Global Influenza Hospital Surveillance Network

Version 2020-11-06

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. The Global Influenza Hospital Surveillance Network (GIHSN) is a platform able to generate strong epidemiological and medical evidence on **influenza severity** and to support vaccine strain selection through **timely sharing of clinical and laboratory data**. The GIHSN is a network of not-for profit institutions coordinating local hospitals in several countries following the same core protocol[1].

The GISHN is a unique hospital active surveillance network using a standard protocol complementary to WHO GISRS, offering:

- The largest yearly case series of patients hospitalized with influenza worldwide from all age groups for both northern hemisphere (NH) and southern hemisphere (SH) allowing to better understand influenza severity and related risk factors;
- Linking clinical data with viral genome sequencing information to inform WHO vaccine strains selection;
- An alert system in case of influenza pandemic/strain mutation, to contribute to country response and international collaboration.

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

Study objectives

1. Support international capacities developed through the Global Influenza Surveillance and Response System (GISRS) of laboratories to link clinical information to genetic sequencing of influenza strains to expand the support of the biannual WHO vaccine strain selection process.
2. Link clinical and virological (including sequence) data in hospitalized patients with acute respiratory infections, emphasizing capture of cases that test positive for influenza and are vaccine failures.
3. Quantify the distribution of the different influenza strains (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) among these severe cases

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

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 organized to cover the main putative influenza season ie. *[complete with planned start and end date for the study – can be informed by virologic surveillance data]*

This study will focus on *[select population category among the following options: (i) all ages, (ii) elderly (60+), (iiii) 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 72 hours and has stayed in hospital for at least 1 night (therefore a patient admitted before midnight of the previous day).

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

For patients less than 5 years	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 (polypnea)	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
Acute asthma or exacerbation	493.92	J45.901
Pneumonia and influenza	480 to 488	J09-J18
Acute respiratory failure	518.82	J96
Acute 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, not otherwise specified	995.90-995.94	R65.10, R65.11, R65.20, A41.9
Nausea and vomiting	078.82; 787.0; 787.01-787.03	R11; R11.0; R11.10 - R11.12; R11.2

For patients 5 years and older	ICD 9 Codes	ICD 10 Codes
Acute upper or lower respiratory disease	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
Acute asthma or exacerbation	493.92	J45.901
Acute Heart failure	428-429.0	I50-I50.9; I51.4
Pneumonia and influenza	480-488	J09-J18

Bronchitis and exacerbations of Chronic Pulmonary Obstructive disease	490, 491.21 and 491.22,	J40; J44.0; J44.1
Acute respiratory failure	518.82	J96
Myalgia	729.1	M79.1
Acute 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, syncope and collapse	780.01-780.02; 780.09; 780.2; 780.31-780.32	R40.20, R40.4, R40.0, R40.1, R55, 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 not otherwise specified	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

Inclusion criteria

Patients aged 5 years and older will be included in the study if they present with up to seven days of 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 o 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), Nasal Congestion (478.19)

Patients<5 years will be included if indications for admission (table 1), occurred up to seven days between the onset of symptoms and hospital admission.

Swabbing procedures

Acceptable respiratory samples for influenza testing include nasopharyngeal or nasal swab, and nasal wash or aspirate (Use centers for Disease Control and Prevention (CDC) guidance for specimen collection as reference. https://www.cdc.gov/flu/pdf/freeresources/healthcare/flu-specimen-collection-guide.pdf). Each patient meeting the inclusion criteria and providing consent would ideally have the following specimens collected:

- A nasopharyngeal or nasal swab combined with an oropharyngeal swab in a viral transport media (VTM)

Sample management and laboratory procedures

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

- Influenza A (H1N1pdm09 and H3N2), influenza B (B/Yamagata, B/Victoria)
- *When samples tested for other respiratory viruses, results should be captured in the database*
- *If possible, SARS-CoV-2 testing should be performed and laboratory results reported*

Notice: the GIHSN main goals are related to influenza epidemiology but do not preclude broad testing for other respiratory pathogens *[If testing for other respiratory viruses is performed, the following can be considered* coronavirus, metapneumovirus, bocavirus, respiratory syncytial viruses, adenovirus, parainfluenza viruses, *rhinovirus and SARS-CoV-*

2. Testing for respiratory viruses other than influenza can be carried out after the study ends (if samples are stored appropriately].

Genetic sequence data (GSD) must be generated for a minimum of 50 to 100 influenza positive specimens according to agreed schedule in table 3. Samples for GSD will be selected using specific criteria to be agreed upon and distributed by the GIHSN Independent Scientific Committee prior to the start of the 2020/21 Northern Hemisphere influenza season.

If the site has no capacities to generate genetic sequence data, the site may ship its specimens to the GIHSN sequencing platform at the National Influenza Center in Lyon, France, under the Terms of Reference for sharing materials in GISRS. Shipments are organized by the National Influenza Center in Lyon.

