Global Influenza Hospital Surveillance Network

Version 2024-06-03

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

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

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

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 2023 through 31st of October 2024, 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 (either because of the various non-pharmaceutic interventions put in place to respond to the public health crisis or possibly due to SARS-CoV-2 interference.

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 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. 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

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. ECDC modified case definition for influenza like-illness (ILI) in 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

3. 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

4. Laboratory confirmed influenza – a hospitalized person who has a positive laboratory test for influenza within 48 hours of hospital admission

5. Laboratory confirmed Covid-19 – a hospitalized person who has a positive laboratory test for Covid-19 with 48 hours of 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*
- *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 *[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].

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 will be selected based on Ct values <30.

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.

Data would be uploaded **every last Wednesday of each month**. If sequencing capacity available on site, genome sequencing data should be upload 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.

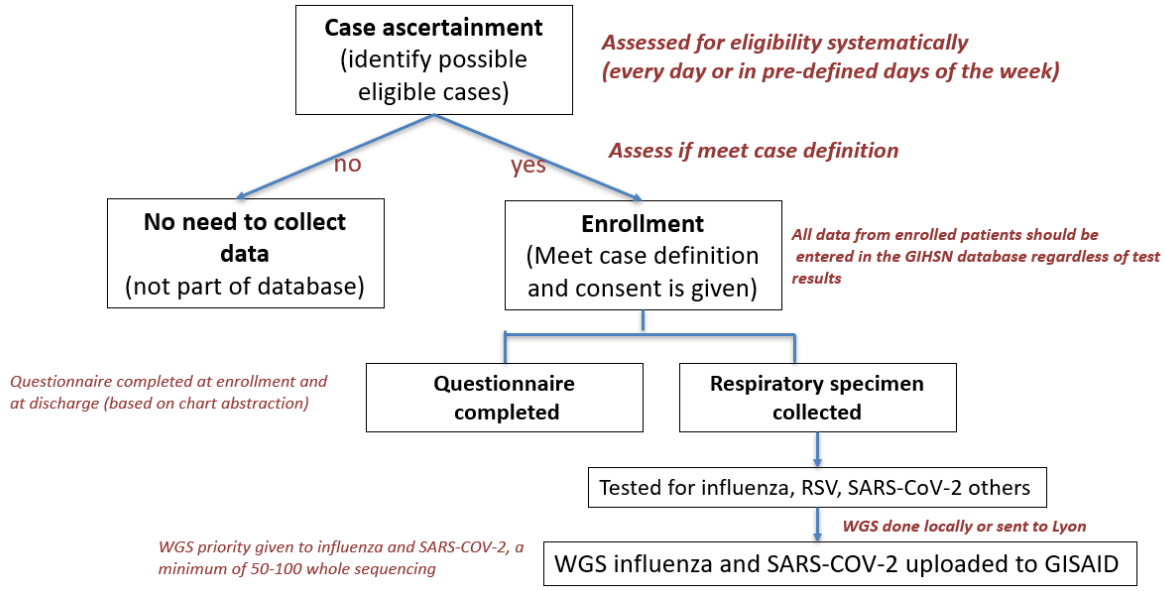
All sites must submit WGS to the GISAID EpiFlu™ database (http://gisaid.org/EPI_ISL/123456) in a timeframe so that results are available for the site's respective WHO Vaccine Composition Meeting (VCM). In addition, GSD for COVID-19 (if performed) are encouraged to be submitted to GISAID database to add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

Sample size, data collection and analysis

Sample size

There is no limit number for sample size, as this is a surveillance activity. *[Describe whether the site expects to collect clinical and respiratory samples from all patients or propose a sampling frame if the expected number of patients to be screened is too high. The sampling scheme should be focused on influenza. Other respiratory viruses can be incorporated in the same sampling frame according to resources available and/or use of multiplex testing tools. Sites that can generate information for other respiratory viruses (especially SARS-COV2 and RSV) will be strong applicants, to ensure global monitoring and awareness of respiratory virus circulation after the substantially disrupted season seen in 2020/21. Applicants should clearly describe their proposal screening, enrolment, and testing strategies, including if testing for other respiratory viruses will be performed, and how they can meet the year-round surveillance requirements. This should consider local capacity and resources. See suggested Sampling Strategy in box below].*

Besides the laboratory, clinical and epidemiologic data collected from all patients enrolled, a subset of them will have to undergo whole genome sequencing. The minimum number of WGS viruses from 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].* In the hypothesis of low influenza activity, sites are encouraged to undergo WGS for SARS-CoV2. The total number of 50-100 WGS per site is expected to be observed. Sites are asked to upload WGS for influenza and SARS-COV2 identified in GIHSN participating patients in GISAID with the unique identifier (GIHSN tag).

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 2023 – October 2024). 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 (independently 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 analysis. To be able to describe the cases based on disease presentation and distribution of epidemiologic and clinical characteristics, the selection of participants cannot be biased.

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, or the data should be uploaded monthly to the Impact Health-Care database using the excel file template provided to participating sites. 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) 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.

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.