Global Influenza Hospital Surveillance Network

Version 2025-03-20

Global Influenza Hospital-based Surveillance Network (GIHSN)

Core Protocol

HIGHLIGHTS

- Sites need to do **YEAR-ROUND surveillance** for respiratory illness hospitalizations (from November 1st to October 31st the following year)
- Sites should use a **SYSTEMATIC screening** approach (e.g., assess eligibility of patients **everyday, week-days**, or **3 times/week**) and **explain their strategy to the FIE** because it is important to understand the sampling frame used by each site (i.e., how and when patients are approached) to allow for data analysis and interpretation of results
- Sites should **apply case definition** (there is a list of slightly modified case definitions in the protocol and questionnaire (e.g., WHO SARI case definition)
- Sites should perform **SYSTEMATIC testing for all enrolled patients** using PCR for Influenza and when possible, testing for other respiratory viruses (multiplex-PCR)
- Sites should **SYSTEMATICALLY complete a questionnaire for all enrolled patients** to capture information on the entire continuum of influenza illness, from pre-hospital signs, symptoms and management to hospital documented disease severity, as well as treatment and clinical outcomes.
- Sites should perform **Whole Genome Sequencing of a minimum of 50 to 100 influenza viruses** (lower CT values increase the chance for sequencing) or alternatively send those samples to the NIC's sequencing platform in Lyon, France, or to the WHO Collaborating Centers.
- Sites should **share their data EVERY MONTH**, preferably every last Wednesday of each month, even if some patients have incomplete data to follow an incremental data management process.

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**. GIHSN is a network of not-for profit institutions coordinating local hospitals in several countries following the same core protocol[1].

The GIHSN 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 severe acute respiratory infections worldwide from all age groups for both northern hemisphere (NH) and southern hemisphere (SH), allowing to better understand severity and risk factors of influenza and other respiratory viruses, including SARS-CoV2 and RSV.
- Linking clinical data with viral genome sequencing information to inform WHO vaccine strains selection.
- An alert system in case of influenza or other respiratory virus pandemic/strain mutation, to contribute to country response and international collaboration.

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

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

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 of viral genome) data in hospitalized patients with acute respiratory infections
3. Quantify the distribution of the different influenza strains (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) among these severe cases

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 from 1st November 2024 through 31st of October 2025, a year-round surveillance organized to cover the circulation of influenza viruses and other main respiratory viruses in the context of changing epidemiology of these viruses during the COVID-19 pandemic.

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 respiratory illness

- Patients whose indication for admission suggest possible association with a recent virus infection (see list of acute events that could be linked with a virus infection in table 1 as example).
- In this case, [a study nurse, doctor…] will identify cases using hospital admission registries, chart review or available records, ***all*** eligible patients hospitalized in the previous 72 hours and who has stayed in hospital for at least 1 night (therefore a patient admitted before midnight of the previous day).

Table 1. Example of admission diagnoses possibly associated with an influenza infection that could be taken into account when looking for eligible patients. 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

Sampling strategy suggestion for year-round surveillance:

- Depending on the local circumstances, if number of screened and enrolled participants are expected to overwhelm local hospital capacity, the site can develop a sampling strategy to keep the surveillance throughout the year (i.e., November 2024 – October 2025). We suggest that, in this situation, the site can define 3 days of the week for systematic screening and enrolment of patients. Respiratory samples would also be collected during these days of the week from all patients who meet the case definition and consent to participate in the surveillance. Clinical information would be collected from all enrolled patients (independent of laboratory results).
- It is important to avoid selecting patients for enrolment based on severity or vaccination status. This is because we want to be able to pool data for analysis. To be able to describe cases based on disease presentation and distribution of epidemiologic and clinical characteristics, the selection of participants cannot be biased. Understanding the randomization of cases to be selected would not be feasible, the next best strategy is to use a systematic approach for case selection.

