

Case-control study to assess potential risk factors related to human illness caused by Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Version 2

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This document was adapted from a protocol developed by the Consortium for the Standardization for Influenza Seroepidemiology (CONWISE), 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. More information on the CONWISE network can be found on their website: www.CONWISE.tghn.org.

PROTOCOL SUMMARY

This investigation will provide data to evaluate exposures and risk factors for human cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) to determine those that are related to infection. This protocol outlines a case-control study and the epidemiological methods to guide data collection to assess risk factors for illness caused by MERS coronavirus (MERS-CoV) infection. Health care personnel and the evaluation of other contacts are addressed in a separate protocol.

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 RATIONNALE

The novel Coronavirus now known as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first detected in a patient living in Saudi Arabia in September of 2012. Since that time, sporadic cases, small clusters, and in large outbreaks have been reported in several countries. While the source of the virus is currently unknown, it is thought to originate in animals. Human-to-human transmission has also been documented on multiple occasions. Although finding the putative animal reservoir is an important step in controlling spread of the virus, a more immediate need is to understand the route and mode of transmission to humans, and the types of exposures that result in infection. Several possibilities exist, including direct contact with an infected animal, which could be either the reservoir species or an intermediate host species; contact with or consumption of unprocessed animal products; contact with the environment where an infected animal has recently been; or consumption of a food or beverage which has been contaminated by animal excreta. All of these have been implicated in other zoonotic infections. Learning the mode of transmission to humans will allow measures to be taken to interrupt transmission. This investigation will provide data to evaluate risk factors for infection by reviewing exposures of known cases and comparing them to rates of exposure in similar uninfected individuals in the general population.

Current information on the MERS-CoV and cases can be found on the WHO website: http://www.who.int/csr/disease/coronavirus_infections/en/index.html.

A separate protocol is available specifically for assessment of exposed Health Care Personnel and contacts of cases (see <http://consise.tghn.org/articles/novel-coronavirus-MERS-CoV/>).

1.1 OBJECTIVES

The data collected from this study will be used to refine/update recommendations for surveillance and case definitions, to characterize the key epidemiological transmission features of MERS-CoV virus, help understand spread, severity, spectrum of disease, impact on the community and to inform operational models for implementation of countermeasures such as case isolation, contact tracing and quarantine.

The primary objective of this study is to:

- Identify modifiable non-human exposures that lead to human MERS-CoV infection

2.0 STUDY PROCEDURES

2.1 METHODOLOGY

The study uses a case-control design that examines the differences in types of exposures between symptomatic individuals with laboratory confirmed MERS-CoV infection and healthy controls in order to determine the risk associated with that exposure. A standard questionnaire has been provided in this protocol (Appendix A), however, the study must begin with less structured interviews of confirmed cases (or their proxies if unable to respond due to critical illness or death) in order to develop hypotheses about the possible exposures. Once these hypotheses have been developed, they can be tested through this case control study. For example, many of the cases might report that they ate a fruit such as dates in the week before they became ill. However, many people in the region eat dates frequently. The purpose of

the case control study is to determine if a case was more likely to have eaten dates in the 14 days before he became ill than a similar uninfected person in the community.

Ideally, this study should be done prospectively, enrolling new cases as they are identified and selection controls at the same time. However, it will be necessary to do the study retrospectively for many of the cases as they occurred some time ago. For retrospective cases the period of interest is still the 14 days before the onset of their illness however as the controls have not been sick, the same 14 day period can be used if the elapsed time is short enough to allow sufficient recall. Controls should be chosen at random from the area of residence of the cases and of the same age and sex as the cases.

2.2 STUDY POPULATION

Study subjects will include only index cases who have been classified as probable cases or confirmed according to the current WHO case definitions (see section 2.4.2 below). If the case is part of a cluster, only the case which is thought to be the “index case” or first person infected in the cluster will be included. This will exclude cases for whom the transmission may have occurred from exposure to the index case (i.e. human-to-human transmission). While there are many questions about the mode of transmission and risk factors for human-to-human transmission, the primary purpose of this study is to determine the *non-human* source of infection, such as exposures to animals or contaminated food products. As many of the known cases have occurred as part of clusters in which human-to-human transmission is suspected to have occurred, it will be important to identify the *index* case in the cluster to include in the study. The index case, who presumably had a non-human exposure as his or her source of infection, should be included as a study participant regardless of whether he/she is laboratory confirmed or classified as probable on the basis of exposure and clinical data as defined in the current case definitions.