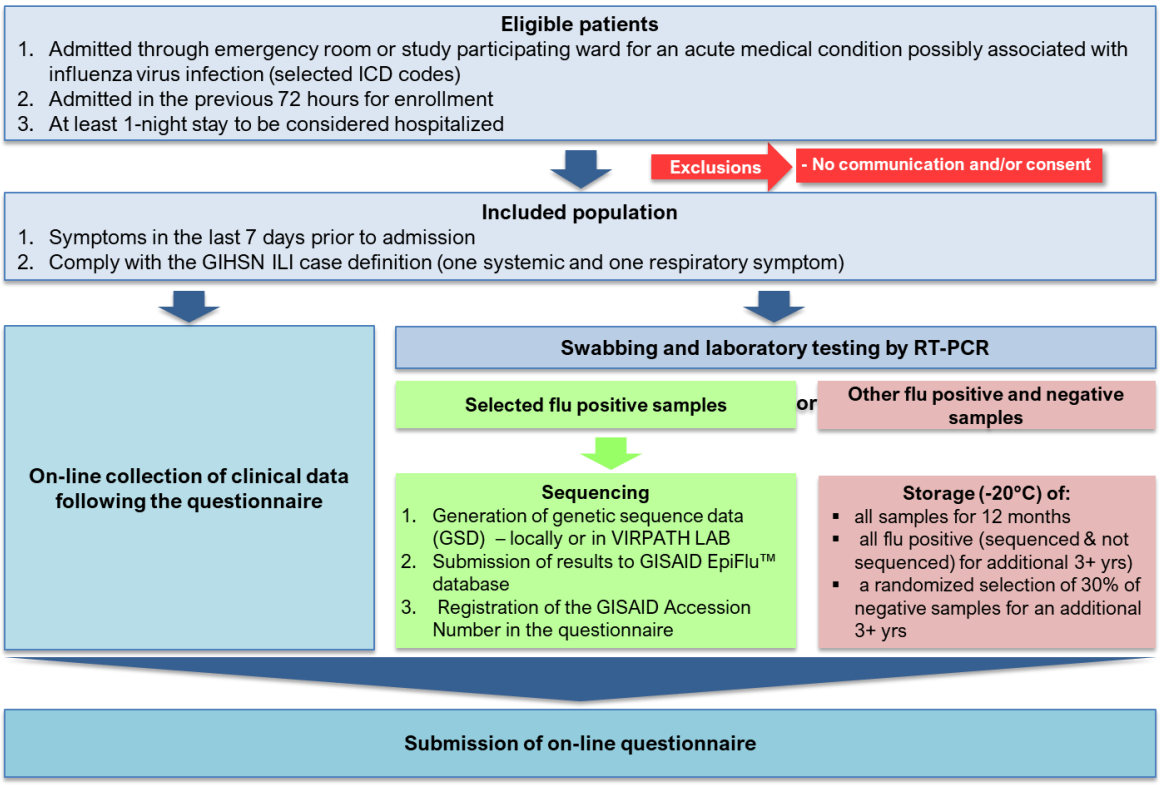
All sites must submit GSD to the GISAID EpiFlu™ database (http://gisaid.org/EPI_ISL/123456) in a timeframe so that results are available for the site's respective WHO Vaccine Composition Meeting (VCM). In addition, GSD for COVID-19 (if performed) are encouraged to be submitted to GISAID database to add to public knowledge and support WHO initiatives.

Table 3. Sequencing scheme for all samples (subjects of all ages):

Hemisphere	***Early season***	***ICU/deaths and vaccine failures***	***Samples per month***
Northern	*all samples until 15 January*	*All*	*10-30 (during season)*
Southern	*all samples until 15 July*	*All*	*10-30 (during season)*
Intertropical	*NA*	*All*	*5-15 (all year)*

Storage (-20C or -70C) of all influenza positive and negative study samples should be completed for a minimum of one year. All influenza positive (and SARS-CoV-2 positive, if performed) samples plus a subset of 30% of negative samples should be stored for an additional 3 years. This will assure sample availability for additional retrospective investigations (e.g. SARS-CoV-2 or pathogen discovery initiatives) if necessary.

Study process



Sample size, data collection and analysis

Sample size

The number of **sequenced** laboratory confirmed influenza cases we expect per site is between 50-100. The number of hospitals (***study setting and population***) to involve in this study should be planned to reach the agreed minimum target.

Data collection

Trained [study nurses, doctor….] collect relevant information by a combination of face-to-face interviews 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

Real time completion of e-CRF for all cases should be performed, and this data uploaded on a regular basis to GIHSN database. Please note that if e-CRF data flow is not possible, Xcel data sheets can be used. COVID-19 diagnostics results should be reported if testing has been performed. Sites are strongly encouraged to share data with WHO's Global Influenza Surveillance and Response System (GISRS).

A descriptive analysis of the seasonal results will be presented by each site at the GIHSN Global Annual Meeting.

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.