Investigation of Zoonotic Respiratory Infection in Humans Exposed to a Confirmed Source

Working Document

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

This protocol is relevant for zoonotic influenzas, that is, when transmission is occurring largely from animal-to-human and there may or may not be human-to-human transmission established. A comprehensive assessment of contacts – including household, familial, social occupational and health care associated contacts – of confirmed and probable influenza 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 influenza virus. 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 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 influenza infection. Health care personnel are treated separately in a separate protocol. The protocol outlines the investigation of laboratory confirmed and probable influenza infection, along with their close contacts.

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.

CONTENTS

1.0   SCIENTIFIC BACKGROUND

Influenza pandemics emerge when efficient transmission of a novel influenza virus emerges in the human population, to which (most of) the population has not yet been exposed. Such novel influenza viruses occur when influenza viruses present in zoonotic sources jump species or create a new virus after merging with an existing human virus. The 2009 H1N1 pandemic resulted from a re-assortment of pig viruses[1]. Numerous zoonotic outbreaks with H5N1 viruses have occurred over the past two decades, with so far limited transmission to humans and as of yet unclear potential for sustained human to human transmission, but with so far very high CFRs recorded[2]. Incidental human infections following exposure to other zoonotic viruses (H7N7, H7N9, H9N2) have occurred as well[3,4].

A zoonotic outbreak can be detected in the source (through surveillance or clinical reports), but often, an outbreak will only be identified once a human infection with a zoonotic infection has been confirmed, e.g., following admission to hospital due to a severe infection. The zoonotic source is than assumed based on the most likely exposure during the estimated time of infection (e.g., market, backyard, farm, fair). While it may not be possible to virologically confirm the source retrospectively, clinical evaluation of morbidity and mortality can still be supportive.

We focus here on the seroepidemiology element of a comprehensive investigation of contacts of confirmed cases where the source of infection is an animal. The main strength of seroepidemiology studies is the potential to study the full impact of an outbreak, that is both symptomatic and asymptomatic transmission and extent of infection, and to assess the proportion of people who remain susceptible following additional exposure[2]. On a population level, this can be achieved via cross sectional or longitudinal seroepidemiological studies (see CONSISE protocols: *Prospective longitudinal cohort study of influenza infection during epidemic periods* and *Cross sectional survey of prevalence of cross-reactive antibodies before and after an epidemic of a novel influenza virus*). By adding a serological component into outbreak investigations, additional insight is gained into the specific dynamics.

However, seroepidemiologic investigations should not be limited to serological assessments. They should be comprehensive, including at least also clinical, epidemiological and virological aspects, and link to environmental and animal studies. Therefore, it is recommended to liaise with relevant local professionals in these areas of expertise, including veterinary and environmental services to optimize each investigation. Furthermore, one or more other markers and outcomes of an outbreak can be included in specific outbreak protocols (e.g., genetics, cellular immunology, behavioral studies, economic assessments, mathematical modeling of transmission dynamics). If this is deemed feasible, relevant experts are to be included in the outbreak investigation team as well.

1.1 STUDY RATIONALE

Early warning for an impending emergence of a virus with pandemic potential can come from zoonotic outbreaks whereby human exposure to a zoonotic source occurs. The risk of such a zoonotic outbreak resulting in sustained human-to human transmission, and the outcomes if transmission occurs can be assessed through careful investigations. To optimize preparedness for a new influenza pandemic, protocols for systematic investigations of close contacts of infected patients to evaluate the extent of infection and into the transmission potential of the new virus. By building, where possible, on previously developed, tested and modified protocols, advantages can be gained from experiences in executing protocols in real life outbreaks. By standardizing protocols as much as possible, optimal scientific output and public health benefit can be realized.

