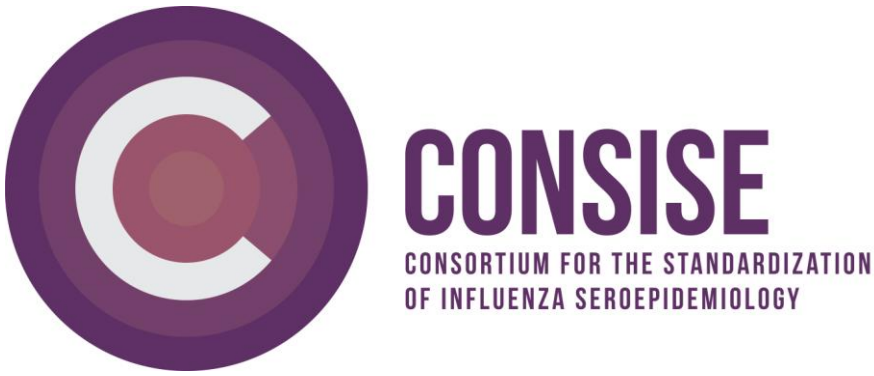
Prospective study of household transmission of influenza

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

Title: Prospective study of household transmission of influenza.

Study Design: Prospective cohort study of household contacts of cases of confirmed influenza.

Study Duration: Study enrolment will be up to one year after the start of an epidemic/pandemic, but focused on the early epidemic phase before widespread community transmission.

Study Visits: Enrolled households will complete a minimum of four home visits within a month of enrolment. Respiratory specimens, sera, and information on risk factors and symptoms will be collected from index cases and their household members.

Primary objectives: 1: To determine the household secondary infection risk, and factors associated with variability in the secondary infection risk. 2: To characterize secondary cases including their range of clinical presentation and the asymptomatic fraction. 3: To investigate serologic response following confirmed influenza infection.

Endpoints: Study outcome measures include PCR-confirmed influenza, serologically confirmed influenza and reported illnesses among household contacts.

CONTENTS

1.0 BACKGROUND INFORMATION

1.1. SCIENTIFIC BACKGROUND

The detection and spread of a new pandemic influenza virus is characterized by real uncertainty over the key epidemiological, clinical and virological characteristics of this novel virus and in particular its ability to spread in the human population and its virulence (case-severity).

The household, defined as a person or a group of people living in the same residence, provides a strategic setting to track influenza infections among close contacts of cases because the denominator is well-defined, exposure is similar and follow-up of household contacts is feasible. It is also important to monitor transmission in households where up to 30% of influenza virus transmission is believed to occur to understand the clinical spectrum of infection [1,2]. Household transmission studies allow us to systematically measure these dynamics [3].

COMMENT: It is possible to define households and household contacts in other ways, for example including only persons who commonly reside in the same household as the index case as well as residing there for at least one night during the household exposure period. The definition of household and household contact may need to be clarified in certain settings, where there can be variation depending on political, historical, and cultural factors. One possible generic definition of a household is a dwelling or group of dwellings with a shared kitchen or common opening onto a shared household space. This will be discussed in section 2.2 below.

A substantial fraction of both seasonal and pandemic influenza virus infections are asymptomatic or associated with mild disease that does not require medical attention [4]. Infections identified in household contacts could potentially be generalizable to naturally-acquired pandemic influenza virus infections (in contrast to for example only cases presenting for ambulatory care among which there would be fewer mild cases). By following individuals with similar levels of exposure to infection, i.e. exposure within the household to an index case with confirmed influenza, household studies can permit identification of this fraction.[3,5] More generally, follow-up of household contacts that develop infection can provide useful information about the range of clinical presentations and risk (by for example age) of asymptomatic and symptomatic influenza.

Humoral antibody provides the body with protection against influenza virus infection. Higher titers of humoral antibody against a specific strain correlate with protection against infection by that strain [6]. Because humoral antibody titers tend to rise following influenza virus infection and remain elevated for a prolonged period, surveillance of antibody seroprevalence in a population can permit inference about the cumulative incidence of infection in that population [7]. Inferences based on seroprevalence are simpler for pandemic viruses where initial seroprevalence is very low. The characteristics of rises in antibody titer following influenza virus infection can vary by strain and method of ascertainment. For example in the 2009 pandemic, around 90% of patients with medically-attended PCR-confirmed influenza infection had significant rises in antibody titer against

the pandemic virus, 2-3 weeks after infection.[8] Household studies provide the opportunity to follow-up confirmed cases to ascertain these antibody kinetics.

1.1.1 RATIONALE

The intention of this study is to allow an early understanding of some of the key clinical, epidemiological and virological characteristics of the pandemic influenza virus. The study is not intended as a case-counting system, but rather as a rapid surveillance tool for collecting information on important epidemiologic parameters in a sample of laboratory confirmed cases of infection and their household (and non-household) contacts in the early stages of a pandemic.