Inclusion criteria (Case Definition)

Patients aged *[Define the patient population from your sentinel surveillance site]* will be included in the study if they present with up to seven or ten days of community onset influenza like-illness *[Choose the case definition used in your sentinel surveillance site to be included in the protocol based on Table 2 and delete the other options]*.

Table 2.

1. Severe acute respiratory infection (SARI) case definition (https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari)

An acute respiratory infection with:

- history of fever or measured fever of ≥ 38C°
- and cough
- with onset within the last 10 days
- and requires hospitalization

2. Extended SARI case definition

An acute respiratory infection with cough and onset within 10 days that requires hospitalization (no fever required)

3. ECDC modified case definition for influenza like-illness (ILI) in the last 7 days

Combination of:

- at least one of the following four systemic symptoms: fever or feverishness, headache, myalgia, or malaise
- at least one of the following three respiratory symptoms: cough, sore throat or shortness of breath

4. Acute respiratory illness case definition: Acute onset of at least one of the following four respiratory symptoms: cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection

5. Cases tested for influenza: a hospitalized person who has been tested for influenza within 72 hours of hospital admission

Swabbing procedures

Acceptable respiratory samples for influenza testing and other main respiratory viruses 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 are tested for other respiratory viruses, results should be captured in the database
- SARS-CoV-2 testing should be performed, and laboratory results reported

Notice: the GIHSN main goals are related to influenza epidemiology but also includes broad testing for other respiratory pathogens. Testing for respiratory viruses other than influenza can be carried out after the study ends (if samples are stored appropriately).

Whole Genome Sequencing

Whole genome sequencing (WGS) must be generated for a minimum of 50 to 100 influenza positive specimens according to agreed schedule in table 3.

Samples for WGS should be selected based on Ct values. For sites sending specimens or RNA extracts to the National Influenza Centre (NIC) in Lyon, France, or one of the WHO Coordinating Centres you are asked to select samples with Ct values < 28. If you do not have enough influenza specimens to do WGS, you can complement the requested 50-100 specimens by adding SARS-Cov2 sequencing. If WGS is available on site for RSV positive specimens, these can be shared in the GIHSN, but no specific funding will be granted for WGS of RSV positives. The network priority is Influenza, followed by SARS-CoV2.

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 Centre in Lyon, France, under the Terms of Reference for sharing materials in GISRS. Shipments are organized by the National Influenza Centre in Lyon.

If sequencing capacity available on site, genome sequencing data should be uploaded into GISAID as soon as they have results available. If the GIHSN sequencing platform in Lyon is needed to support WGS activities, samples will be shipped in regular batches at least 3 weeks before the WHO strain selection meeting.

All sites must submit WGS to the GISAID EpiFlu™ database (http://gisaid.org/EPI_ISL/123456) in a timeframe so that results are available for the WHO Vaccine Composition Meetings (VCM). In addition, WGS for COVID-19 (if performed) are encouraged to be submitted to GISAID database to add to public knowledge and support WHO initiatives, as well as any RSV WGS data you may perform locally.

For a site that has 50-100 influenza viruses identified through the GIHSN, all specimens or RNA extract can undergo WGS, and all the data should be uploaded to GISAID and linked to the epi data (using the GISAID Accession Number provided by the GISAID system at data submission).

If a site has more than 100 specimens of influenza confirmed cases, a selection of which samples to prioritize for sequencing may be necessary, depending on local resources. In this case, specimens will be first prioritized based on Ct value (e.g., <28), then a systematic selection approach can be done. For instance, select every other sample or every 4th sample for

