Seroepidemiological Investigation of Close Contacts of Novel Coronavirus (MERS-CoV) Patients

Working Draft

Developed by

The Consortium for the Standardization of Influenza Seroepidemiology (CONSISE): A Global Partnership to Develop Influenza Investigation Protocols and Standardize Seroepidemiology to Inform Public Health Policy

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PROTOCOL SUMMARY

A comprehensive assessment of all contacts – including household, familial, social occupational and health care associated contacts – of confirmed and probable MERS-CoV cases is warranted to determine the extent of (asymptomatic) infections, routes and risk of transmission, and guide efforts for prevention of (human to human) transmission of the MERS-CoV virus. This investigation outlines how to find and test all close contacts of laboratory confirmed and probable MERS-CoV patients. This protocol also outlines a case-control study and the epidemiological methods to guide data collection for the comprehensive assessment of the cases and controls to assess risk factors for MERS-CoV infection.

Health care personnel are treated separately in a separate protocol (see http://consise.tghn.org/articles/novel-coronavirus-ncov/).

This investigation will provide data to evaluate some of the key clinical, epidemiological, serological and virological characteristics of the first cases and their contacts to inform the development and updating of national and international policy and guidance to manage cases and reduce the spread and impact 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.

Details of who and how this protocol was developed are provided in section 6.0.
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1.0 SCIENTIFIC BACKGROUND AND RATIONALE

As of 31 May 2013, 50 laboratory-confirmed cases of human infection with novel coronavirus (MERS-CoV) have been reported to WHO\(^1\): from Jordan, Qatar, Saudi Arabia, the United Kingdom (UK), Germany, France, Tunisia and United Arab Emirates. It is suspected that MERS-CoV is a zoonotic virus, which may have arisen from animal exposures, and zoonotic transmission in the Arabian Peninsula, but information on exposures is limited and an animal reservoir is unknown. Human-to-human transmission is suspected and likely to have occurred several clusters in: a health care facility in Saudi Arabia; among ICU health care workers in a hospital in Zarqa, Jordan; and separate familial clusters in the Saudi Arabia, UK, France, Italy and Tunisia. Follow-up investigations by Ministry of Health officials have taken place for all cases from other cases and suggest that no further confirmed or probable cases occurred. At this stage, however, it is difficult to ascertain whether other primary zoonotic or secondary human-to-human transmission cases have been missed.

Coronaviruses are a large, diverse group of viruses that affect many animal species and infection in humans can cause a wide range of respiratory illnesses, typically with “common cold” symptoms. Genetic sequence data indicate that this MERS-CoV is a beta-coronavirus similar genetically to bat coronaviruses, but antigenically and genetically distinct from any other coronavirus previously described in humans, including the coronavirus (SARS-CoV) that caused severe acute respiratory syndrome (SARS). Most cases have reported severe acute respiratory symptoms requiring hospitalization and intensive care. Eighteen of the 31 cases have been fatal.

A comprehensive assessment of known contacts – household, familial, social and occupational – of confirmed and probable MERS-CoV cases is warranted to determine the extent of secondary infections, identify 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, epidemiological, Immunological and virological characteristics of cases and their contacts to inform the development and updating of national and international policy and guidance to manage cases and reduce the spread and impact of MERS-CoV infection. We also provide methods to conduct a case-control study to evaluate risk factors for infection.


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.

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\(^1\) More information on MERS-CoV can be found on the WHO Website: [http://www.who.int/csr/disease/coronavirus_infections/en/index.html](http://www.who.int/csr/disease/coronavirus_infections/en/index.html)
The primary objectives of this study are to:

- 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
- Estimate frequency of age-specific MERS-CoV infections (as measured by virologic and serologic tests) in relation to human and other exposures (i.e., that is evaluate determinants/risk factors [including sources] for infection)
- Evaluate (modifiable) risk factors (e.g., exposures, behaviors, practices) for human MERS-CoV infection
- Quantify proportion of asymptomatic/sub-clinical MERS-CoV infections

Comprehensive study investigations, such as the one described below, can provide rich data to assess numerous secondary outcomes including, but are not limited to:

- Assess evidence of MERS-CoV antibodies in relation to MERS-CoV virus shedding in infected patients.
- Allow for the calculation of parameters that will allow for estimation of the transmission potential of MERS-CoV. For example data collected in this study can contribute to estimation of the incubation period\(^2\), serial interval\(^3\), the basic reproductive number (\(R_0\))\(^4\), and preliminary case-severity ratios (e.g, case-hospitalization and case-fatality ratios\(^5\)).