In the context of serological surveillance, information provided by this study is also essential to clarify the sensitivity and specificity of serologic measures of infection.

1.2 OBJECTIVES

1.2.1 PRIMARY OBJECTIVES

There are three primary objectives of this household transmission study:

1. To estimate the secondary infection risk for household contacts on an individual basis, and factors associated with variation in the secondary infection risk.
2. To characterize secondary cases including the range of clinical presentation and the asymptomatic fraction.
3. To investigate serologic response following confirmed influenza virus infection.

1.2.2 SECONDARY OBJECTIVES

Household transmission studies provide rich data that can permit evaluation of secondary objectives such as, but not limited to:

1. To estimate household serial intervals.
2. To estimate the effectiveness and safety of antiviral treatment and prophylaxis.
3. To estimate duration of infectiousness.
4. To characterize duration and severity of influenza-associated illnesses.

COMMENT: Many other secondary objectives can be investigated in terms of clinical, virological, serological, and behavioral factors. These are not discussed further.

1.3 RELEVANT DEFINITIONS

Index case: the first subject with a laboratory confirmed influenza infection in a household.

Household: for the purposes of this study, a household is defined as a person or a group of people living in the same residence. In practice, the technical definition may vary[9].

Household contact: any person living in the same household as the index case, defined explicitly in section 2.2.

Household secondary infection risk (SIR): the proportion of household contacts of an index case who subsequently become infected with influenza.

2.0 STUDY DESIGNS AND PROCEDURES

2.1 STUDY DESIGN

In this cohort study, index cases are identified by surveillance of ill individuals for recent infection with a novel influenza virus, followed by collection of clinical, virological and serological data from their household members (and potentially other close contacts).

This cohort study is therefore a case-ascertained study and could be referred to as a household transmission study [3]. This is distinct from a cohort study in which a group of disease-free households are recruited and then followed over time. Household transmission studies are more efficient than cohort studies of initially uninfected people when interest is in early ascertainment of the clinical, epidemiological and virological characteristics of the pandemic influenza virus because the risk of primary or secondary infection in such a "sleeping" cohort would be expected to be low during the early stage of the pandemic before community transmission was established or widespread.

Key considerations in the study design are ascertainment of index cases and their households, and the scope, method, duration and intensity of follow-up.

COMMENT: It is possible to conduct retrospective evaluation of household transmission [3], although prospective evaluation is likely to provide more reliable and detailed information and the opportunity to obtain more useful biological specimens.

COMMENT: Potential bias may be introduced by over-ascertaining index cases in children (more likely to be symptomatic and more likely to be bought to the doctor if symptomatic) and therefore over-representation of households with children. Children may transmit more than adults – longer excretion, poorer hygiene, closer contacts. See later section on analysis.

2.2 STUDY POPULATION

The study population is households containing two or more individuals where at least one individual is infected with influenza (the index case).

2.2.1 IDENTIFICATION OF INDEX CASES

An index case is any person meeting the following case definition:

1. Acute upper respiratory tract infection with recent onset, AND
2. Respiratory specimen testing positive for pandemic influenza by specific real-time PCR (or if a specific assay has not yet been developed, a positive result for influenza A by PCR confirmed as pandemic influenza by sequencing of the PCR amplicon).

3. The first date of onset of illness in the household since first assumed date of introduction of the virus into the community

COMMENT: It is possible to limit the clinical criteria to fever or other specific symptoms. It is possible to broaden the laboratory criteria to include serology or other approaches to confirming infections.

COMMENT: If there are a large number of eligible index cases, and it is infeasible to follow up all households, a sampling strategy for inclusion in this study must be determined. For example, it may be logistically efficient to focus on specific geographic areas.

COMMENT: Primary interest is to investigate lab confirmed cases, but this may be complicated by reporting and testing delays. In some settings, it may be worthwhile enrolling patients when they first present or become symptomatic, and then exclude if they are confirmed as cases.

COMMENT: In some situations, PCR-confirmed cases may need to be notified to relevant authorities, potentially adding complexity to the study conduct.

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

2.2.2 DEFINITION OF HOUSEHOLDS AND HOUSEHOLD CONTACTS

A household is defined as a group of two or more people living together in a domestic residence (residential institutions, such as boarding schools, dormitories, hostels or prisons will be excluded). A household contact is defined as any person who had resided in the same household as the index case for at least one night during the household exposure period (one day before to seven days after onset of illness in the index case) [10].

COMMENT: It is possible to define households and household contacts in other ways, for example including only persons who commonly reside in the same household as the index case as well as residing there for at least one night during the household exposure period. The definition of household and household contact may need to be clarified in certain settings, where there can be variation depending on political, historical, and cultural factors. One possible generic definition of a household is a dwelling or group of dwellings with a shared kitchen or common opening onto a shared household space.