2.2.1 CASE DEFINITIONS

Case definitions for reporting are provided by WHO and are subject to change as more information becomes available.¹

CONFIRMED CASE

A confirmed case of MERS-CoV is a person with laboratory confirmation of infection with MERS-CoV.

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/).

COMMENT: The demonstration of asymptomatic infection is useful for epidemiological investigations and should be pursued as part of case investigations, however, the burden of proof

¹ WHO Case Definitions for nCoV:

http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html

must be higher due to the risk misclassification because of false positive tests due to laboratory contamination. Generally, in most viral infections, an immunological response such as development of specific antibodies would be expected even with mild or asymptomatic infection and as such serological testing may be useful as additional confirmation of the diagnosis. Additional steps to reconfirm asymptomatic cases, or any case in which the diagnosis is suspect, could include re-extraction of RNA from the original clinical specimen and testing for different virus target genes, ideally in an independent lab.

Probable Case

Three combinations of clinical, epidemiological and laboratory criteria can define a probable case:

1. 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 specimen²

AND

The patient has a direct epidemiologic-link with a confirmed MERS-CoV case³.

2. 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)⁴.

AND

A resident of or traveler to Middle Eastern countries where MERS-CoV virus is believed to be circulating in the 14 days before onset of illness.

3. 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).

² 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.

³ 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

⁴ 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.

AND

The patient has a direct epidemiologic-link with a confirmed MERS-CoV case

2.3 SUBJECT RECRUITMENT

2.3.1 SUBJECT RECRUITMENT AND DATA COLLECTION

RECRUITMENT OF CASES

Primary study subjects are laboratory confirmed cases of MERS-CoV infection. If cases are part of a cluster, only the index case – that is, the case with the earliest date of onset of illness – should be included in the analysis. (note, it may be useful to collect the same data from all of the cases in the cluster as there are a number of other questions that may be studied but for the purposes of this study, only the index case will be included.)

As stated above, probable cases should generally not be included in the analysis as they by definition are cases with exposure to known cases and as such are part of a cluster in which MERS-CoV transmission may have occurred from person to person. The one exception may be if during an interview with a confirmed case, it is discovered that a contact, such as another family member, would meet the definition for probable case AND that the probable case occurred earlier, making him or her the likely index case.

COMMENT: In some clusters, more than one index case may appear simultaneously (co-primary/co-index cases) and it is possible to tease out the transmission dynamics and identify the index case; another option for preliminary analysis is to exclude these clusters.

RECRUITMENT OF CONTROLS

To understand how rates of exposures to potential sources of infection differ between cases and uninfected individuals, it is necessary to recruit age and sex matched control subjects who live in approximately the same neighborhood as the case. Controls should be randomly selected as described below and asked for their consent to participate in the study.

To maximize the power to show differences in exposures, it may be desirable to recruit as many as four controls for each case.

Controls should be of the same sex as their respective case and from the same general area where the case lives.

Age matching can be done within a range that depends on the age of the case for which the control is being selected, as outlined below:

Age of case	Age range of control
< 5 y.o.	Within ± 1 year of age
5 to 18 y.o.	Within ± 3 years of age
≥ 18 y.o.	Within ± 5 years of age

COMMENT: Currently, circulation of this virus in the community is thought to be nonexistent or minimal at most and the numbers of infections low. For that reason, prospective controls who have not had recent respiratory illness can be enrolled without laboratory confirmation of the absence of MERS-CoV infection. However, if the situation changes in the future, it will be necessary to exclude controls from the study who are determined to have had MERS-CoV infection through serological testing.

