



Global Influenza Hospital-based Surveillance Network (GIHSN) Core Protocol

Rationale

To establish the *[specify country/city]* branch of the global influenza hospital-based surveillance network. This network, based on a public-private partnership, includes hospitals in multiple countries following the same core protocol¹. This network will allow a better understanding of global influenza epidemiology through its broad geographical coverage; standardization of data collection; and its expected sustainability over sequential influenza seasons. It will focus on estimating the incidence of severe influenza disease. In addition, whenever possible, it will provide the framework for estimating effectiveness of seasonal influenza vaccines in prevention of severe cases in various age and risk groups.

Note: Main parts requiring country/site adaptations are specified in *blue*

Objectives

1. To evaluate the burden of severe influenza disease, defined as hospitalization related to community acquired influenza or complications following an influenza infection
2. To quantify the distribution of the different influenza strains (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) among these severe cases
3. Notice: the GIHSN goals are related to influenza epidemiology *[Optional: If testing for other respiratory viruses is performed]* To estimate the relative incidence of influenza compared to other respiratory viruses
4. *[Optional: If vaccine coverage is sufficient for some age group]* To measure the effectiveness of influenza seasonal vaccines to prevent these hospitalizations using a case control design

Design: Prospective epidemiological *active* surveillance study

Study setting and population

The study will take place in *[specify number]* hospitals. *[Describe further the hospitals: names, catchment area, specialty, size]*. The study period will be organised to cover the main influenza season ie. *[complete with planned start and end date for the study – can be informed by virologic surveillance data]*

¹ This core protocol has been adapted from the initial version developed by Joan Puig-Barberà (Centre for Public Health Research, Valencia, Spain).



This study will focus on *[select population category among the following options: (i) all ages, (ii) elderly (60+), (iii) adults (18+), (iv) children (<18) (v) high risk groups (to be further defined)]*

Eligibility criteria

Enrolment will be based on:

- Patients with an acute process
- Patients whose indication for admission was any of a predefined set of conditions, described as possibly associated with a recent influenza infection (see table 1).
- In this case, [a study nurse, doctor...] will identify by hospital admission registries, chart review or available records, **all** eligible patients hospitalized in the previous 24-48 hours
- Patients resident, belonging to the source population base

Table 1. Admission diagnoses possibly associated with an influenza infection.
International Classification of Diseases Code version 9 and 10.

For Patients 5 years old or older	ICD 9 Codes	ICD 10 Codes
Acute respiratory infection	382.9; 460-466	J00-J06, J20-J22, H66.90
Acute myocardial infarction or acute coronary syndrome	410-411 and 413-414	I20-I25.9
Asthma	493-493.92	J45.2-J45.22, J45.9-J45.998, J44-J44.9
Heart failure	428-429.0	I50-I50.9; I51.4
Pneumonia and influenza	480-488	J09-J18
Chronic Pulmonary Obstructive disease	490, 491, 492, 496	J40-J44.9
Myalgia	729.1	M79.1
Metabolic failure (diabetic coma, renal dysfunction, acid-base disturbances, alterations to the water balance)	250.1- 250.3; 584-586; 276-277	E11.9, E10.9, E11.65, E10.65, E10.11, E11.01, E10.641, E11.641, E10.69, E11.00, E10.10, E11.69, N17.0, N17.1, N17.2, N17.8, N17.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6M, N18.9, N19, E87.0, E87.1, E87.2, E87.3, E87.4, E87.5, E87.6, E87.70, E87.71, E87.79, E86.0, E86.1
Altered consciousness, convulsions, febrile-convulsions	780.01-780.02; 780.09; 780.31-780.32	R40.20, R40.4, R40.0, R40.1, R56.00, R56.01



Dyspnea/respiratory abnormality	786.0	R06.0, R06-R06.9
Respiratory abnormality	786.00	R06.9
Shortness of breath	786.05	R06.02
Respiratory abnormality nec	786.09	R06.3, R06.00, R06.09, R06.83
Respiratory symptoms/chest symptoms	786.9	R06.89
Fever or fever unknown origin or non specified	780.6-780.60	R50, R50.9
Cough	786.2	R05
Sepsis, Systemic inflammatory response syndrome	995.90-995.94	R65.10, R65.11, R65.20, A41.9