COMENT: Many other secondary objectives can be investigated in terms of epidemiological, immunological, clinical, virological, economic, genetic, behavioral, 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

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\(^2\) Incubation period is defined as the period of time between an exposure resulting in infection until the onset of clinical symptoms of disease.

\(^3\) Serial interval is defined as the period of time from the onset of symptoms in the index case to the onset of symptoms in a contact case.

\(^4\) The reproduction number, \(R_0\), is defined as the average number of secondary cases of an infectious disease that result from one infected person in a susceptible population.

\(^5\) Case hospitalization ratio (CHR) is defined as the proportion of those affected (with symptoms) that are admitted to hospital. The case fatality ratio (CFR) is defined as the proportion of those affected who die as a direct or indirect consequence of their infection.
The first stage of this investigation focuses on finding and testing (virologically and serologically) all close contacts of laboratory-confirmed MERS-CoV patients. The second stage of the study will be to conduct a case-control study to evaluate risk factors for infection.

The case-control study design will examine the differences in types of exposures between individuals with laboratory-confirmed or serologically confirmed MERS-CoV infection and controls.

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 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.

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.

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.

On 8 March a probable case of MERS-CoV was defined by WHO as:

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

- A person with an acute respiratory infection (this may include but is not limited to cases with a history of fever or measured fever) with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome, [ARDS]); AND

WHO Case Definitions for MERS-CoV can be found here: http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html
• no possibility of laboratory confirmation for MERS-CoV either because the patient or samples are not available for testing; AND
• close contact** with a laboratory-confirmed case.

2.3.1.2 CONFIRMED CASE

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 or from a robust measure* of an increase in specific MERS-CoV antibody titre in appropriately timed acute and convalescent sera.

*COMMENT: See section 2.4.2 below.

2.3.2 CONTACTS OF A CONFIRMED HUMAN NCOV 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 household, social, familial or occupational contacts. Contacts should have a minimum amount of face-to-face contact (within a meter) with the patient of at least 5 minutes during the time frame of interest (this must be specified in the protocol). Contacts can include household members, family contacts, relatives, visitors, neighbors, colleagues, teachers, classmates, co-workers, transport contacts, and others.

COMMENT: Identification of close 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. The definition of contacts used for this study should be clearly defined and reported.

COMMENT: The definition of a contact for the purposes of this study is different than contacts as defined as a probable case.

Comment: Health Care Personnel should be investigated using a separate protocol. See CONSISE MERS-CoV HCP Protocol.

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 known contacts of a confirmed MERS-CoV case.
All efforts will be made to identify every close contact 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 (e.g., by the Ministry of Health (or equivalent)). At the time of recruitment, combined nasal and throat swabs for virologic confirmation, blood for serologic confirmation and minimum epidemiologic 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 ideally as soon as possible after identification of a confirmed case to query about the possible development of illness. Contacts will be monitored daily for ten days after the last known exposure to an ill confirmed or probable MERS-CoV case. A baseline clotted blood sample will be taken at time of first interview and sent to a reference laboratory.

If any contact is ill with clinical symptoms (fever and cough) at initial visit or within 14 days since the date of last exposure with an ill confirmed case they will be treated as a symptomatic contact. The follow-up of a symptomatic contact will involve collection of respiratory specimens for urgent molecular testing to determine MERS-CoV infection and collection of sera at least 14 days after an acute baseline sample is collected and (ideally every 2 weeks until/) after resolution of symptoms.

Ill contacts found to have evidence of MERS-CoV infection will be re-classified as confirmed cases and all contacts of these cases should be identified and recruited for inclusion in the study if not already done.

COMMENT: If feasible, consider serial sera collection of all recruited subjects at baseline, 2-week, 4-week or 6-week intervals.

2.4.1.2 RECRUITMENT OF AN ADDITIONAL CONTROL POPULATION

To conduct a case-control study, a control population (other than seronegative contacts) will be recruited.

To strengthen the study of risks of infection, another control population without known contact with a confirmed source for infection will be identified and recruited. The purpose of a control population, is to evaluate non-human exposure risk factors for infection.