COMMENT: It is also possible to extend this study to include close or casual contacts of index cases other than household members as defined above. For example the study could include people who visited the household, or those who stayed overnight (for example in slumber parties), or contacts in other specific settings such as school or work. It is important to have a clear definition of a close or casual contact, and/or valid measures of degree of exposure to infection.

2.3 STUDY PROCEDURES

2.3.1 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 etc) using a generic protocol such as this one prior to an epidemic/pandemic. Once a novel influenza virus is detected anywhere in the world, the study design, questionnaires, sampling and consent forms can be modified rapidly to the actual situation. This may still have to be resubmmitted 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.

2.3.2 DURATION OF FOLLOW-UP

The duration of follow-up for households is 28 days.

COMMENT: The duration of follow-up may vary depending on the characteristics and transmission dynamics of the virus, antibody kinetics and specific research priorities.

2.3.3 RECRUITMENT PERIOD

This study will be conducted in the early phase of the pandemic (see Figure, Time Period “A”). Recruitment will begin with identification of the first laboratory-confirmed cases of new pandemic influenza in a country.

COMMENT: If there is a strong local notification system, then it might be possible to rely on these notifications for index case identification. Another option is to identify geographical locations with early outbreaks and intensifying surveillance to identify index cases.

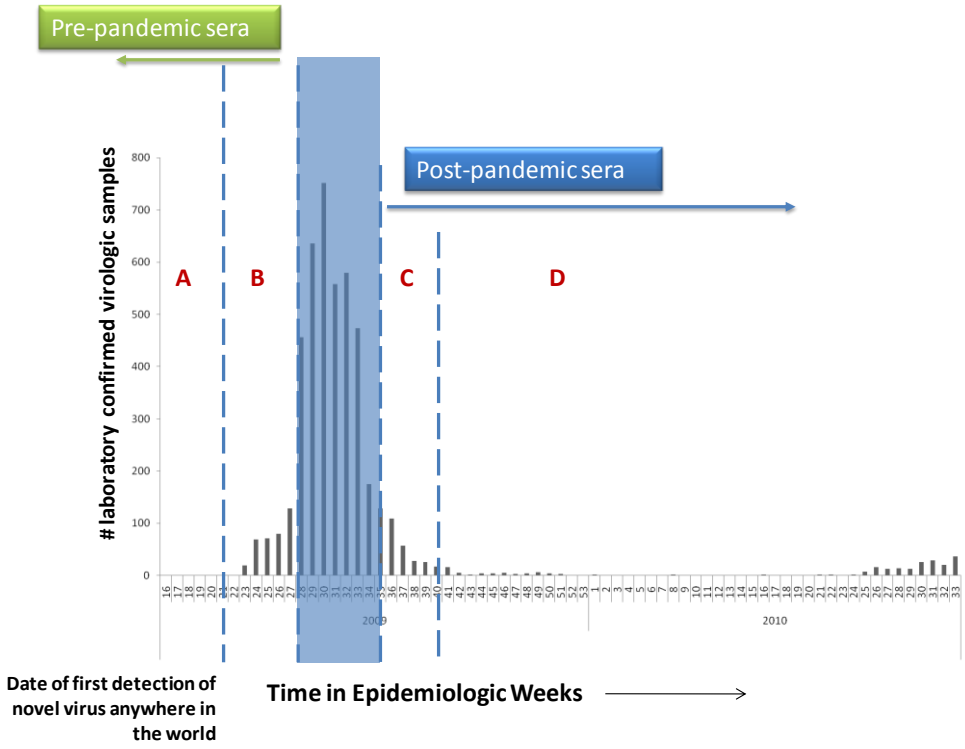


Figure 1 Characterization of sera collection timing in relation to national epidemic curve

Legend: The legend shows a hypothetical curve of disease activity in a country. The arrows indicate when sera could be collected for this protocol. "A" and "B" indicate timings when pre-epidemic sera could be collected, the shaded area indicates example of peak activity and "D" represents the time when post-epidemic sera should ideally be collected. "C" indicates the time period in which an early sample of sera could be collected for a preliminary, early estimate although it should be noted that collecting sera in this time period will underestimate the infection rate. The time period "C" might be used if, for example, a vaccination campaign is being planned which could complicate later interpretation of results.

The intention of this study is to provide rapid and early information on the clinical, epidemiological and virological characteristics of the pandemic influenza virus. Recruitment will therefore focus on the early stage of the pandemic. In the 2009 pandemic, similar studies were conducted for the first 2-3 months after identification of initial cases in April 2009 [3].

COMMENT: It is also possible to delay commencement of the study, and/or to extend follow-up for a longer period, including the period of peak pandemic influenza activity, depending on the specific objectives of the study. This raises potential analytical issues – in particular the competing risk of acquiring infection from outside of the household as well as creating difficulties with interpretation of serologic data.