1.2 OBJECTIVES

There are three primary objectives of this study:

1. Measure age-specific infection among close contacts of confirmed influenza patients in relation to zoonotic exposure

2. Identify (modifiable) risk factors for human infection

3. Quantify proportion of asymptomatic/sub-clinical infection

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

4. Identify (modifiable) risk factors for clinical and serological outcomes (e.g., disease/hospitalization/death)

5. Identify clusters and assess (risk factors for) potential human-to-human transmission

6. Assess serological outcomes in relation to human (and animal) virus shedding

COMMENT: Many other secondary objectives can be investigated in terms of epidemiological, immunological, clinical, virological, economic, genetic, behavioral, environmental, and animal factors. These are not discussed in detail in this protocol.

2.0 STUDY PROCEDURES

Here we describe a comprehensive assessment of contacts – including household, familial, social occupational contacts – of confirmed zoonotic influenza cases, which 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 influenza. 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 study will be implemented following virological confirmation of a zoonotic influenza in a human and/or animal source (Figure 1). The basic study design is a cross-sectional survey to estimate age-specific seroprevalence of infection following identification of a novel influenza, and a case-control analysis to identify risk factors for human infection. If further resources are available, we recommend a longitudinal follow-up to outcome and/or to seroconversion, with a first measurement as soon as possible after outbreak detection.

Core study: Cross sectional serosurvey 6-8 weeks after source detection followed by case (seropositive)-control (seronegative) analysis to identify risk factors for human infection; an unexposed control population may also be included in the core-study

Extended study: Cross sectional serosurvey as soon as source is confirmed with longitudinal follow-up of all subjects or random/selected sub-group every 6 weeks until outbreak or outbreak investigation is over; cohort analysis of risk factors

COMMENT: The exact timing of the core study and follow-up intervals with need to be modified with scientific knowledge of the outbreak of the novel virus under investigation. We make recommendations here for follow-up if the outbreak were due to H5N1 or H7N9.

COMMENT: Although not described as part of this investigation, we recommended that in conjunction with this investigation, environmental sampling and animal investigations should supplement these activities (Figure 1) in collaboration with relevant parties.
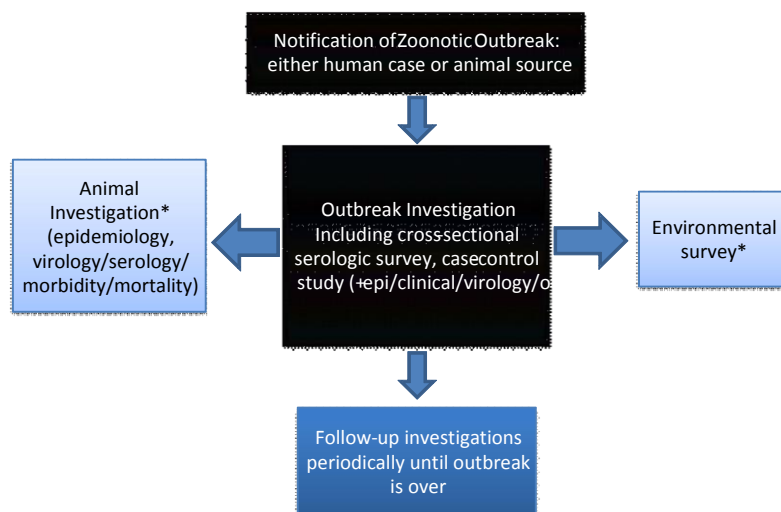

Figure 1. Study Design and Related Activities
*in collaboration with relevant bodies/parties

2.1   STUDY POPULATION

The specific study population for this investigation will depend on the source and local context of the outbreak (e.g., rural farm, industrial farm, market, country/state fair; Table 2). This study aims to enroll individuals (excluding health care personnel; *see CONSISE Protocol: Seroepidemiological Assessment of Health Care Personnel for Patients with Influenza*) who have had contact with confirmed zoonotic case(s) (either human or animal).

