a baby? Yes no unknown  
If yes, date of delivery (dd/mm/yyyy): \_\_\_/\_\_\_/\_\_\_

### SECTION 3 EXPOSURE QUESTIONS

COMMENT: Exposure history should be focused on a specified time period before the symptom onset of the MERS-CoV case. If the subject is a case, then exposure should be focused 14 days before symptom onset. If the subject is a contact, the time frame should be approximately the same as that for the case – the 14 days before onset of illness in the case. If a contact develops a symptomatic illness and tests positive for MERS-CoV, that is, becomes a confirmed case, the questionnaire should be re-administered covering the 14-day period before illness onset.

#### RECENT TRAVEL HISTORY

The following questions relate to travel within the 14 days before the illness of the case and the animals encountered during these travels.

##### Recent Travel History

- 3.1. List the areas to which you have travelled in the last 14 days before the illness of the case.
- 3.1.1. Town name and country:  
3.1.1.1. Dates Travelled: \_\_\_\_\_ to \_\_\_\_\_
- 3.1.2. Town name and country:  
3.1.2.1. Dates Travelled: \_\_\_\_\_ to \_\_\_\_\_
- 3.1.3. Town name and country:  
3.1.3.1. Dates Travelled: \_\_\_\_\_ to \_\_\_\_\_
- 3.1.4. Have you attended any recent festivals or pilgrimages? Yes no  
3.1.4.1. If yes, specify event and location: \_\_\_\_\_

#### HUMAN EXPOSURES

3.2. Have you had contact within the 14 days before the illness of the case with a person who had a respiratory illness or diarrhoea?

Yes No Unknown

If yes,

- 3.2.1. What was the approximate date when the other person became ill?:

(dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_

- 3.2.2. Did you sleep in the same room as the ill person during their illness? Yes no Unknown
- 3.2.2.1. if yes, how many nights during the last 14:
- 3.2.3. Did you travel in the same vehicle as the ill person during their illness? Yes no Unknown
- 3.2.3.1. if yes, how many hours roughly)? <1hr 1-3hr 3-5hr >5hr
- 3.2.4. Did you have close physical contact (touching the infected person, providing care during their illness) of any kind with the case-patient during their illness?
- 3.2.4.1. If so, please describe nature of contact: \_\_\_\_\_
- 3.2.5. Did you have contact with any body fluids such as urine, blood, sputum, or faeces? Yes no Unknown
- 3.2.5.1. If yes, please specify type of fluid and date: \_\_\_\_\_;  
(dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_
- 3.2.6. Did you eat meals with the ill person during their illness?
- 3.2.6.1. If yes, did you generally eat the same food as the sick person?
- 3.2.7. Did you visit or care for the sick person while he or she was in hospital? Yes no Unknown
- 3.2.7.1. If yes, was he or she on a ventilator at the time? Yes no Unknown
- 3.2.8. Did the person to whom you were exposed have primarily a respiratory-type illness (e.g. coughing and/or sneezing) or an intestinal-type illness (e.g. vomiting and/or diarrhoea)? Respiratory Intestinal
- 3.2.9. Was or is the other person with the illness proven or strongly suspected to have infection with the novel coronavirus? Yes no Unknown
- 3.3. Have you in the 14 days before your illness before **the illness of the case**:
- 3.3.1. been a patient in hospital? Yes no Unknown
- if Yes, Name and address of Hospital: \_\_\_\_\_
- date of visit (dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_
- 3.3.2. been treated in an outpatient facility for any illness? Yes no Unknown
- if Yes, Name and address of outpatient facility: \_\_\_\_\_
- date of visit (dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_
- 3.3.3. \_visited a traditional healer? Yes no Unknown
- if Yes, Name and address of traditional healer: \_\_\_\_\_
- date of visit (dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_
- 3.3.4. attended a funeral? Yes no Unknown

if Yes, Name of person that was buried: \_\_\_\_\_

date of funerals (dd/mm/yyyy)? \_\_\_/\_\_\_/\_\_\_

## ANIMAL EXPOSURES

The following questions address **animal exposures** during the 14-day period before **the illness of the case**.