2.3.4 RECRUITMENT OF INDEX CASES

Index cases meeting the inclusion criteria will be recruited from local ambulatory care clinics. Informed consent from index cases should be obtained at this time, preferably along with

preliminary assent to participate from the household. At recruitment, a baseline questionnaire will be administered to collect basic socio-demographic and clinical information on the confirmed cases and to collect details of their household contacts together with biological sampling.

COMMENT: Ambulatory care clinics together with the public will need to be alerted to identify suspect cases (e.g. persons with acute respiratory illness returning from a pandemic affected area or with recent history of contact with a laboratory confirmed case), who will need to be laboratory investigated.

COMMENT: Alternative strategies for recruitment of index cases includes selection of index cases from among school outbreaks[11-13] or from among hospitalized cases although these approaches may lead to biases for various reasons. [3]

2.3.5 INFORMED CONSENT

During the home visit, the purpose of the study will be explained to all household contacts and their consent obtained by a trained nurse. Consent for children aged 17 years or younger will be obtained from their parents. Assent will also be obtained for children aged between 7 through 17 years.

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

COMMENT: If less than 100% of household members consent, there will be incomplete information on infections in household contacts. It may be possible to tease out the transmission dynamics based on incomplete data; another option for preliminary analysis is to exclude these households.

2.3.6 BASELINE QUESTIONNAIRE

The baseline head of household questionnaire is intended to identify relevant information on all eligible household members, and relevant information on the household environment. Examples of relevant information on household members include age, sex, symptoms, influenza vaccination history, pre-existing health conditions, and medications prescribed including receipt of antiviral treatment or prophylaxis. An example of relevant information on the household environment includes household size and location.

2.3.7 FOLLOW-UP

Following recruitment of index cases, a home visit is conducted to establish eligible participants, to collect relevant socio-demographic and clinical information, and to allow virologic confirmation of co-primary or secondary cases and baseline antibody seroprevalence. This initial home visit should be conducted as soon as possible (ideally within 2-3 of symptom onset) after identification and recruitment of the index case. At the initial home visit, respiratory specimens will be collected from *all* members of the household for virologic testing, a baseline questionnaire will be administered, and serum specimens will be collected from all willing household members regardless of illness.

Symptom diaries will be provided for all household members to complete over the following 10 days.

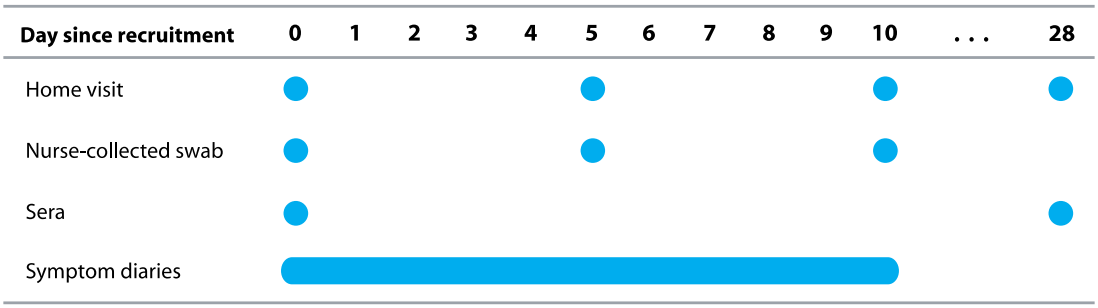
Subsequent home visits will be undertaken after 5 (±1), 10 (±2) and 28 (±5) days. At the day 5 and day 10 visits, respiratory specimens will be collected from all members of the household for virologic testing, irrespective of symptoms, and at the day 28 visit serum specimens will be collected from all consenting household members. Home visit nurses will also check the completeness of symptom diaries and on day 10 the symptom diaries will be collected.

It is assumed that detectable virus shedding following influenza infection lasts for 4-7 days following illness onset [14], although information from this study would help to clarify the duration of shedding among individuals with confirmed infection. For household transmission studies in which the primary objective is to precisely estimate the secondary risk of infection, the optimal timing of a single home visit is around 6 days after illness onset in the index case[15]. Therefore a home visit is planned 5 (±1) days after index case recruitment in this protocol. This is because an earlier home visit might miss secondary cases that appear later, while a later home visit might miss the earliest secondary cases in which shedding has ceased. This home visit is also an opportunity to identify additional/new household contacts of the index case during the exposure period.

In this protocol a home visit is also planned 10 (±2) days after index case recruitment, to provide additional virologic data and permit identification of tertiary cases.

A final home visit is planned 28 (±5) days after index case recruitment, for collection of convalescent sera from all willing household members. The timing of this visit should be late enough to identify rises in antibody titers among infected individuals.

Error! Reference source not found. **below provides an overview of the follow-up procedures.**



COMMENT: An alternative, if capacity permits, is to include more frequent home visits. This would provide richer virologic data and could identify additional secondary cases.