RANDOM SELECTION OF CONTROLS

Controls will be selected randomly. There are several ways to do this, the simplest is the most direct – to go to the area where the case lives and select them directly through a random selection process on site. Once arriving at the home of the case, select the closest dwelling to the case home. If a decision is needed about the closest dwelling, for example if there are two dwellings on either side equal distance from the case home, decide the direction by a coin toss. When arriving at the home, inquire about the members of the household to determine if any residents would meet the requirements for a control in terms of matching the case in age and sex. If multiple members of the household would qualify, choose by a coin toss (if only two) or drawing numbers at random. Only use one member of a given household for a control. Continue on until four controls are selected for each case. If the residence is a multi-family dwelling such as an apartment building, choose the floor to start on by random number drawing. Choose the direction to proceed on the selected floor by a coin toss. Choose the first apartment on the floor, if there are multiple, by random number drawing. If no suitable control is found in the first apartment, continue through consecutive apartments on the floor after choosing the direction from the first apartment by coin toss. Alternatively, a simple random sample of families in the neighborhood can be selected using random numbers and a list of households, if available.

INFORMED CONSENT

During the visit to both cases and controls, the purpose of the study will be explained to all eligible subjects 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 may vary by country. Check with local IRB requirements.

MINIMUM DATA COLLECTION

After enrollment and informed consent is obtained, a standardized minimum data set will be collected. A template of the study questionnaire for the use of all cases and contacts can be found in Appendix A. These include some identifying information, demographic information, and date of onset.

RISK FACTORS FOR HUMAN INFECTION

In addition to the minimum dataset, detailed questions to evaluate risk factors for human infection with MERS-CoV will be asked in a questionnaire (Appendix A). These are included in the data collection form in under the section for “exposures”. These questions are more specific and include aspects of timing of, frequency and duration of exposure(s).

2.3.2 PREVENTION OF MERS-COV TRANSMISSION IN FRONT-LINE STAFF

Prior to 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 the personnel acting as a vector of MERS-CoV transmission between subjects members or between households. If N-95 respirators are to be used, they should be fit tested in advance.

2.4 SPECIMEN COLLECTION AND LABORATORY TESTING

2.4.1 SPECIMEN COLLECTION, TRANSPORTATION

Laboratory testing is necessary to prospectively identify cases and, if needed, to eliminate individuals who have been infected from the control group. Please refer to the current WHO laboratory guidance for appropriate collection, storage, shipment, and testing procedures. Current WHO lab guidance is available at: http://www.who.int/csr/disease/coronavirus_infections/LaboratoryTestingNovelCoronavirus_21Dec12.pdf

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

2.4.2 LABORATORY PROCEDURES

VIROLOGIC TESTING

COMMENT: Limited available data suggests that lower respiratory specimens such as sputum, endotracheal aspirates, or bronchoalveolar lavage, will have a higher yield for testing than upper respiratory specimens such as nasopharyngeal swabs. Ideally, multiple respiratory specimens should be collected from different respiratory sites on multiple days to maximize detection of MERS-CoV. A person suspected to have MERS-CoV infection but who has a nasopharyngeal swab collected that tested negative for MERS-CoV should have repeat testing on subsequent days if strongly suspected to have MERS-CoV infection. MERS-CoV has also been found in stool of infected patients, which may provide an additional of confirmation.

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 RT-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. Case definitions can be found

at: http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html

Member States are requested to immediately notify WHO.

See full details for virologic laboratory testing of MERS-CoV can be found

here: http://www.who.int/csr/disease/coronavirus_infections/LaboratoryTestingNovelCoronavirus_21Dec12.pdf.

COMMENT: there is currently no provision for case confirmation using a serological assay, however, this may become available in the near future. Investigators should refer to current WHO case definitions for determining case classification.

SEROLOGIC METHODS

The methods described in this section may be useful if it becomes necessary to exclude infected individuals from the control group.

COMMENT: Validated serologic assays for MERS-CoV are currently limited but are being pursued by a small number of laboratories across the globe. Here we provide details of the only published serologic testing available for MERS-CoV.^{1,2}

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 up to the discretion of member states carrying out the research, but WHO/EMRO strongly support such collaboration and would willingly facilitate collaboration and possible shipment elsewhere for testing.