COMMENT: If feasible, a similar number of individuals, who are not contacts of cases, should be included as control population(s). Ideally, and if logistically feasible and resources allow, multiple in-country and out-of-country control groups would give insight in the extent of and risk factors for asymptomatic infection with and without a recognized human source of MERS-CoV exposure.

Examples of additional control populations include:

- A similar number of residents from the same geographic region (of similar age and matched on sex); or
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- A similar number of residents from a separate geographic location within the same country (of similar age and matched on sex); or
- A similar number of residents from a neighboring country (of similar age and matched on sex).
- A similar number of randomly selected subjects (of similar age and matched on sex) from the country

COMMENT: If feasible, consider paired sera collection of enrolled controls at baseline and end of study.

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 may vary by country. Check with local IRB requirements.

2.4.3 MINIMUM DATA COLLECTION

After enrollment and informed consent is obtained, we recommend that a standardized minimum data set be collected with any specimens for MERS-CoV testing (and date of specimen collection) including: age, gender, location, exposure (date of first and last known exposures, duration, proximity) to confirmed case-patient, occupation, signs and symptoms, underlying conditions, risk factors (i.e., exposures) for infection and severe disease, a history of the use of respiratory protection, any treatments or other potentially relevant medication.

A template of the study questionnaire for the use of all cases, contacts and controls can be found in Appendix B.

2.4.4 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 B). These are included in the data collection form in Appendix B under the section for "exposures". These questions are more specific and include aspects of timing of, frequency and duration of exposure(s). The questionnaire should be administered each time sera are collected.

2.4.5 PREVENTION OF NCOV 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.

2.5 SPECIMEN COLLECTION AND LABORATORY EVALUATIONS

2.5.1 SPECIMEN COLLECTION, TRANSPORTATION

Cut and paste guidance from WHO lab guidance, here:

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.

2.5.2 LABORATORY PROCEDURES

2.5.1.1 VIROLOGIC TESTING

MERS-CoV case definitions can be found at:

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.

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

2.5.1.2 SEROLOGIC METHODS

COMMENT: The development and validation of 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, but we are aware of pending publications from Public Health England (formerly the UK Health Protection Agency).
CONSISE  Seroepidemiological Investigation of Close Contacts of MERS-CoV Patients

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)\(^1\,^2\)

COMMENT: If appropriately timed and collected paired acute and convalescent sera are collected, a four-fold rise in titer is indicative of seroconversion.

### 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 OUTCOMES

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

1. Describe the presentation and clinical course of disease with MERS-CoV infection
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. Evaluate source(s), risk exposures, and (modifiable) risk factors for human infection with MERS-CoV
4. Quantify proportion of asymptomatic/sub-clinical MERS-CoV infection

#### 3.2 STATISTICAL ANALYSES

##### 3.2.1 FOR PRIMARY OBJECTIVE 1

**CLINICAL PRESENTATION AND COURSE OF DISEASE**
The proportion of symptoms of subjects with evidence of infection (individuals with RT-PCR positive or serologic positive results) should be calculated.

**ESTIMATE 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, AR 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 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 ARs by subject type (e.g., household contacts, occupational contacts) or by age.

**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:

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

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

**RISK FACTORS FOR HUMAN INFECTION**

One way to measure risk factors for infection is to compare the exposures (behaviors and practices) of your cases (i.e., laboratory confirmed and sero-positive individuals) versus controls (i.e., sero-negative close contacts OR your specific control population, if included).

**To assess human-to-human transmission:** To evaluate human-to-human transmission, a comparison of human exposures of cases (seropositive and laboratory confirmed patients) vs controls (seronegative close contacts OR your specific control population, if included).

**To assess non-human exposures resulting in transmission:** Compare the non-human exposures of cases (laboratory or serologically confirmed subjects) vs. controls (control population defined in section 2.4.1.2).

COMMENT: Controls could be matched on some factors including age and sex. However, prior to matching, it should be acknowledged that the factors matched for can no longer be identified as risk
factors, thus if this still needs to be established, matching is not advisable. If indeed there is no (longer a) need to explore the association of certain factors with the outcomes of interest, matching can increase power. In addition, it might be advantageous to choose more than one control group depending on the risk factor of concern. For example, if the majority of cases are from a high SES, matching on SES will allow the evaluation of specific practices that are limited to that social stratum and might be done if there is a question of a bias in case detection. That is, if there is concern that cases might have been detected in part because of the fact that they belong to a particular SES then matching on SES will allow the investigator to evaluate specific activities that result in exposure. However, not matching will result in the incorrect finding that SES itself is a risk factor. If there is no concern about bias in case finding, then matching on this characteristic is less important. The use of both matched and unmatched control groups can help to better understand this phenomenon.