2.1.1   CONTACTS OF CONFIRMED HUMAN CASE

For the purposes of this study, a close contact of a confirmed human case is defined as an individual who has had direct (i.e., either face-to-face within 2 meters, or physical) contact with a confirmed human case, from one day before illness onset until the day that the case was isolated in the hospital for treatment or died or recovered. The individual should have a minimum amount of close contact of at least 5 minutes. Contacts can include household members, family contacts, relatives, visitors, neighbors, colleagues, teachers, classmates, co-workers, transport contacts, and others.

COMMENT: The specific definition of a close contact in terms of duration and distance may vary depending on the characteristics of the novel virus; however if there is variation in the definition between close contacts between studies, studies will be limited in their comparability.   The users of this protocol should document and report their definition of contact in terms of duration, distance and nature of contact.

COMMENT: Not all confirmed cases will develop symptoms or require treatment at a medical facility. Therefore the time period of exposure of a contact may be linked to last detection of virus by rRT-PCR in a clinical sample.

HEALTH CARE PERSONNEL

Health care personnel are not included in this study. A specific protocol for health care workers has been developed (*see CONSISE protocol: Seroepidemiological Assessment of Health Care Personnel for Patients with Influenza*).

2.1.2   CONTACTS OF CONFIRMED ANIMAL SOURCE

For the purposes of this study, a contact to a confirmed animal case is defined as an individual living within 3* km of the location where animal case was identified; or working for a minimum of 1 hour* in location (e.g., market, farm) where animal case was identified from one day before outbreak is identified until outbreak declared over or 10 days after last detection of virus.

Furthermore, if the *presumed* zoonotic source of an outbreak first detected via a confirmed human case can be identified (e.g., farm, market, fair), close contacts of the *presumed* zoonotic source

should be identified the same way as if the outbreak was detected based on a confirmed animal case.

*COMMENT: The geographic area from which contacts are sought in relation to the confirmed animal source will vary depending on where the outbreak is identified. The user is requested to specify in their reporting their criteria in terms of distance and time for recruitment of cases, to allow adjustment between studies.

Table 1: Selection of subjects for outbreak investigation, including serologic investigation

Outbreak Identification	Source of outbreak	Subjects	To evaluate
If confirmed source is animal†	Zoonotic source known	Close contacts*† of source: individuals living near or working at zoonotic source (e.g., village, market, animal farms, vets)	Animal-to-human transmission; and possible human-to-human transmission
If confirmed source is human‡	Zoonotic source assumed/suspected	Close contacts**† of confirmed case(s) as well as those living/working (being at) within 1-3km radius from where human case is presumed to have been infected*	Animal-to-human transmission; and possible human-to-human transmission
	Source is patient; exposure to zoonotic source unknown	Close contacts**† of confirmed case(s)	Human-to-human transmission

†identified through surveillance or notification
‡ identified before animal infection
* specified living within a maximum 3km distance or outbreak source, but may depend on location of outbreak; working at source will require a minimum time spent at source (e.g., see above for duration)
** if human case presents in health care system, subjects should include health care workers secondary transmission. There is a separate protocol for the assessment of HCP
 †Contacts can include household members, family contacts, relatives, visitors, neighbors, colleagues, teachers, classmates, co-workers, transport contacts, and others

2.1.3 SAMPLE SIZE CONSIDERATIONS

If the number of contacts is small, the aim should be to include all eligible contacts if resources permit. However, if the number of potential contacts is large then a sampling frame should be considered. For example:

[alt]   Depending on the context, the search for contacts can be more restricted, e.g., those living within 1, 2 or 3km* radius of source and/or those spending more time in close proximity to confirmed or suspected source.

[alt]   If census data is available data for the population under consideration and provided (prior) ethical approval has been obtained to contact individuals or households at random until sample size met. If households are chosen, aim to include all individuals in household.

*COMMENT: The geographic area from which contacts are sought in relation to the confirmed animal source will vary depending on where the outbreak is identified. The user of this protocol is requested to specify in their reporting their criteria in terms of distance and time for recruitment of cases, to allow adjustment between studies.

