

# Prospective longitudinal cohort study of influenza infection during epidemic periods

*Working Document*

Developed by

**The Consortium for the Standardization of Influenza  
Seroepidemiology (CONSIDE):**

A Global Partnership to Develop Influenza Investigation Protocols  
and Standardize Seroepidemiology to Inform Public Health Policy



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## PROTOCOL SUMMARY

**Title:** A prospective longitudinal cohort study of influenza infection during epidemic periods

**Study Design:** Prospective cohort study

**Population:** Households drawn at random from a population such as a large town, city or region for which surveillance for laboratory confirmed severe cases is also available.

**Primary objectives:** 1) To determine the age-specific and overall risk of infection for a well-defined portion of an epidemic period, 2) To determine age-specific and overall rates of severe disease per infection

**Individual-level endpoints:** We will measure the following from participants in the study:

- Antibody titer against the strain of interest at baseline and follow-up
- Characteristics of clinical illnesses among participants and their household members
- Attendance to a health-care facility with respiratory symptoms during the period of the study.

**Population-level endpoints:** Using individual-level endpoint data we will calculate the following population-level endpoints:

- Proportion of age groups infected during the study period
- Overall proportion of the population infected during the study period
- Age-specific risk of outcomes (such as admission to hospital or intensive care, dependent on the availability of auxiliary data)

**CONTENTS**

Protocol Summary ..... 2

Contents ..... 3

1.0 Scientific Background ..... 4

    1.1 Objectives ..... 4

2.0 Study Design ..... 5

    2.1 Overview ..... 5

    2.2 Timing ..... 5

    2.3 Recruitment ..... 5

    2.4 Baseline ..... 5

    2.5 Follow-up ..... 6

3.0 Study Population ..... 6

    3.1 Selection Criteria ..... 6

    3.2 Eligibility Criteria ..... 8

4.0 Study Procedures ..... 8

    4.1 Ethical Considerations ..... 8

    4.2 Subject Recruitment and Data Collection ..... 8

    4.3 Laboratory Evaluations ..... 10

5.0 Endpoints ..... 11

    5.1 Population End-points ..... 11

    5.2 Statistical Analyses ..... 12

6.0 Background of CONWISE ..... 14

7.0 References ..... 17

Appendix A Authors, Reviewers & CONWISE Steering Committee ..... 19

    Authors ..... 19

    Reviewers ..... 19

    CONWISE Steering Committee ..... 19

## 1.0 SCIENTIFIC BACKGROUND

Many influenza infections result in either mild symptoms or in no symptoms at all [1]. The proportion of infections that do not produce a clinical case almost certainly varies between strains of influenza [2 {Centers for Disease Control and Prevention, 1997 #1470,3} and, possibly, from year to year for the same strain. Therefore, it is challenging to interpret clinical surveillance data in terms of a proportion infected for the population as a whole or for a sub groups (for example, children).

There are times when an accurate knowledge of the proportion of people infected in a community can be valuable. For example, after the spring wave of the 2009 pandemic in the northern hemisphere, there was considerable variation in the number of reported severe cases between apparently similar countries. Without good data with which to estimate the number of infections in affected countries, it was difficult to predict the likely severity of the autumn wave [4].

Timely serological surveys will help to improve situational awareness for health policy makers during future pandemics. Longitudinal cohort studies provide one possible design for community based surveillance [2,5]. Other designs are cross-sectional cohort studies (e.g., [6]) and discarded clinical sample studies [7]. Longitudinal cohort studies produce paired samples, which give better statistical power to detect changes in cumulative incidence, per sample obtained, than is possible with unpaired samples.

## 1.1 OBJECTIVES

### PRIMARY OBJECTIVES

1) To determine the age-specific and overall risk of infection for a well-defined portion of an epidemic period, 2) To determine age-specific and overall rates of severe disease per infection

### SECONDARY OBJECTIVES

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

- To determine the age-specific and overall risk of infection for a period larger than the duration of the study (for example, for the entire first wave, even though the study runs for only a portion of that period)
- To determine the age-specific rate of experiencing symptoms when infected with influenza
- To identify Individual and household risk factors for infection

- Household versus community based transmission estimates
- Protection against infection and illness provided by pre-existing homologous and heterologous antibodies.

## 2.0 STUDY DESIGN

### 2.1 OVERVIEW

This is a prospective longitudinal cohort serological study with two rounds of recruitment: baseline and follow-up.

### 2.2 TIMING

The study will be initiated as quickly as possible prior to the start of the epidemic wave of interest. During pandemics, many populations will have a substantial lead time prior to the takeoff of local transmission and it may be possible to complete the baseline recruitment prior to the start of the main wave. In other populations, this will not be possible.