The reported practices among cases and (possibly matched, see above) controls 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 analyze the associations.

**COMMENT:** Calculating the odds ratio in an unmatched case-control study is different than in a matched-case control study (e.g., consider conditional regression).

**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.

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

Individuals in the study survey that are found to have serological evidence of acute nCoV infection that 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:

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

**4.0 REPORTING OF FINDINGS**

**4.1 REPORTING OF FINDINGS**

Any deviations of 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 close familial, social and HCP contacts, environmental sampling including testing of areas around the infected household, farms, markets and potential contaminated water sources and retrospective animal mortality investigations should supplement these activities in collaboration with relevant parties (Figure 1), in particular if the objective would include identifying a zoonotic source of infection among index and/or contacts of the index.

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

*In collaboration with relevant bodies/parties

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**6.0 BACKGROUND OF CONSISE**

This protocol *Seroepidemiological Investigation of Close Contacts of nCoV patients* was developed by CONSISE, the Consortium for the Standardization of Influenza Seroepidemiology, 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.

Recognizing this gap, several institutions including the World Health Organization (WHO), the Public Health Agency Canada (PHAC), European Centres for Disease Control (ECDC), US Centers for Disease Control and Prevention (USCDC), Imperial College London (ICL), UK Health Protection Agency (UKHPA), University of Hong Kong, the WHO Collaborating Centre for Reference and Research on Influenza in Melbourne, Australia, and many other research institutions formed a partnership to develop best practices and standardize influenza seroepidemiological methods. Three global meetings have been held.
to date, the first in Canada hosted by PHAC in early 2011 and the second in Stockholm Sweden in December 2011 hosted by ECDC, and a third meeting held in Hong Kong in January 2013.

During the December 2011 meeting, it was decided that **seven generic detailed protocols should be developed** that can be used in pandemic outbreak settings and for routine serologic collection during non-pandemic seasons. In doing so, our aim is to adopt a common framework for serological studies, standardize methodology and reporting. With the emergence of novel Coronavirus (nCoV) in the Middle East in 2012, CONSISE modified their zoonotic and household protocols to create a protocol specific to investigate the epidemiology, serologic and virologic of close contacts of confirmed and probable nCoV patients.

This study protocol was developed by CONSISE as a tool to be modified and adapted to local needs during the event of a human outbreak with a novel respiratory virus, notably nCoV. It was created in consultation with and reviewed by an ad hoc group of technical experts and has undergone preliminary review. Individuals who have reviewed this protocol are listed in Appendix A. We suggest that seroepidemiologic studies which are part of a comprehensive outbreak investigation of contacts, as proposed in this protocol, will be most productive.

Specifically, this protocol “Seroepidemiological Investigation of Close Contacts of nCoV patients” was drafted by CONSISE members with input from many partners (Appendix A) and influenced by the following protocols, shared with CONSISE for the purposes of developing this protocol:

- **Outbreak investigation of human cases of influenza A (H5N1) and other novel influenza A viruses in Bangladesh**, shared by Steve Luby and Katharine Sturm-Ramirez icddr,b and USCDC
- **Prospective Study of Individuals Exposed to Confirmed Cases of Human Influenza A (H5N1) Infection in China & Matched Case-Control Study of Risk Factors for Human Infection with Avian Influenza A (H5N1) Virus**, shared by Yu Hongjie China Centers for Disease Control
- **Sero-epidemiological Investigation of H5N1 in Cambodia**, shared by Sirenda Vong Institut Pasteur du Cambodia
- **Protocol for Avian Influenza Outbreak**, shared by Marianne van der Sande RIVM, the Netherlands
- **Assessment of Health Care Personnel for Patient with Novel Coronavirus**, shared by Anthony Mounts, World Health Organization
- The protocol used in the following study by Reynolds et al 2006 *Factors associated with nosocomial SARS-CoV transmission among healthcare workers in Hanoi, Vietnam, 2003* ^9^

### Table 1 – CONSISE Protocols Under Development

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### 2. Cross sectional seroprevalence study of a novel influenza virus infection prior and post epidemic periods