COMMENT: An alternative is to survey household contacts for illnesses prospectively (for example by regular telephone contact) and only visit homes in which one or more household contact reports illness. However, this approach is likely to underascertain infections among household contacts

because of underreporting of illnesses and because not all infections may lead to a clinical illness meeting surveillance criteria.[3] The rationale for collecting swabs from asymptomatic household contacts is to estimate the proportion of infections that are asymptomatic, and to maximize the number of secondary infections that are correctly identified.

COMMENT: Collection of serology is an extremely important component in this study protocol. Acute and convalescent sera collected from PCR-confirmed cases can be used to develop and validate serologic assays, while sera collected from household contacts may give important insights into the risk of infection (particularly asymptomatic infection) and the correlation of protection against infection versus pre-existing antibodies against the pandemic virus or other viruses.

COMMENT: In the proposed design, the index case should truly be the person in the household to contract infection, as described in section 4.1. If this criteria may not be met in particular households, for example household contacts are identified with infection at the initial home visit, those households might be excluded from analyses of transmission dynamics. If the study design is broadened to follow up any confirmed case, including non-index cases by design, it can be difficult to interpret the results because of the uncertainties over the reliability of retrospective information on introduction of infection to the household, and the lack of laboratory data across the entire outbreak of infection in a household.

COMMENT: If a new potential secondary case is identified at the day 10 home visit, or if a new potential secondary case is identified after that visit, it is possible to include additional home visits for example at day 15, and provide additional symptom diaries.

COMMENT: In some settings it may not be feasible to conduct home visits, and there are a number of alternatives. It is possible to invite participating household members to visit a specific location such as a local ambulatory care clinic for follow-up, although this may be less acceptable to participants. It is possible to actively follow up households by telephone interview to provide information on illnesses among household contacts [3]. Finally, it is possible to follow up households for example by post, SMS or internet. If only illness data are collected, it may be possible to use other sources of information to correct estimates of the secondary infection risk.[3]

COMMENT: As an alternative to collection of respiratory specimens by trained nurses during home visits, it may be feasible to request participants to swab themselves. With appropriate training, self-swabs can be a valid alternative for virologic confirmation of influenza infections [16,17].

2.3.8 SYMPTOM DIARIES

Symptom diaries will be provided to each household member to record presence or absence of various signs or symptoms including body temperature, feverishness, cough, sore throat, headache, myalgia, coryza, phlegm, etc. each day. Symptoms will be self-reported by household members aged 15 years or older, and proxy reported by adults for any children below the age of 15.

It is important for household members to confirm absence of clinical signs and symptoms in the symptom diary, for example by ticking a box titled “no symptoms today” or by answering “no” to each symptom listed.

COMMENT: In the context of a new virus with uncertain clinical presentation and spectrum, symptom diaries may be broadened to include vomiting, diarrhea, abdominal pain, etc. Symptom diaries may be requested for longer than 10 days, for example 14 or 21 days.

2.3.9 COMPENSATION AND INCENTIVES TO PARTICIPATE

Households and participants will not be compensated for their participation in the study.

COMMENT: It is possible to offer compensation to participants for participation in the study, and/or for specific interactions such as collection of sera.

2.3.10 PREVENTION OF INFLUENZA IN FRONT-LINE STAFF

Front-line staff including study nurses will be trained in infection control procedures including proper hand hygiene and the correct use of gloves, gowns and surgical 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 nurses acting as a vector of infection between household members or between households.

COMMENT: Depending on the genetic and antigenic characteristics of the new strain, there may also be an argument for the administration of seasonal influenza vaccination to the front-line staff members.

COMMENT: Depending on the transmissibility and severity of the new strain, there may also be an argument for stricter infection control procedures among the front-line staff, such as use of goggles, face shields, N95 respirators etc.

3.0 LABORATORY EVALUATIONS

The precise test protocols are still being evaluated but it is intended that the Haemagglutination-Inhibition (HI) assay and a Virus Neutralisation protocol will be used in seroepidemiological studies.

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/RecAllabtestsAug07.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]

Virus sequence data can be used to clarify household transmission chains [18,19] and could be incorporated into epidemiological analysis of the early spread of the pandemic virus. Analytic methods to estimate the basic reproductive number based on sequence data are in development.

4.0 STATISTICAL CONSIDERATIONS

4.1 STUDY OUTCOME MEASURES

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

- PCR-confirmed and serologically confirmed influenza infection among household contacts.
- Association of risk factors with PCR-confirmed infection, serologic infection and illness among household contacts.
- Characteristics of clinical illnesses among household contacts with PCR confirmed and serological confirmed infection
- Characteristics of the serologic response in PCR-confirmed index and secondary cases

4.2 SAMPLE SIZE CONSIDERATIONS

Table 1 below indicates the precision available for estimates of the secondary infection risk based on studies of differing sample sizes. Larger studies would also permit more robust analysis of potential factors affecting the secondary infection risk, more precise estimation of the asymptomatic fraction, and more detailed characterization of serologic responses following infection.