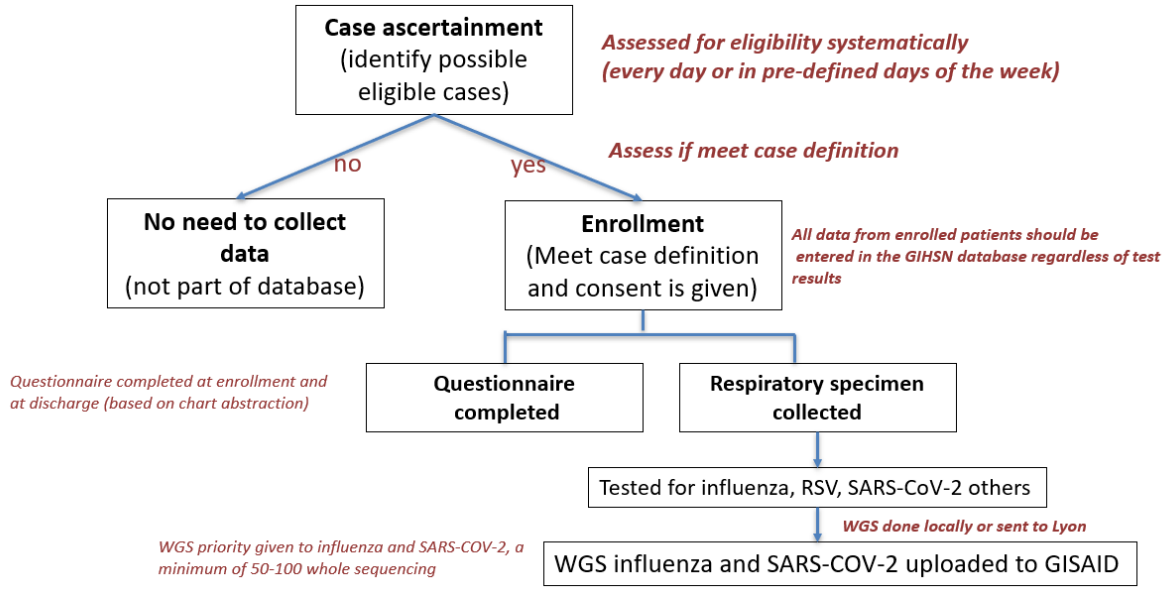
sequencing or shipment for sequencing at GIHSN reference laboratory. The systematic selection of samples to be sequenced can help avoiding selecting bias and facilitate analysis when looking at the association between clinical features of patients or breakthrough influenza and the influenza viruses circulating, considering clade level data when needed.

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

Hemisphere	***Early season***	***Later in the season or off season***
Northern	*all samples until 15 January*	*10-30 per month*
Southern	*all samples until 15 July*	*10-30 per month*
Intertropical	*NA*	*5-15 per month (all year)*

Storage (-20C or -70C) of all influenza positive and negative study samples should be carried out for a minimum of one year. This will assure sample availability for additional retrospective investigations (e.g. SARS-CoV-2 or pathogen discovery initiatives) if necessary.

Study process



Case ascertainment will aim to identify patients hospitalized with health conditions or signs/symptoms that could be associated with acute respiratory illness. Once the eligible case is identified, the study team will apply the case definition and ask for consent to participate in the surveillance. A standardized questionnaire should gather information early in the process of enrollment, but also be used to collect clinical outcomes by the time the patient is discharged or dead.

Respiratory specimens should be collected from all patients accepting to participate in the study. Samples will be sent to the laboratory and the clinical and epidemiology data will be entered in a local database or in the GIHSN electronic case-reporting form (eCRF) system.

Data collection and analysis

Trained staff [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 questionnaire).

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.

Real time completion of electronic Case Report Form (eCRF) for all patients enrolled should be performed, or the data should be uploaded monthly to the Impact Healthcare data entry platform using the Excel file template provided to participating sites. Excel files should be uploaded on the GIHSN data entry platform **every last Wednesday of each month.**

Sites are strongly encouraged to share data with WHO's Global Influenza Surveillance and Response System (GISRS) and with local health authorities in ongoing bases.

A descriptive analysis of the seasonal results will be presented by each site at the GIHSN Global Annual Meeting. Analysis of aggregated data can be proposed, describing the season or combining data from various sites and/or years for pooled analyses. This will be presented in the Annual Report of the GIHSN and displayed in the form of aggregated indicators and graphs accessible via the GIHSN website.

Ethical considerations

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

Good Epidemiological Practice procedures will be implemented in all the study process.