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<td>Determine age specific cumulative incidence of infection with a novel influenza virus in the population</td>
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<tr>
<td></td>
<td>Estimate household secondary infection risk, and factors associated with variation in the secondary infection risk</td>
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<td></td>
<td>Characterize secondary cases including clinical presentation and asymptomatic fraction</td>
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<td>Investigate serological response following confirmed influenza infection</td>
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### 3. Household transmission studies for pandemic influenza

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<tr>
<td></td>
<td>Describe the clinical spectrum of infection including the asymptomatic fraction</td>
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<td>Estimate overall clinical attack rates (by subgroup and clinical risk group)</td>
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<td>Describe correlation between infection, disease and serology</td>
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### 4. Closed setting outbreak investigation protocol for pandemic influenza

### 5. Assessment of Health Care Personnel

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<td>Detect the presence of human-to-human transmission of a novel virus within a health care setting</td>
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</table>

### 6. Seroepidemiology of human influenza virus infection using residual sera/convenience samples for establishing baselines and/or monitoring trends over time

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<td></td>
<td>Estimate population immune status/susceptibility to relevant influenza viruses</td>
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<td>Estimate incidence in previous-seasons for the different relevant influenza viruses</td>
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### 7. Investigation of Zoonotic Influenza Infection in Humans

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<tbody>
<tr>
<td></td>
<td>Measure age-specific infection in relation to zoonotic exposure</td>
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<tr>
<td></td>
<td>Identify (modifiable) risk factors for human infection</td>
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</tbody>
</table>

Source: 5

Questions about the generic protocol should be directed to m.vankerkhove@imperial.ac.uk while questions related to the country-specific protocols for which this protocol was based on should be directed to the contact points mentioned for those protocols.

We hope you find this protocol helpful.

www.CONSISE.tghn.org
REFERENCES


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CONSISE STEERING COMMITTEE

CONSISE’s steering committee is composed of individuals (Table A1) from several organizations including the World Health Organization, the US Centres for Disease Control and Prevention, the European Centres
for Disease Prevention and Control (ECDC), Public Health England (Formerly the UK Health Protection Agency), Imperial College London, the WHO Collaborating Centre for Reference and Research on Influenza (Melbourne, Australia), University of Hong Kong, Oxford University Clinical Research Unit in Hanoi, and Public Health Agency of Canada.

**Table A1 CONSISE Steering Committee Members**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Angus Nicoll</td>
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</tr>
<tr>
<td>Eeva Broberg</td>
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<tr>
<td>John Wood</td>
<td>NIBSC, Medicines and Healthcare Products Regulatory Agency, UK</td>
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<tr>
<td>Othmar Engelhardt</td>
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<tr>
<td>Maria Van Kerkhove</td>
<td>MRC Centre for Outbreak Analysis and Modelling, Imperial College</td>
</tr>
<tr>
<td>Steven Riley</td>
<td>London, UK</td>
</tr>
<tr>
<td>Anthony Mounts</td>
<td>World Health Organization</td>
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<tr>
<td>Wenqing Zhang</td>
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<tr>
<td>Karen Laurie</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza, Melbourne,</td>
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<td></td>
<td>Australia</td>
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<tr>
<td>Jackie Katz</td>
<td>US Centres for Disease Control and Prevention, Atlanta, United States</td>
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<tr>
<td>Tim Uyeki</td>
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<td>Malik Peiris</td>
<td>The University of Hong Kong, School of Public Health, Department of</td>
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<td>Benjamin Cowling</td>
<td>Community Medicine, Hong Kong</td>
</tr>
<tr>
<td>Katja Hoeschler</td>
<td>Public Health England, London, UK</td>
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<tr>
<td>Richard Pebody</td>
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<tr>
<td>Peter Horby</td>
<td>Oxford University Clinical Research Unit in Hanoi, Vietnam</td>
</tr>
<tr>
<td>Monique St-Laurent</td>
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<td></td>
<td>Netherlands</td>
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<tr>
<td>Olav Hungnes</td>
<td>Norwegian Institute of Public Health, Norway</td>
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</table>
APPENDIX B  DATA COLLECTION FORM

Questionnaire for Seroepidemiological Investigation of Close Contacts of nCoV patients

The following questionnaire should be used for all cases and controls included in the above listed investigation. This questionnaire is separated into sections: General questions, Exposure questions, Symptom and Course of Disease questions and Background Demographic questions and represent the minimum questions that should be asked to all subjects. 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 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.