For the very young pediatric population (0 to less than 5 years of age)	ICD 9 Codes	ICD 10 Codes
Acute upper or lower respiratory disease	382.9; 460 to 466	J00-J06, J20-J22
Dyspnea, breathing anomaly, shortness of breath, tachypnea	786.0; 786.00; 786.05-786.07; 786.09; 786.9	R06.0, R06, R06.9, R06.3, R06.00, R06.09, R06.83, R06.02, R06.82, R06.2, R06.89
Asthma	493-493.92	J45.2-J45.22, J45.9-J45.998, J44-J44.9
Pneumonia and influenza	480 to 488	J09-J18
Heart failure	428-429.0	I50-I50.9; I51.4
Myalgia	729.1	M79.1
Altered consciousness, convulsions, febrile convulsions	780.01-780.02; 780.09; 780.31- 780.32	R40.20, R40.4, R40.0, R40.1, R56.00, R56.01
Fever or fever unknown origin or non specified	780.6-780.60	R50, R50.9
Cough	786.2	R05
Gastrointestinal manifestations	009.0; 009.3	A09.0; A09.9
Sepsis, Systemic inflammatory response syndrome	995.90-995.94	R65.10, R65.11, R65.20, A41.9

Inclusion criteria

Patients 5 years old and older will be included in the study if they refer a seven days or less antecedent of a community onset influenza like-illness (see definition in table 2).

Table 2. Modified European Centre for Diseases Control definition of influenza like-illness (ILI)

Combination of:



- at least one of the following four systemic symptoms (ICD-9-CM code): Fever or feverishness (780.6), headache (784.0), myalgia, (729.1) or malaise (780.79);
- at least one of the following three respiratory symptoms (ICD-9-CM code): b) Cough (786.2), sore throat (787.2) or shortness of breath (786.05).

Patients less than 5 years will be included if indications for admission (table 1), occurred within seven days or less between the beginning of symptoms and admission to hospital.

Exclusion criteria

- Institutionalized.
- Non-resident or not belonging to the predefined population study base (that is the cases' source population to be defined according to the study setting and population, plus the eligibility criteria)
- Hospitalized in the previous 30 days

(NOTE: for more specific definitions and statistical analysis exclusion criteria, please refer to the annex of the GIHSN Standardized Operating Procedures and to the GIHSN Analysis Protocol)

Swabbing procedures

A nasopharyngeal swab for all patients and a pharyngeal swab for adults (14 years of age or older) and a nasal sample for children (less than 14 years old) will be obtained from each patient in case they comply with inclusion criteria and give consent.

Sample management and laboratory procedures

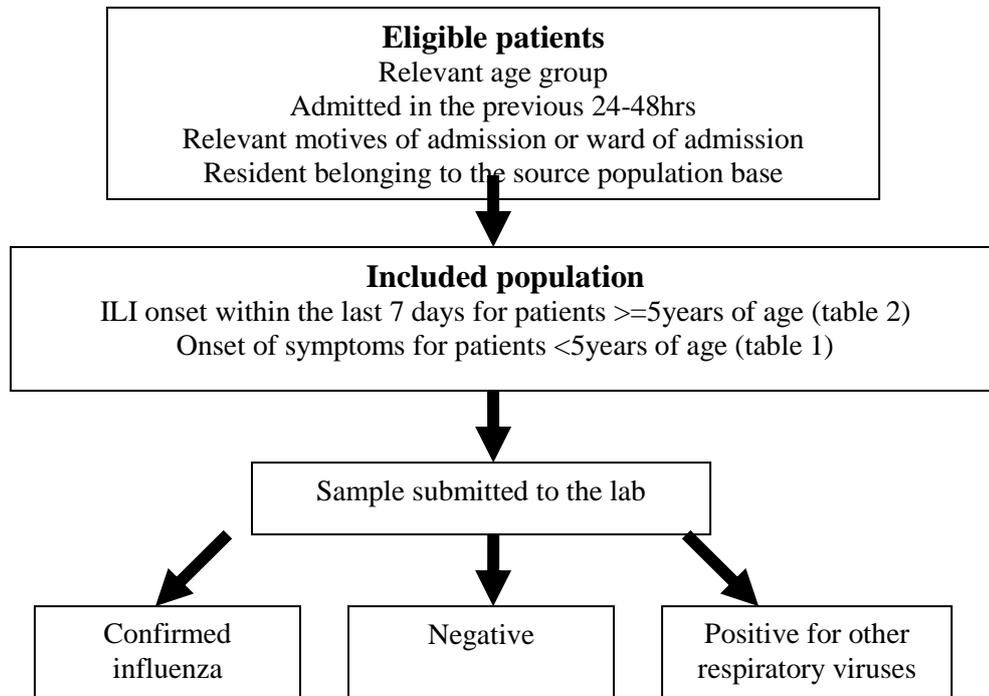
All samples will be kept at -20°C until sent to reference laboratory. Multiplex real-time RT-PCR will be performed on the samples to detect the presence of:

- influenza A (H1N1n and H3N2), influenza B (B/Yamagata, B/Victoria)

Notice: the GIHSN goals are related to influenza epidemiology *[If testing for other respiratory viruses is performed, the following can be considered coronavirus, metapneumovirus, bocavirus, respiratory syncytial viruses, adenovirus, parainfluenza viruses, rhinovirus. Analysis for respiratory viruses other than influenza can be carried out after the study ends if samples are stored appropriately].*



Study process



Sample size, data collection and analysis

Sample size

The minimal number of laboratory confirmed influenza cases we expect per site is 100. The number of hospitals (*study setting and population*) to involve in this study should be planned to reach at least this minimum target.

Data collection

Trained [study nurses, doctor....] collect relevant information by a combination of face-to-face interview of patients and attending physicians, and by reviewing clinical records (refer to both questionnaires, younger than 5 years old and 5 years and older).

Influenza vaccination status is obtained by asking the patient (or representative) if he or she had received the influenza vaccine of the current season, the date of vaccination, and if the vaccine had been administered at least two weeks before the onset of symptoms. Whenever possible, this information will be validated by existing registers, vaccination cards or through contacting the place where the vaccine was administered.



Data analysis

A descriptive analysis of the frequency of laboratory results by epidemiological week, age group, and comorbidities will be conducted. If possible, hospitalization rates by age group according to population denominators (based on the size of the hospital catchment area) and for each different virus will be also estimated.

Nested test-negative study for vaccine effectiveness (optional)

If the vaccine coverage is sufficient for some age group, we will try to evaluate the effectiveness of influenza seasonal vaccines to prevent these hospitalizations using a test-negative design.

For this analysis, we will exclude patients if they have vaccination contra-indication, have been hospitalized in the previous 30 days or if they had had a previous laboratory confirmed influenza infection during the season. Only patients admitted in the period lasting from the week of the first laboratory confirmed influenza cases until the week of last laboratory confirmed influenza cases will be included in this analysis.

In the test negative design, the comparison groups are influenza-positive admissions compared to influenza-negative admissions.

Frequency distribution will be reported for influenza-positive and influenza-negative admissions.

Vaccine effectiveness (VE) is defined as $100 \times (1 - \text{adjusted vaccination odds ratio [OR]})$, where OR compares influenza vaccination status in influenza-positive admissions with influenza vaccination status in influenza-negative admissions. An adjusted OR will be obtained using a multivariable logistic regression model. Subgroup analyses for (VE) will be performed depending on the population characteristics and vaccination coverage.

See the GIHSN Analysis Protocol ([at 30 Aug 2013 under review](#)) for a more detailed description of the statistical analysis

Ethical considerations

Approval by the local Research Ethics Committee will be obtained. The confidentiality legislation and requirements in the handling in personal information will be strictly followed. Informed written consent will be required for enrolment. No intervention, apart the nasopharyngeal, nasal and pharyngeal sampling is associated with the study. Good Epidemiological Practice procedures will be implemented in all the study process.