The timing of the follow-up will depend on the specific public health questions that need to be addressed and on the timing of available interventions. It may be better to initiate follow-up as soon as there have been a substantial number of severe cases, or it may be better to initiate follow-up later but with sufficient time to complete laboratory work and analyses samples prior the arrival of vaccine. For studies of seasonal influenza, follow-up would most likely be completed after the end of influenza activity.

### 2.3 RECRUITMENT

Initially, using one of a variety of possible methods (random digit dialing [2], proximity to random points in space[8], membership of existing cohort [5]) households will be contacted. A representative of the household will be invited to join the study and to recruit other members of their household. The full details of the study are then explained to all potential recruits in a face-to-face meeting; either at the household or at a clinic. Each individual is consented individually to join the study (as appropriate by age).

### 2.4 BASELINE

Each participant answers a questionnaire and gives a blood sample. The blood sample is handled so as to preserve the integrity of the sera, and passed to a qualified laboratory for analyses. All

participants are given a symptom diary and may also be provided with a telephone hotline number they can call if they are unwell. All participants are consented to additional follow-up contact.

## 2.5 FOLLOW-UP

Each participant is either visited in their home or asked to return to the study clinic (as appropriate). They are asked to return their symptom diaries and to answer a second questionnaire. Biological and Blood samples are taken from each individual (described further below).

## 3.0 STUDY POPULATION

This study aims to be representative of a specific population. Therefore, the population under consideration must be clearly defined.

### 3.1 SELECTION CRITERIA

**COMMENT:** Your selection criteria will depend on the country and local context where the study will occur and therefore we have provided several alternatives. Choose one of the following three alternatives as the basis for recruiting a study population.

*[Alt 1]* We will obtain a list of all residential and personal mobile phone numbers. We will select numbers at random from this list and invite the respondent and their household to join the study. When we call a phone number, we will first ask whether the respondent is over the age of *[local age of consent]*. If they are not, we will ask how many household members who are over the age of consent are present. We will ask the respondent to name them, we will choose from those present at random and ask to speak to the selected adult. We will describe the study briefly to the responding adult and try to arrange an appointment for them and other members of their household to attend the study clinic.

We will try to call each randomly selected number 3 times at different times of the day. We will record all attempted calls.

We will record the number of people that we speak to, the number that allow us to complete our call, the number that agree to attend the clinic and the number that actually do attend clinic.

*[Alt 2]* We will select a number of points in space at random using a standard geographical information system (GIS) such as Google Maps ([www.maps.google.com](http://www.maps.google.com)). We will conduct a visual census at those points and record the addresses (or other unique descriptors) of the closest *[insert number]* households. We will then approach

households in a random order. When somebody answers the door, we will first ask whether the respondent is over the age of *[local age of consent]*. If they are not, we will ask how many household members who are over the age of consent are present. We will ask the respondent to name them, we will choose from those present at random and ask to speak to the selected adult. We will describe the study briefly to the responding adult and try to arrange an time for us to return to the household to formally recruit them to the study.

We will try each randomly selected household 3 times at different times of the day. We will record all attempted calls.

We will record the number of people that we speak to, the number that allow us to complete our introduction, and the number that agree to us returning to recruit them and other household members.

*[Alt 3]* We will obtain a list of individuals, along with their phone numbers and addresses from the previously established study *[insert study name here]*. All these individuals have indicated that they are willing to be contacted and recruited into other health related studies. We will select individuals from the previous study at random. We call that individual and describe the study briefly to them and try to arrange an appointment for them and other members of their household to attend the study clinic.

*[Alt 4]* We will work with local government agencies to obtain a list of all households in the population and we will select households at random from that list. When somebody answers the door, we will first ask whether the respondent is over the age of *[local age of consent]*. If they are not, we will ask how many household members who are over the age of consent are present. We will ask the respondent to name them, we will choose from those present at random and ask to speak to the selected adult. We will describe the study briefly to the responding adult and try to arrange an time for us to return to the household to formally recruit them to the study.

We will try each randomly selected household 3 times at different times of the day. We will record all attempted calls.

We will record the number of people that we speak to, the number that allow us to complete our introduction, and the number that agree to us returning to recruit them and other household members.

### 3.2 ELIGIBILITY CRITERIA

Our inclusion criteria will be: informed consent for study participation by the volunteer, or, for children, by a parent or legal guardian (for children over *[insert local age of assent]* but younger than *[insert local age of consent]*; over 1 year of age. Our exclusion criteria are: children under 1 yr of age.