COMMENT: The time period of exposures should be 14 days prior to symptom onset for cases AND should be the same 14 day period for controls.

SECTION 1 GENERAL QUESTIONS

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

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

General questions

1.1. What is your full name: ________________________________

1.2. Place of primary residence: ________________________________

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: ________________________________

1.5. Do you practice any sports?

1.6. Do you own a car?

1.7. What is the highest education level you finished? (add mult choice)

1.8. What is your household income level (provide ranges and circle best fit)?

Personal living situation

1.9. What is your current family status? (single, married, living with a partner, other…)
1.10. How many people live in your household with you?
   1.10.1. Children under age 18: _____
   1.10.2. Adults over age 18 years: _______

1.11. Do you have servants?
   If yes,
   1.11.1. how many?
   1.11.2. for what kind of service do they provide? Please specify
   1.11.3. do they live in your house?
   1.11.4. what nationality are they?

1.12. What type of dwelling do you live in? Apartment, detached house, other, please specify
   1.12.1. Do you have air-conditioning in your house?
   1.12.2. What is the size of your family living space (square meters):

SECTION 2 EXPOSURE QUESTIONS

COMMENT: Exposure history should be focused on a specified time period before the symptom onset of the nCoV 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.

COMMENT: The time period of exposures should be 14 days prior to symptom onset for cases AND should be the same 14 day period for controls.

EXPOSURE TO nCOV CASE-PATIENT

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 is known or strongly suspected to be infected with the novel coronavirus.
   2.1. Did you sleep in the same room as the infected person? Yes/no, if yes, how many nights
   2.2. Did you travel in the same vehicle as the infected person? Yes/no, if yes, how many hours (roughly)? <1/1-5, etc
   2.3. Did you have close physical contact (touching the infected person) of any kind with the case-patient?
      2.3.1. If so, please describe nature of contact
   2.4. Did you eat meals with the infected person?
      2.4.1. If yes, did you generally eat the same food as the infected person?
3. In the 14 days prior to symptom onset (or administration of the questionnaire, if interviewee is a control), were you physically close to anyone else with a respiratory illness who was having symptoms at the time but was not diagnosed as having infection with the novel coronavirus?

Yes/no. (if no, skip the following questions in this section and go to the next section on recent travel.)

If yes,

3.1. Did you sleep in the same room as the sick person? Yes/no, if yes, how many nights

3.2. Did you travel in the same vehicle as the sick person? Yes/no, if yes, how many hours roughly)? <1/1-5, etc

3.3. Did you have close physical contact (touching the sick person) of any kind with the case-patient?

3.3.1. If so, please describe nature of contact

3.4. Did you eat meals with the sick person?

3.4.1. If yes, did you generally eat the same food as the infected person?

RECENT TRAVEL HISTORY AND ANIMALS ENCOUNTERED

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

COMMENT: The time period of exposures should be 14 days prior to symptom onset for cases AND should be the same 14 day period for controls.

Recent Travel History

1.1 List the areas within the country you travelled to between (specify time period here).

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________

List all countries you travelled to between (specify time period here).

1.2. Country Name:

1.2.1. Dates Travelled: _________________ to ______________

1.3. Country Name:

1.3.1. Dates Travelled: _________________ to ______________

1.4. Country Name:

1.4.1. Dates Travelled: _________________ to ______________

1.5. Country Name:

1.5.1. Dates Travelled: _________________ to ______________

1.6. Country Name:
1.6.1. Dates Travelled: ______________ to ______________

Animal exposures during these travels

1.7. Did you have contact (touching) with domestic or wild animals during any of these travels?
1.8. Did you physically touch an animal of any kind during these trips?
   If yes, what kind of animal(s) ______________ and in which country: ______________
   If yes, what kind of animal(s) ______________ and in which country: ______________
1.9. Did you visit a market selling live animals? Y/N
1.10. Did you physically touch an animal of any kind at these markets? Y/N
   If yes, what kind of animal(s) ______________
1.11. Did you visit any other venue at which live animals were present? Y/N
   (COMMENT: specify examples depending on the country: e.g., farm, camel race or falconry events)
   1.11.1. If yes, please specify venues ______________
   1.11.2. Please specify any animals you touched.
1.12. Did you eat anything while at these events?
   1.12.1. Event 1: ______________ Food consumed: ______________
   1.12.2. Event 2: ______________ Food consumed: ______________
1.12.3. Did you have direct contact with animals (either alive or dead?) while there? If yes, what type of animals?
   1.12.3.1. Did you touch any items such as fences, textiles, or other physical objects that may have had contact with animals while there? If yes, please specify.
   1.12.3.2. Did you have contact with any body fluids, secretions, or excrement of animals while there? If yes, please specify.