The following laboratory assay results are currently available for defining a case as MERS-CoV antibody positive and full details can be found in^{1,2}.

- Screening for antibodies reactive to MERS-CoV by indirect immunofluorescence assay (IFA) described by^{1,2}
- It is strongly recommended that confirmatory serologic testing should be done using microneutralization or ELISA-based assays using appropriately timed sera (ideally paired acute and convalescent sera)^{1,2}

2.5 ETHICAL CONSIDERATIONS

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

COMMENT: It is strongly recommended that ethical approval is 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 prior to an outbreak. 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.

3.0 STUDY ENDPOINTS & 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 OUTCOME

The following will be assessed as study endpoint corresponding to the study's primary objective:

- The ratio of the odds of exposure vs. odds of no exposure to a variety of potential sources of infection in cases vs. controls.
- The exposure or combination of exposures that best explain the resulting infection based on a regression model of all exposures.

3.2 STATISTICAL ANALYSES

3.2.1 FOR PRIMARY OBJECTIVE

RISK FACTORS FOR HUMAN INFECTION

The reported practices among cases and matched controls should be compared using appropriate statistical tests, e.g., Bivariate associations between risk factors and 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 analyze the associations to determine which best explains the resulting infection.

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.³

4.0 REPORTING OF FINDINGS

Any deviations of the study methodologies should be reported along with the results to aid in the interpretation of findings and to assist others in improving future versions of the protocol.

5.0 COMPLEMENTARY STUDIES

Although not described as part of this investigation, we recommended that in conjunction with this case control study, full epidemiological and virological outbreak investigations around new cases, including (1) further investigations of close familial, social and health care worker contacts, (2) environmental sampling including testing of areas around the infected household, farms, markets and potential contaminated water sources and (3) retrospective animal mortality investigations should supplement these activities in collaboration with relevant parties, in particular if the objective would include identifying a zoonotic source of infection among index and/or contacts of the index.

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

The following questionnaire should be used for all cases and controls included in the investigation. The time frame for the questions to cases is the 14 day period before the onset of their illness. For cases that happened in the past, it is useful to use memory prompts such as birthdays, holidays, or other memorable events that occurred around the same time to help the interviewee recall the specific time frame of interest. For controls, ideally the same time frame would be asked about as for the cases, however for retrospective cases in the remote past, this is not generally feasible. In that situation, the 14 day period just before the interview can be used as a reference. For cases that are enrolled prospectively when they are diagnosed, controls should be chosen at that time and the time frame of reference for the questions should be the same as for the case.

If the case has died or is otherwise unable to answer questions, a proxy such as a close relative who knows the person well can answer the questions for him or her.

Each subject should be allocated a unique identification number.

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

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

SECTION 1 GENERAL QUESTIONS

Identification number: _____

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

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

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

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: ____/____/____ (mm/dd/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 the highest education level you finished? (add mult 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. for 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? Y/N please specify: _____
- 2.5. List any underlying chronic diseases you might have:
- Diabetes: yes no
- If yes, insulin used: yes no
- Emphysema, chronic bronchitis or other chronic lung disease besides asthma: yes no
- If yes, are medications used for treatment? Yes no (if yes, specify: _____)
- Asthma: yes no
- 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
- If yes, is dialysis needed? Yes no
- Chronic liver disease such as hepatitis: yes no
- Heart disease: yes no
- If yes, please specify
- Deficient immune system? Yes no
- If yes, describe specific condition: _____
- History of cancer treatment in the last year? yes no
- If yes, please give name of cancer and time of last treatment: _____
- Hematological disorder such as chronic anemia? Yes no
- 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

2.9.1. How many weeks?

2.10. If female, have you recently had a baby? Yes no

2.10.1. 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-patient. If the subject is a case, then exposure should be focused 14 days prior to symptom onset or a time period should be specified. For controls, ideally the same time frame would be asked about as for the cases, however for retrospective cases in the remote past, this is not generally feasible. In that situation, the 14 day period just before the interview can be used as a reference. For cases that are enrolled prospectively when they are diagnosed, controls should be chosen at that time and the time frame of reference for the questions should be the same as for the case.