### 3.4. Animal contact

- 3.4.1. Were any animals or birds, including pets, food-producing animals, work animals or hunting animals (including falcons), kept in or around your home during this period?  
3.4.1.1. If yes, what kind and how many? \_\_\_\_\_
- 3.4.2. Were you aware of any other animals present in or outside around your house during this time (e.g. bats, rodents, stray cats/dogs, foxes, reptiles)? \_\_\_\_\_
- 3.4.3. Did you notice any animal faeces or urine in or outside around your home during this time? Yes no Unknown
- 3.4.4. Are there regularly wild birds in and around the house? Yes no Unknown
- 3.4.5. Did you have physical contact (touch) with domestic animals (e.g. cattle, goat, sheep, camels, poultry, pigs) or wild animals? Yes no Unknown  
3.4.5.1. If yes, what kind of animal(s) \_\_\_\_\_  
3.4.5.2. Where did the contact occur (location and type of venue)? \_\_\_\_\_
- 3.4.6. Did you visit a market selling live animals? Yes no Unknown  
3.4.6.1. If yes, what kinds of animals were sold there? \_\_\_\_\_
- 3.4.7. Did you visit any other venue at which live animals were present (e.g. farm, camel race or falconry events)? Yes no Unknown
- 3.4.8. If you answered yes to 3.3.6 or 3.3.7, please provide dates for each visit (dd/mm/yyyy):  
3.4.8.1. Venue: \_\_\_\_\_, date visited (dd/mm/yyyy) \_\_\_/\_\_\_/\_\_\_  
3.4.8.2. Venue: \_\_\_\_\_, date visited (dd/mm/yyyy) \_\_\_/\_\_\_/\_\_\_
- 3.4.9. Did you eat or drink anything while there? If yes, please specify:
- 3.4.10. Did you have direct contact with animals while there?
- 3.4.11. Did you touch any items such as fences, textiles, machinery, clothing, or other physical objects that may have had contact with animals on the farm? Yes no Unknown  
3.4.11.1. If yes, please specify \_\_\_\_\_
- 3.4.12. Did you have contact with any carcasses, body fluids, secretions, urine or excrement of animals on the farm while there? Yes no Unknown
- 3.4.13. Have you personally participated in the slaughter or ritual sacrifice of an animal?

Yes no Unknown

3.4.13.1. If yes, name type of animal(s) and give dates:

3.4.13.2. \_\_\_\_\_; (dd/mm/yyyy)\_\_\_/\_\_\_/\_\_\_

3.4.13.3. \_\_\_\_\_; (dd/mm/yyyy)\_\_\_/\_\_\_/\_\_\_

## FOOD EXPOSURES

### 3.4. The following series of questions are focused on food exposures in the 14 days before the case's symptom onset.

3.4.1. In the 14 days before **the case's symptom onset** did you eat any of the following food items raw, that is, uncooked? Answer Yes no Unknown

3.4.1.1. fresh fruits, if yes, specify type: \_\_\_\_\_

3.4.1.2. dried fruits, if yes, specify type: \_\_\_\_\_

3.4.1.3. vegetable, if yes, specify type: \_\_\_\_\_

3.4.1.4. salads, if yes, specify type: \_\_\_\_\_

3.4.1.5. other? Please specify \_\_\_\_\_

3.4.2. Did you drink fresh (i.e. not canned or processed) fruit or vegetable juices? Yes no Unknown

3.4.2.1. If yes, please specify juice type: \_\_\_\_\_

3.4.3. Did you eat any uncooked or partially cooked meat or eggs?

3.4.3.1. If yes, specify type of food consumed: \_\_\_\_\_

3.4.3.2. If yes, specify body part consumed (e.g., flesh, blood, etc.): \_\_\_\_\_

3.4.4. Have you personally cooked or otherwise handled raw meat in preparation for a meal?

3.4.4.1. If yes, specify type of meat: \_\_\_\_\_

3.4.5. Did you drink any unpasteurized milk? Yes no Unknown

3.4.5.1. If yes, specify from what kind of animal: \_\_\_\_\_