For the case-control study, the overall sample size will be determined by the number of confirmed cases of human infection with zoonotic influenza and the asymptomatic or sub-clinical persons with positive influenza (e.g., avian influenza A H5N1) antibody (cases). The following table shows the power to detect the odds ratio of exposure in cases relative to controls (seronegative persons) under two-sided type I error rate 0.05 and based on the assumptions that there are 20 cases (lab confirmed or seropositive) in the study, the probability of exposure in controls is 0.5, and the correlation coefficient for exposure between matched cases and controls is 0.2.   With four controls matched to each case, this study would have 86% power to detect the odds ratio of exposure that is at least 6 in cases relative to controls.

Table 2 Sample Size Calculations for Case-Control Study

Controls/per	Odds ratio	Power
4	4	66%
	5	78%
	6	86%
5	4	69%
	5	81%
	6	88%
6	4	71%
	5	82%
	6	89%

Source: [5]

2.1.4   ELIGIBILITY CRITERIA

Inclusion: Contacts of all ages, including young children.

COMMENT: Ideally, the study should include subjects of all ages, but it may be difficult to obtain blood samples from children of young ages.

Exclusion: No informed consent

2.2   ETHICAL CONSIDERATIONS

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

Comment: It is advised that you obtain ethical approval from relevant bodies (e.g., national Ministries of Health, Agriculture, etc) using a generic protocol such as this one prior to an outbreak. Once a novel virus is identified, the study design, questionnaires, sampling and consent forms can be modified rapidly to the actual situation. This may still have to be resubmitted to 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.

2.2.1 SUBJECT CONFIDENTIALITY

Enrolled subjects will be assigned a study identification number by study personnel for labeling of study questionnaires and clinical specimens. The link to specific individuals will be maintained by the *[enter organization carrying out this work]* and will not be disclosed to any other research personnel. Data provided to any agency supporting data analysis will include only the study identification number.

2.3 SUBJECT RECUITMENT AND DATA COLLECTION

2.3.1 RECRUITMENT OF SUBJECTS

Once an animal or human case is identified at a site –whether a market, farm, village or another location – the trained investigation team should identify all eligible subjects according to section 3.0 above. As discussed in section 3.0, the study population will be determined by whether the virus infection was confirmed in an animal or human source.

2.3.2 INFORMED CONSENT

During the site visit at the location where the human and/or animal source is confirmed, the purpose of the study will be explained to all eligible subjects and their consent obtained by a trained member of the outbreak 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.

2.3.3 MINIMUM DATASET

After enrollment and informed consent is obtained, a questionnaire will be administered. We recommend that a standardized minimum of epidemiologic and clinical data to be collected with any sera include the following:

> Age, gender, location, exposure (duration, proximity, intensity), occupation, symptoms, underlying conditions, risk factors (exposure) for infection (and severe disease (other than underlying conditions), vaccination (seasonal and pandemic) use, respiratory protection and antiviral use.

WHO has drafted a data collection form to be used for influenza viruses with pandemic potential, which will be used in the investigation. This data reporting form entitled "WHO Minimum Data Set Report Form: Human infection with an influenza virus with pandemic potential" can be found here: (add hyper link).

COMMENT: CONSISE considers the WHO report form the set default, including any WHO modifications for specific zoonotic pathogens.

2.3.4 RISK FACTORS FOR HUMAN INFECTION

A more detailed questionnaire will be used to evaluate risk factors for human infection, e.g., for humans exposed to a human source, for humans exposed to a confirmed zoonotic source, for humans exposed to a presumed zoonotic source, or for health care workers. These questions should be more specific and include aspects of timing of, frequency and duration of exposure(s) in the 14 days prior to symptom onset.

COMMENT: A bank of questions is under development by CONSISE. These questions will be organized under general headings such as: Demographic Information; medical and vaccination history; exposure; contact, etc, and will be provided on the CONSISE website (www.CONSISE.tghn.org). The user will be able to choose questions from this question bank for the user to develop their own questionnaire.