RECENT TRAVEL HISTORY

The following questions relate to travel within the 14 days prior to illness (or administration of the questionnaire, if interviewee is a control) and the animals you encountered during these travels.

Recent Travel History

3.1. List the areas to which you have travelled in the last 14 days before onset of illness (or administration of the questionnaire, if interviewee is a control).

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 your illness (or administration of the questionnaire, if the interviewee is a control) with a person who had a respiratory illness or diarrhea?

Yes No

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

- 3.2.2.1. if yes, how many nights of the last 14:
- 3.2.3. Did you travel in the same vehicle as the ill person during their illness? Yes no
- 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 feces? Yes no
- 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
- 3.2.7.1. If yes, was he or she on a ventilator at the time? Yes no
- 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 diarrhea)? 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
- 3.3. Have you in the 14 days before your illness (**or administration of the questionnaire, if the interviewee is a control**):
- 3.3.1. been a patient in hospital? Yes no
- 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
- if Yes, Name and address of outpatient facility: _____
- 3.3.3. date of visit (dd/mm/yyyy)? ___/___/___ visited a traditional healer?
Yes no
- if Yes, Name and address of traditional healer: _____
- 3.3.4. date of visit (dd/mm/yyyy)? ___/___/___ attended a funeral?
Yes no
- 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 patient's illness (or administration of the questionnaire, if interviewee is a control).

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 feces or urine in or outside around your home during this time?
Yes no
- 3.4.4. Are there regularly wild birds in and around the house? Yes no
- 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
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?
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)?
- 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
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
- 3.4.13. Have you personally participated in the slaughter or ritual sacrifice of an animal? Yes No
3.4.13.1. If yes, name 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 prior to the case-patient's symptom onset (or administration of the questionnaire, if interviewee is a control).

- 3.4.1. In the 14 days prior to your illness (or administration of the questionnaire, if interviewee is a control) did you eat any of the following food items raw, that is uncooked? (Answer Yes/no)
- 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
- 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 animal 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? Y / N
- 3.4.5.1. If yes, specify from what kind of animal: _____

APPENDIX B: CONSIDE PROTOCOLS UNDER DEVELOPMENT

More information on CONSIDE as well as other protocols for use in investigation of outbreaks can be found on the CONSIDE website: www.CONSIDE.tghn.org. All CONSIDE protocols are made freely available and can be adapted as needed.

Protocol	Primary Objectives	
Epidemic/Pandemic	1. Prospective Longitudinal cohort study of influenza virus infection during epidemic periods	Determine age specific cumulative incidence of infection during an influenza epidemic
	2. Cross sectional seroprevalence study of a novel influenza virus infection prior and post epidemic periods	Determine age specific cumulative incidence of infection with a novel influenza virus in the population Measure prevalence of cross-reactive antibodies to the novel virus Estimate household secondary infection risk, and factors associated with variation in the secondary infection risk
	3. Household transmission studies for pandemic influenza	Characterize secondary cases including clinical presentation and asymptomatic fraction Investigate serological response following confirmed influenza infection
	4. Closed setting outbreak investigation protocol for pandemic influenza	Describe the clinical spectrum of infection including the asymptomatic fraction Estimate overall clinical attack rates (by subgroup and clinical risk group)
	5. Assessment of Health Care Personnel	Describe correlation between infection, disease and serology Detect the presence of human-to-human transmission of a novel virus within a health care setting
Seasonal Influenzas	6. Seroepidemiology of human influenza virus infection using residual sera/convenience samples for establishing baselines and/or monitoring trends over time	Estimate population immune status/susceptibility to relevant influenza viruses Estimate incidence in previous-seasons for the different relevant influenza viruses
Zoonotic Influenzas	7. Investigation of Zoonotic Influenza Infection in Humans	Measure age-specific infection in relation to zoonotic exposure Identify (modifiable) risk factors for human infection