### 4.0 STUDY PROCEDURES

*[Alt 1]* Volunteers will arrive at the clinic in family groups.

*[Alt 2]* The study team will return to the volunteer household at the specified time.

### 4.1 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, Agriculture, etc) using a generic protocol such as this one prior to an epidemic/pandemic. Once a novel influenza virus is identified 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 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.

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### 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.

### 4.2 SUBJECT RECRUITMENT AND DATA COLLECTION

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#### 4.2.1 ENROLLMENT

The study will be described in detail to all members of the household who are present. Each will be given a copy of the study consent form to review during the verbal presentation. Each member of the household will be asked to join the study individually and will sign the consent form if appropriate.



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#### 4.2.2 RECRUITMENT OF SUBJECTS

Once ethical approval is gained, the study team should identify all eligible subjects according to section 3.2 above.

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#### 4.2.3 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 aged 17 years or younger will be obtained from their parents. 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.

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#### 4.2.4 MINIMUM DATASET

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

Age, gender, vaccination status, district of residence, occupation, recent symptoms, underlying conditions, possible risk factors for infection and severe disease, previous vaccination history, and history of recent antiviral use.

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#### 4.2.5 QUESTIONNAIRE

**COMMENT:** A bank of questions under general headings such as: Demographic Information; medical and vaccination history; exposure; contact, etc is currently being developed by CONSISE and will be provided on the CONSISE website ([www.CONSISE.tghn.org](http://www.CONSISE.tghn.org)) for the user to develop their own questionnaire

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#### 4.2.6 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 - according to local requirements and standards - to participants for participation in the study, and/or for specific interactions such as collection of sera.

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#### 4.2.7 PREVENTION OF INFLUENZA 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 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 infection between household members or between households.

### 4.3 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.

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#### 4.3.1 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/](http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/)

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#### 4.3.2 VIROLOGIC METHODS

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##### 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>

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##### 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](http://www.who.int/influenza/gisrs_laboratory/cnic_realtime_rt_pcr_protocol_a_h7n9.pdf)

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#### 4.3.3 SEROLOGIC METHODS

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##### H5N1

[to be added]

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##### 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 CONSIDE website for further information about H7N9 serologic assays: [www.CONSIDE.tghn.org](http://www.CONSIDE.tghn.org).

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## POSITIVE CRITERIA OF LABORATORY ASSAYS

### H5N1

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[to be added]

### H7N9

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[to be added]

## 5.0 ENDPOINTS

Some aspects of this study design rely on access to auxiliary time series data (ATSD) that describes, at least approximately, the time course of the epidemic. For example, weekly influenza-like-illness data from a sentinel surveillance network of family doctors [9] or laboratory confirmed clinical cases [10].

### 5.1 POPULATION END-POINTS

#### 5.1.1 PRIMARY POPULATION END-POINTS

The following will be assessed as study endpoints corresponding to the study’s primary objectives. These rely only on data from the study and commonly available population census data.

- Age-specific cumulative incidence of the study population: i.e., the proportion of each age class that exhibits a four-fold rise or greater in antibody and does not report having being vaccinated.
- Estimated age-specific cumulative incidence at the population level: Expected proportion of the overall population that would have exhibited a four-fold rise or greater in antibody titer, adjusted for differences in the age stratification of the study participants and the overall population



### 5.1.2 SECONDARY POPULATION END-POINTS

The following will be assessed as study endpoints corresponding to the study's secondary objectives. These outcomes require some additional data.

- Estimated age-specific cumulative incidence during the first wave of infection: Expected proportion of each age class that would have exhibited a four-fold rise or greater in antibody titre, had the study design been able to accurately bracket the wave of infection. This outcome requires some proxy data for the time course of the force of infection in the population (see Statistical Analyses) below.
- Age Specific rates of severe outcomes per infection. This outcome requires the age-stratified number of severe outcomes in the population from which the participants were recruited.
- Overall rate of severe outcome per infection.
- Rates of symptoms per infection overall and for specific age groups