2.3.5 EXTENDED STUDY – FOLLOW UP

All subjects interviewed at baseline should be followed up every 6 weeks until the outbreak or investigation is declared over. Depending on updated scientific insight and/or logistical restraints might result in modified time periods between data collection. Sera collection and questionnaire administration should be identical to what was conducted at baseline.

2.3.6 COMPENSATION AND INCENTIVES TO PARTICIPATE

Households and participants can be compensated for their participation in the study in accordance with local requirements and standards.

COMMENT: It may be possible to offer compensation - according to local requirements and standards - to participants for participation in the study, and/or for specific interactions such as collection of sera. Please check with your local IRB regarding compensation.

2.3.7 PREVENTION OF INFLUENZATRANSMISSION IN FRONT-LINE STAFF

Front-line staff including all study personnel will be trained in infection control procedures including proper hand hygiene and the correct use of surgical or respiratory face masks, 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 infection between household members or between households.

3.0 LABORATORY EVALUATIONS

3.1 SPECIMEN COLLECTION, TRANSPORTATION

WHO has provided guidance and protocols for specimen collection, preserving and shipping for H5N1, which can be found here:
http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/

3.2 VIROLOGIC METHODS

3.2.1 H5N1

Recommendations and laboratory procedures for detection of avian influenza A(H5N1) virus in specimens from suspected human cases have been drafted by WHO and are available here:
http://www.who.int/influenza/resources/documents/RecAIlabtestsAug07.pdf

3.2.2 H7N9

Real-time RT-PCR Protocol for the Detection of A(H7N9) Influenza Virus has been provided by WHO and can be found here:
http://www.who.int/influenza/gisrs_laboratory/cnic_realtime_rt_pcr_protocol_a_h7n9.pdf

3.3 SEROLOGIC METHODS

3.3.1 H5N1

[to be added]

3.3.2 H7N9

COMMENT: Serology assays for H7N9 virus are currently being developed in many laboratories worldwide, however sera from confirmed human cases are urgently needed in order to validate assay specificity and sensitivity. See CONSISE website for further information about H7N9 serologic assays: www.CONSISE.tghn.org.

3.3.3 POSITIVE CRITERIA OF LABORATORY ASSAYS

H5N1

[to be added]

H7N9

[to be added]

4.0   ENDPOINTS

4.1   STUDY OUTCOME MEASURES

4.1.1   PRIMARY OUTCOMES

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

- Age-specific infection rates as measured by seropositivity

- Identification of potentially modifiable risk factors for human infection

- Quantification of the proportion of asymptomatic/sub-clinical with infection (seropositivity)

4.1.2   SECONDARY OUTCOMES

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

- Identification of potentially modifiable risk factors for clinical outcome (e.g., disease/death)

- Quantification of the proportion of asymptomatic/sub-clinical with infection (seropositivity)

- Identification of any clusters

- Potential assessment of risk factors for potential human-to-human transmission (depending on the questionnaire used)

4.2 STATISTICAL ANALYSES

4.2.1 FOR PRIMARY OBJECTIVE 1

To calculate age-specific infection rates, we recommend that you use the following age-categories: young children (suggested age group: 0 to <5 years); school-aged children (suggested age group: 5 to <15 years; young adults (suggested age group: 15 to <50 years); older adults (suggested age group: 50 to <65 years); and elderly (suggested age group: ≥ 65 years).

COMMENT: We suggest that you report results for young children, school aged, young adults, adults, and elderly using the above cut offs. However if the exact age is collected, it is possible to report for any age group of interest.

The numerator will be those who tested positive (see section 5.3 for criteria for seropositivity) in the age group and the denominator will be all of those tested in your study sample in the same age group.

COMMENT: Depending on your sample size, it may not be possible to determine age-specific infection rates.

4.2.2 FOR PRIMARY OBJECTIVE 2

To measure risk factors for infection, you need to compare the behaviors and practices of your cases (i.e., sero-positive) versus controls (i.e., sero-negative). Controls could be matched on some factors including age, sex, village of residence and households with infected animals (if applicable). 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.