Table 1: 95% CIs for different secondary infection risk estimates and varying sample sizes assuming 2.9 contacts per index case [20]

number of index cases	number of contacts	Secondary infection risk estimate			
		5%	10%	15%	20%
50	147	(0.0%, 10,0%)	(5.0%, 15.0%)	(10.0%, 20.0%)	(15.0%, 25.0%)
150	441	(2.1%, 7.9%)	(7.1%, 12.9%)	(12.1%, 17.9%)	(17.1%, 22.9%)
250	735	(2.8%, 7.2%)	(7.8%, 12.2%)	(12.8%, 17.2%)	(17.8%, 22.2%)
350	1028	(3.1%, 6.9%)	(8.1%, 11.9%)	(13.1%, 16.9%)	(18.1%, 21.9%)

4.3 STATISTICAL ANALYSIS

4.3.1 FOR PRIMARY OBJECTIVE 1

Primary objective 1: To estimate the household secondary infection risk, and factors associated with variation in the secondary infection risk.

The numerator will be determined as the number of household contacts with PCR-confirmed influenza infection, while the denominator will be determined as the total number of household contacts.

This proportion, which can be referred to as the secondary infection risk [3], represents an overall risk of infection among household contacts for a defined time period. Alternative terminology for this proportion is the secondary attack rate or ratio, but 'secondary infection risk' is preferred since many infections are mild and the measure is neither a rate nor a ratio [3].

The secondary infection risk as measured by the simple proportion above is a mixture of the risk of infection from inside as well as outside the household, and it is possible to formulate mathematical models to estimate the relative contributions of each[21].

For the subset of households with serological data available (assuming compliance with serology will be below 100%), the numerator will be determined as the number of household contacts with a serologically confirmed influenza infection, while the denominator will be the total number of household contacts who provided sera.

COMMENT: The distribution of times between illness onset in the index case and secondary cases, and the empirical estimate of the mean and variance of the clinical onset serial interval may be of interest to other scientists, as this distribution is of relevance for some mathematical models.

COMMENT: It is informative to compare PCR results with symptom diaries, and be wary of contamination of swabs between household members.

4.3.2 FOR PRIMARY OBJECTIVE 2

Primary objective 2: To characterize secondary cases including their clinical presentation and the asymptomatic fraction.

The denominator will be determined as the number of household contacts with PCR-confirmed influenza infection. The numerators of interest are the numbers of those contacts reporting various signs and symptoms of infection (e.g. fever, cough) and the proportion of those contacts reporting no signs or symptoms (i.e. the asymptomatic fraction). If sample size permits, it may also be of interest to determine the proportion of those contacts seeking medical care.

For the subset of household contacts with serologic data, the denominator can be determined as the number of household contacts with serologic evidence of recent infection, with analysis of the numerators described above. This will allow calculation of the asymptomatic fraction as the proportion of household contacts with serologic evidence of infection that did not report any systemic or respiratory signs or symptoms during the follow-up period..

It is also of interest to determine the correlation between virologic and serologic evidence of infection among household contacts, for example by calculating the proportion of household contacts with serologic evidence of infection that had PCR-confirmed influenza virus infection, and vice versa.

4.3.3 FOR PRIMARY OBJECTIVE 3

Primary objective 3: To investigate serologic response following PCR-confirmed influenza infection.

Among household members with PCR-confirmed infection (including index cases and household contacts), endpoints of interest include the convalescent antibody titer, and the ratio between

baseline and convalescent antibody titer since date of onset of illness. The former may be summarized across all cases via the geometric mean titer, while the latter may be summarized across all cases via the geometric mean titer rise.

4.4 REPORTING RESULTS

Reports of the results of this study should include sufficient information to permit pooling of data with similar studies. Important information to report include (1) the number of households, the number of household contacts, and (1) the number of PCR-confirmed cases among household contacts; (2) the number of symptomatic household contacts; (3) the number of household contacts with serologic evidence of infection. If sample size permits, these numbers should be stratified by age.

It is also important to fully document the study design, including the definition of households, 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 BACKGROUND OF CONSISE

The following protocol *Prospective study of household transmission of influenza* was developed by CONSISE, the Consortium for the Standardization of Influenza Seroepidemiology,[22,23] 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[23,24].

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[25-27]. During the past two years, considerable seroepidemiological work was undertaken[24,28]. However, many of the results emerged late, well after when they would have been 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.[24,29]

Recognizing this gap, several institutions including the World Health Organization (WHO), the Public Health Agency Canada (PHAC), European Centres for Disease Prevention and Control (ECDC), US Centers for Disease Control and Prevention (USCDC), Imperial College London (ICL), Public Health

England (UKPHE), 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 and the second in Stockholm Sweden in December 2011 hosted by ECDC, with 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 for serologic studies in pandemic outbreak settings and for serologic studies during non-pandemic seasons[30]. A seventh protocol, specifically for the assessment of health care personnel was added after this meeting (Table 2). In doing so, our aim is to adopt a common framework for serological studies, standardize methodology & reporting. The attached document is one of these protocols.