Food exposures

The following series of questions are focused on food exposures in the 14 days prior to the case-patient’s symptom onset.

COMMENT: The time period of exposures should be 14 days prior to symptom onset for cases AND should be the same 14 day period for controls.

1.12. 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)
   1.12.1. Fresh fruits, if yes, specify type: ______________
   1.12.2. Dried fruits, if yes, specify type: ______________
   1.12.3. Vegetable, if yes, specify type: ______________
   1.12.4. Salads, if yes, specify type: ______________
1.12.5. other? Please specify __________

1.13. Did you drink fresh (i.e. not canned or processed) fruit juices? If yes, please specify.
   Juice type: __________

1.14. Did you eat any uncooked meat?
   1.14.1. If yes, specify type of animal consumed: __________
   1.14.2. If yes, specify body part consumed (e.g., flesh, blood, etc)

1.15. Did you drink any unpasteurized milk? Y/N
   1.15.1. If yes, specify from what kind of animal: __________

**ANIMAL EXPOSURES IN AND AROUND THE HOME**

The following questions address animal exposures during the 14 day period before the patient’s illness.

**COMMENT:** The time period of exposures should be 14 days prior to symptom onset for cases AND should be the same 14 day period for controls.

**Animal contact**

2.1. Were any pets, including work animals or hunting animals, kept in or around your home during this period?
   2.1.1. If yes, what kind and how many? __________
   2.1.2. Were you aware of any other animals present in or outside around your house during this time (e.g. bats, rodents)? __________
   2.1.3. Did you notice any animal feces or urine in or outside around your home during this time? Y/N

2.2. Did you have contact (touch) with domestic or wild animals? Y/N

2.3. Did you physically touch an animal of any kind?
   2.3.1. If yes, what kind of animal(s) __________

2.4. Did you visit a market selling live animals?

2.5. Did you visit any other venue at which live animals were present (e.g. farm, camel race or falconry events)?
   If yes,
   2.5.1. Dates for each visit (dd/mm/yyyy):
      2.5.1.1. Venue: ____________, date visited (dd/mm/yyyy) __/__/____
      2.5.1.2. Venue: ____________, date visited (dd/mm/yyyy) __/__/____
   2.5.2. Did you eat anything while there? If yes, please specify
   2.5.3. Did you have direct contact with animals while there?
2.5.4. Did you touch any items such as fences, textiles, or other physical objects that may have had contact with animals on the farm?

2.5.5. Did you have contact with any body fluids, secretions, urine or excrement of animals on the farm while there?

SECTION 4 BACKGROUND MEDICAL HISTORY

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

Health

3.5. Do you currently smoke cigarettes:  
   yes  
   no

3.5.1. If yes, for how many years?

3.5.2. If yes, how many cigarettes (or other) per day do you smoke

3.6. Did you previously smoke?

3.6.1. If yes, for how many years?

3.6.2. If yes, what did you smoke?  

3.6.3. If yes, how many cigarettes (or other) per day did you used to smoke?

3.7. Do you consume alcoholic beverages?

3.7.1. If yes: how much and what beverage?: Daily/weekly/monthly?

4.1. Is there any hereditary disease running in your family?  Y/N please specify:  

4.2. 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:  

   Kidney failure:  
   yes  
   no
   If yes, is dialysis needed?  
   yes  
   no
   Chronic liver disease such as hepatitis:  
   yes  
   no
   Deficient immune system?  
   yes  
   no
   If yes, describe specific condition:  

   Hematological disorder such as chronic anemia?  
   yes  
   no
   If yes, describe specific condition:  

4.3. Do you have any known allergies (list):  

4.4. What medications do you regularly take:  


4.5. What medications do you sporadically take: __________________________

4.6. If female, are you pregnant? Yes    no
   4.6.1. How many weeks?

4.7. If female, have you recently had a baby? Yes    no
   4.7.1. If yes, date of delivery (dd/mm/yyyy): ____/____/____