The reported practices among cases and (matched) controls should be compared using appropriate statistical tests, e.g., compare proportions with fisher's exact test, compare mean values with t tests and median values with Kruskal Wallis tests.

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. Multivariate 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.[6]

4.2.3 REPORTING RESULTS

Reports of the results of this study should include sufficient information to permit pooling of data with similar studies. It is important to fully document the study design, including the definition of study area and criteria for the selection of cases and controls, the approach to ascertainment of index cases and secondary cases, the duration of follow-up, and the laboratory methods used.

Ideally, information would be collected in a standard format and anonymized data shared among multiple groups running similar protocols. A standard database format is under development.

5.0   OTHER CONSIDERATIONS

Although not described as part of this investigation, we recommended that in conjunction with this outbreak investigation, environmental sampling including testing of areas around the infected household and potential contaminated water sources and retrospective animal mortality investigations should supplement these activities in collaboration with relevant parties. See [7,8] for more details.

6.0   BACKGROUND OF CONSISE

The following protocol *Investigation of Zoonotic Influenza Infection in Humans* was developed by CONSISE, the Consortium for the Standardization of Influenza Seroepidemiology, [9,10] a global partnership aiming to develop influenza investigation protocols and standardize seroepidemiology to inform public health policy. This international partnership was created out of a need, identified during the 2009 H1N1 pandemic, for seroepidemiological data to better estimate infection attack rates and severity of the pandemic virus and to inform policy decisions[10,11].

One of the limitations of surveillance during the 2009 influenza A(H1N1) pandemic (H1N1pdm09) was that seroepidemiological data and analyses based on these were not available in a timely manner[12-14]. During the past two years, considerable seroepidemiological work was undertaken[11,15]. However, many of the results emerged late, well after when they would be most useful to inform policy-related debates, issues and decisions, specifically those around understanding age-specific severity of the pandemic virus. Additionally, despite many H1N1pdm09 seroepidemiological studies being undertaken, the direct comparability of results was limited due to a lack of standardization in the epidemiological data collected and the laboratory methods used to assess the presence of cross-reactive antibodies to the H1N1pdm09 virus. Furthermore, there are more general concerns over the quality assurance of laboratories[11,16].

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, 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. Members of the steering committee are listed in Appendix I. Three global meetings have been held to date, the first in Canada hosted by PHAC in early 2011, 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 six generic detailed protocols should be developed that can be used in pandemic outbreak settings and for routine serologic collection during non-pandemic seasons[9]. A seventh protocol specifically assessing health care personnel was added after the December 2011 meeting (Table 3). In doing so, our aim is to adopt a common framework for serological studies, standardize methodology and reporting. The attached document is one of these protocols.

Table 1 – CONSISE Protocols Under Development

	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
	3. Household transmission studies for pandemic influenza	Estimate household secondary infection risk, and factors associated with variation in the secondary infection risk 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) Describe correlation between infection, disease and serology
	5. Assessment of Health Care Personnel	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

Source: [5]

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 influenza virus. It was created in consultation with and reviewed by an ad hoc group of technical experts and has undergone preliminary review

(see appendix for list of reviewers). We suggest that seroepidemiologic studies which are part of a comprehensive set of investigations will be most useful to address public health questions.

This document is intended as a template that can be used to generate an actual study protocol in the shortest time possible. Therefore, comments or alternatives, that would not appear in an actual protocol, are kept to a minimum. Where they occur, comments are in purple font. Alternate blocks of text that can be included in the final document are marked as [Alt 1], [Alt 2], etc.

Specifically, this protocol *"Outbreak Investigation of Zoonotic Infection in Humans exposed to a confirmed source"* was drafted by CONSISE members Maria Van Kerkhove, Marianne van der Sande, Othmar Engelhardt, John Wood, and Angus Nicoll with input from many partners (Appendix II) 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

Questions about the generic protocol should be directed to Maria Van Kerkhove at 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

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7.0   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.

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