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. This protocol was intended to be used for influenza but may be adapted for other pathogens.

Specifically, this protocol *Prospective study of household transmission of pandemic influenza* was drafted by CONSISE members Benjamin J. Cowling, Richard Pebody, Othmar Engelhardt, John Wood, Angus Nicoll and Maria D. Van Kerkhove with input from many partners and influenced by the following protocols, shared with CONSISE for the purposes of developing this protocol:

- *Household transmission of influenza virus*, provided by the University of Hong Kong (Benjamin Cowling, PI)
- *"The First Few Hundred (FF100)" Project. Epidemiological Protocols for Comprehensive Assessment of Early Swine Influenza Cases in the United Kingdom*, provided by Public Health England (shared by Richard Pebody)
- *First 100 Cases Investigation of Novel Influenza A H1N1 (Swine Flu)*, provided by the South African National Institute for Communicable Diseases (NICD)
- Review of H1N1pdm09 household transmission studies[9]

Questions about this 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 authors of those protocols.

We hope you find this protocol helpful.

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Table 2 – 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: [30]

6.0 REFERENCES

1. Chao DL, Halloran ME, Obenchain VJ, Longini IM, Jr. FluTE, a publicly available stochastic influenza epidemic simulation model. PLoS Computational Biology 2010;6(1):e1000656.

2. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature 2006;442:448-452.

3. Lau LL, Nishiura H, Kelly H, Ip DK, Leung GM, Cowling BJ. Household transmission of 2009 pandemic influenza A(H1N1): a systematic review and meta-analysis. Epidemiology 2012 (in press).

4. Patrozou E, Mermel LA. Does influenza transmission occur from asymptomatic infection or prior to symptom onset? Public Health Reports 2009;124(2):193-6.

5. Jackson ML, France AM, Hancock K, Lu X, Veguilla V, Sun H, Liu F, Hadler J, Harcourt BH, Esposito DH, Zimmerman CM, Katz JM, Fry AM, Schrag SJ. Serologically confirmed household transmission of 2009 pandemic influenza A (H1N1) virus during the first pandemic wave--New York City, April-May 2009. Clinical Infectious Diseases 2011;53(5):455-62.

6. Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. Journal of Hygiene 1972;70(4):767-77.

7. Kelly H, Peck HA, Laurie KL, Wu P, Nishiura H, Cowling BJ. The age-specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination. PLoS ONE 2011;6(8):e21828.

8. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet 2010;375(9720):1100-8.

9. Lau LLH, Nishiura H, Kelly H, Ip DKM, Leung GM, Cowling BJ. Household Transmission of 2009 Pandemic Influenza A (H1N1): A Systematic Review and Meta-analysis. Epidemiology 2012;23(4):531-542 10.1097/EDE.0b013e31825588b8.

10. Carcione D, Giele CM, Goggin LS, Kwan KS, Smith DW, Dowse GK, Mak DB, Effler P. Secondary attack rate of pandemic influenza A(H1N1) 2009 in Western Australian households, 29 May-7 August 2009. Eurosurveillance 2011;16(3).

11. Calatayud L, Kurkela S, Neave PE, Brock A, Perkins S, Zuckerman M, Sudhanva M, Bermingham A, Ellis J, Pebody R, Catchpole M, Heathcock R, Maguire H. Pandemic (H1N1) 2009 virus outbreak in a school in London, April-May 2009: an observational study. Epidemiology and Infection 2010;138(2):183-91.

12. Doyle TJ, Hopkins RS. Low secondary transmission of 2009 pandemic influenza A (H1N1) in households following an outbreak at a summer camp: relationship to timing of exposure. Epidemiology and Infection 2011;139(1):45-51.

13. France AM, Jackson M, Schrag S, Lynch M, Zimmerman C, Biggerstaff M, Hadler J. Household transmission of 2009 influenza A (H1N1) virus after a school-based outbreak in New York City, April-May 2009. Journal of Infectious Diseases 2010;201(7):984-92.

14. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, Valleron AJ. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. American Journal of Epidemiology 2008;167(7):775-85.

15. Klick B, Leung GM, Cowling BJ. Optimal design of studies of influenza transmission in households. I: Case-ascertained studies. Epidemiology and Infection 2011:1-9.

16. Ip DK, Schutten M, Fang VJ, Fung RO, Dutkowski RT, Chan KH, Leung GM, Peiris JS, Cowling BJ. Validation of Self-swab for Virologic Confirmation of Influenza Virus Infections in a Community Setting. Journal of infectious diseases 2012;205(4):631-4.