## 5.2 STATISTICAL ANALYSES

### 5.2.1 PRIMARY POPULATION-ENDPOINTS

Point estimates for the proportion of each age class infected can be computed directly as  $p_i = n_i / N_i$  where  $N_i$  is the number recruited in each age class who do not report relevant vaccination and  $n_i$  is the number who exhibit a four-fold rise or greater in antibody titre. Confidence in these point estimates is best expressed with the upper proportion  $p_{ub}$  and lower proportion  $p_{lb}$  for which the binomial distribution for sample size  $N_i$  is consistent with  $n_i$  with 95% confidence. For example, in the R statistical package, the function `srg.ci.binom` can be loaded from the `idsource` repository with the command `source("http://tinyurl.com/5t7gwnv")` (Note that these functions are not part of a formal R package and do not have associated help files). The following commands give the upper and lower confidence bounds for a study of 100 individuals in each age group in which there were 2 infections observed in the first age group, 5 in the second and 10 in the last:

```
> srg.ci.binom(c(100,100,100),c(2,5,10),0.025)
[1] 0.07040381 0.11285087 0.17622145
> srg.ci.binom(c(100,100,100),c(2,5,10),0.975)
[1] 0.006217941 0.022339832 0.056201029
```

The expected proportion of the overall population that will have been infected during the study period  $p_{over}$  needs to be corrected for the differences between the age distribution in the study participants and those of the overall population. Let  $N_1, N_2, \dots, N_c$  be the number of study participants in each of the  $C$  age groups of interest, with  $N$  equal to the overall number of study



participants. Let  $M_1, M_2, \dots, M_c$  be the numbers in the overall population in the same age groups, with  $M$  the overall population size. The point estimate for the overall proportion infected can then be calculated as

$$p_{over} = \frac{n_1 M_1}{N_1 M} + \frac{n_2 M_2}{N_2 M} + \dots + \frac{n_c M_c}{N_c M},$$

where  $n_1, n_2, \dots, n_c$  were the number of infected study participants in each age group. Confidence intervals for the overall proportion infected can be calculated in a similar same way as the confidence intervals for the individual age groups. First, calculate  $n_{eff}$ , the effective number positive in the study. This is the number we expect would have been positive had our study age groups been perfectly representative of the overall population,  $n_{eff} = p_{over} * N$ . Confidence intervals for  $p_{over}$  can then be calculated based on  $n_{eff}$  and  $N$  in the same way to the age specific confidence bounds outlined above.

Tests for cluster-bias also need to be considered, although such biases are usually smaller in household-based studies than in other studies where individual “clusters” are much larger.

### 5.2.2 SECONDARY POPULATION END-POINTS

COMMENT: An ideal prospective serological study of an influenza infection wave would gather regular serum samples starting prior to the wave, progressing through the wave and continuing for a period beyond the time of last viral circulation (so as to allow time for antibodies to rise in late affected individuals). The estimation of wave-specific infection attack rates for those data would be straightforward: the proportion of individuals that had been infected would be proportional to the number in the study for whom a significant rise in antibody titer was observed. Regular sampling would ensure that the chance of missing a short-lived rise in titer was low. Unfortunately, resource and logistical constraints, coupled with a long diffuse wave in tropical non-pandemic settings, prevents such precise timing for sample acquisition in practice. Therefore, we utilize additional data and some novel statistical methods to account for the rolling nature of recruitment relative to the waves of infection.

The calculation of the secondary study outcomes such as the expected rate of infections had the study been able to perfectly bracket the period of infection are slightly more involved and beyond the scope of this current draft protocol. They require one or more auxiliary data sources from which the relative force of infection for different periods of the study can be calculated. Examples of these types of data are the time series of severe hospital cases and the time series of consultations at a sentinel group of family doctors.



## 6.0 BACKGROUND OF CONSIDE

The following protocol *Prospective longitudinal cohort study of influenza infection during epidemic periods* was developed by CONSIDE, the Consortium for the Standardization of Influenza Seroepidemiology, [11,12] 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[12,13].

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[14,15,16]. During the past two years, considerable seroepidemiological work was undertaken[13,17]. 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[13,18].

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[11]. A seventh protocol specifically assessing health care personnel was added after the December 2011 meeting (Table X). 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 2 – CONSISE Protocols Under Development**

<b>Protocol</b>	<b>Primary Objectives</b>	
<b>Epidemic/Pandemic</b>	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
<b>Seasonal Influenzas</b>	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
	<b>Zoonotic Influenzas</b>	7. Investigation of Zoonotic Influenza Infection in Humans

Source: [11]

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 “A longitudinal cohort study of influenza infection during epidemic periods” was drafted by CONSISE members Steven Riley, Othmar Engelhardt, John Wood, Angus Nicoll and Maria D. Van Kerkhove with input from many partners. It was also and influenced by the following protocols, shared generously with CONSISE for the purposes of developing this protocol:

- *"Hong Kong Influenza Serological Survey Protocol"* shared by Steven Riley and Ben Cowling [2].
- *"The immune landscape of human influenza in households, towns and cities in southern China (FluScape)"* shared by Steven Riley, Jonathon Read, Justin Lessler, Chao Qiang Jiang, Yi Guan, and Derek Cummings[8].
- "Community Influenza Surveillance (CIS) Protocol" shared by Richard Pebody.
- *"Singapore sero-epidemiology cohort study"* shared by Vernon Lee[5]

Questions about the generic protocol should be directed to [m.vankerkhove@imperial.ac.uk](mailto: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.