17. Elliot AJ, Powers C, Thornton A, Obi C, Hill C, Simms I, Waight P, Maguire H, Foord D, Povey E, Wreghitt T, Goddard N, Ellis J, Bermingham A, Sebastianpillai P, Lackenby A, Zambon M, Brown D, Smith GE, Gill ON. Monitoring the emergence of community transmission of influenza A/H1N1 2009 in England: a cross sectional opportunistic survey of self sampled telephone callers to NHS Direct. BMJ 2009;339:b3403.

18. Papenburg J, Baz M, Hamelin ME, Rheaume C, Carbonneau J, Ouakki M, Rouleau I, Hardy I, Skowronski D, Roger M, Charest H, De Serres G, Boivin G. Household transmission of the 2009 pandemic A/H1N1 influenza virus: elevated laboratory-confirmed secondary attack rates and evidence of asymptomatic infections. Clinical Infectious Diseases 2010;51(9):1033-41.

19. Poon LL, Chan KH, Chu DK, Fung CC, Cheng CK, Ip DK, Leung GM, Peiris JS, Cowling BJ. Viral genetic sequence variations in pandemic H1N1/2009 and seasonal H3N2 influenza viruses within an individual, a household and a community. Journal of clinical virology 2011;52(2):146-50.

20. Pebody RG, Harris R, Kafatos G, Chamberland M, Campbell C, Nguyen-Van-Tam JS, McLean E, Andrews N, White PJ, Wynne-Evans E, Green J, Ellis J, Wreghitt T, Bracebridge S, Ihekweazu C, Oliver I, Smith G, Hawkins C, Salmon R, Smyth B, McMenamin J, Zambon M, Phin N, Watson JM. Use of antiviral drugs to reduce household transmission of pandemic (H1N1) 2009, United Kingdom. Emerging Infectious Diseases 2011;17(6):990-9.

21. Donnelly CA, Finelli L, Cauchemez S, Olsen SJ, Doshi S, Jackson ML, Kennedy ED, Kamimoto L, Marchbanks TL, Morgan OW, Patel M, Swerdlow DL, Ferguson NM, the pH1N1 Household Investigations Working Group. Serial Intervals and the Temporal Distribution of Secondary Infections within Households of 2009 Pandemic Influenza A (H1N1): Implications for Influenza Control Recommendations. Clinical Infectious Diseases 2011;52(suppl 1):S123-S130.

22. ConSISE. The Consortium for the Standardization of Influenza Seroepidemiology (ConSISE). place holder under development.

23. Laurie KL, Huston P, Riley S, Katz JM, Willison DJ, Tam JS, Mounts AW, Hoschler K, Miller E, Vandemaele K, Broberg E, Van Kerkhove MD, Nicoll A. Influenza serological studies to inform

public health action: best practices to optimise timing, quality and reporting. Influenza and Other Respiratory Viruses 2012;doi: 10.1111/j.1750-2659.2012.0370a.x Online 30 April 2012.

24. WHO. Seroepidemiological studies of pandemic influenza A (H1N1) 2009 virus. Weekly Epidemiologic Record 2010;24:229-236.

25. Van Kerkhove MD, Asikainen T, Becker NG, Bjorge S, Desenclos J-C, dos Santos T, Fraser C, Leung GM, Lipsitch M, Longini IM, Jr., McBryde ES, Roth CE, Shay DK, Smith DJ, Wallinga J, White PJ, Ferguson NM, Riley S, for the WHO Informal Network for Mathematical Modelling for Pandemic Influenza. Studies Needed to Address Public Health Challenges of the 2009 H1N1 Influenza Pandemic: Insights from Modeling. PLoS Med 2010;7(6):e1000275.

26. Nicoll A, Ammon A, Amato Gauci A, Ciancio BC, Zucs P, Devaux I, Plata F, Mazick A, Mølbak K, Asikainen T, Kramarz P. Experience and lessons from surveillance and studies of the 2009 pandemic in Europe. Public Health 2010;124:14-23

27. Briand S, Mounts AW, Chamberland M. Challenges of global surveillance during an influenza pandemic. Public Health 2011;125(5):247-256.

28. Broberg E, Nicoll A, Amato-Gauci A. Seroprevalence to Influenza A(H1N1) 2009 Virus Where Are We? Clinical and Vaccine Immunology 2011;18(8):1205-1212.

29. Wood JM, Major D, Heath A, Newman RW, Hoeschler K, Stephenson I, Clark T, Katz JM, Zambon MC. Reproducibility of serology assays for pandemic influenza H1N1: Collaborative study to evaluate a candidate WHO International Standard. Vaccine 2012;30(2):210-217.

30. Van Kerkhove MD, Broberg E, Engelhardt OG, Wood J, Nicoll A, on behalf of the CONSISE steering committee. The Consortium for the Standardization of Influenza Seroepidemiology (CONSISE): A Global Partnership to Standardize Influenza Seroepidemiology and Develop Influenza Investigation Protocols to Inform Public Health Policy. Influenza and Other Respiratory Viruses 2012;Published online: 2012 Dec 26. doi: 10.1111/irv.12068. [Epub ahead of print].

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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

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