[www.CONSISE.tghn.org](http://www.CONSISE.tghn.org)





## 7.0 REFERENCES

1. Webster R, Bean W, Gorman O, Chambers T, Kawaoka Y (1992) Evolution and ecology of influenza A viruses. *Microbiol Rev* 56: 152-179.
2. Riley S, Kwok KO, Wu KM, Ning DY, Cowling BJ, et al. (2011) Epidemiological Characteristics of 2009 (H1N1) Pandemic Influenza Based on Paired Sera from a Longitudinal Community Cohort Study. *PLoS Med* 8: e1000442.
3. Centers for Disease Control and Prevention (1997) Isolation of avian influenza A(H5N1) viruses from humans--Hong Kong, May-December 1997. *MMWR* 46: 1204-1207.
4. Lipsitch M, Riley S, Cauchemez S, Ghani AC, Ferguson NM (2009) Managing and Reducing Uncertainty in an Emerging Influenza Pandemic. *N Engl J Med* 361: 112-115.
5. Chen M, Lee VJ, Lim WY, Barr IG, Lin RT, et al. (2010) 2009 influenza A(H1N1) seroconversion rates and risk factors among distinct adult cohorts in Singapore. *JAMA* 303: 1383-1391.
6. Wu JT, Ma ES, Lee CK, Chu DK, Ho PL, et al. (2011) A serial cross-sectional serologic survey of 2009 Pandemic (H1N1) in Hong Kong: implications for future pandemic influenza surveillance. *Influenza Other Respi Viruses* 5: 190-194.
7. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, et al. (2010) Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *The Lancet* 375: 1100-1108.
8. Lessler J, Cummings DA, Read JM, Wang S, Zhu H, et al. (2011) Location-specific patterns of exposure to recent pre-pandemic strains of influenza A in southern China. *Nature Communications* 423.
9. Fleming DM, & Elliot AJ (2008) Lessons from 40 years' surveillance of influenza in England and Wales. *epidemiology and Infection* 136: 866-875.
10. Castro-Jiménez MA (2009) Epidemiologic analysis of the laboratory-confirmed cases of influenza A(H1N1)v in Colombia. *Euro surveillance : bulletin européen sur les maladies transmissibles* 14: p.19284.
11. Van Kerkhove MD, Broberg E, Engelhardt OG, Wood J, Nicoll A, et al. (2012) 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* Published online: 2012 Dec 26. doi: 10.1111/irv.12068. [Epub ahead of print].
12. Laurie KL, Huston P, Riley S, Katz JM, Willison DJ, et al. (2012) Influenza serological studies to inform public health action: best practices to optimise timing, quality and reporting.



Influenza and Other Respiratory Viruses doi: 10.1111/j.1750-2659.2012.0370a.x Online 30 April 2012.

13. WHO (2010) Seroepidemiological studies of pandemic influenza A (H1N1) 2009 virus. *Weekly Epidemiologic Record* 24: 229-236.
14. Van Kerkhove MD, Asikainen T, Becker NG, Bjorge S, Desenclos J-C, et al. (2010) Studies Needed to Address Public Health Challenges of the 2009 H1N1 Influenza Pandemic: Insights from Modeling. *PLoS Med* 7: e1000275.
15. Nicoll A, Ammon A, Amato Gauci A, Ciancio BC, Zucs P, et al. (2010) Experience and lessons from surveillance and studies of the 2009 pandemic in Europe. *Public Health* 124: 14-23
16. Briand S, Mounts AW, Chamberland M (2011) Challenges of global surveillance during an influenza pandemic. *Public Health* 125: 247-256.
17. Broberg E, Nicoll A, Amato-Gauci A (2011) Seroprevalence to Influenza A(H1N1) 2009 Virus Where Are We? *Clinical and Vaccine Immunology* 18: 1205-1212.
18. Wood JM, Major D, Heath A, Newman RW, Hoeschler K, et al. (2012) Reproducibility of serology assays for pandemic influenza H1N1: Collaborative study to evaluate a candidate WHO International Standard. *Vaccine* 30: 210-217.

**APPENDIX A AUTHORS, REVIEWERS & CONSIDE STEERING COMMITTEE**

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**CONSIDE STEERING COMMITTEE**

CONSIDE’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 CONSIDE Steering Committee Members**

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