Global Influenza Hospital Surveillance Network

Foundation for Influenza Epidemiology

Call for proposal: Year-round surveillance 2024-25

GLOBAL INFLUENZA HOSPITAL SURVEILLANCE NETWORK: LINKING EPIDEMIOLOGICAL AND CLINICAL DATA TO VIROLOGICAL INFORMATION

OBJECTIVE

The Foundation for Influenza Epidemiology seeks to support hospital-based sentinel surveillance sites that can improve our understanding of influenza epidemiology and other respiratory viruses and contribute to the WHO's vaccine strain selection process by monitoring influenza virus circulation and hospital-associated disease burden as part of the Global Influenza Hospital Surveillance Network (GIHSN).

We are looking for non-profit institutions with experience in hospital-based surveillance for influenza and other respiratory viruses that would be willing to participate in the GIHSN using a standardized protocol[1] for case ascertainment and respiratory sample collection.

The GIHSN has been around for the past 12 years, covering influenza circulation in the Northern and Southern Hemispheres. The network has changed over time, focusing on linking epidemiologic and clinical data with WGS information during the 2019/2020 season. During the 2020/21 season, due to the COVID-19 pandemic, changes in patterns of influenza and other respiratory viruses were observed, with substantial reduction in detection of non-COVID-19 respiratory cases. These changes in the epidemiology of other respiratory viruses need to be carefully monitored. The reduction in infectious diseases associated with influenza and RSV, for instance, could lead to an increase in the number of susceptible populations, facilitating large or unforeseen outbreaks in the communities. Since the 2021-22, the GIHSN proposes a year-round surveillance for the monitoring of respiratory viruses, to continue supporting public health officials' effort to understand the circulation and evolution of respiratory viruses, especially influenza.

Although influenza surveillance is critical for GIHSN, the network supports sites to include other respiratory viruses as part of their surveillance if laboratory capacity exist locally. The COVID-19 pandemic has highlighted the importance of rapid sharing of surveillance data, not only in the context of the pandemic but also to understand the circulation and burden of other common respiratory viruses that could guide public health decision making. The GIHSN promotes sharing of surveillance data with local health authorities, WHO and the scientific community at large. Currently, laboratory data on WGS are also actively shared by being uploaded into GISAID – a global initiative that provides open-access to genomic data from influenza and SARS-COV-2 viruses.

As such, the following specific objectives are underscored for the year-round surveillance call for tender:

- Screening and inclusion of hospitalized patients with respiratory illness meeting protocol case definition[1] year-round (from November 1st to October 31st the following year).

- Collection of epidemiologic and clinical data for all participating patients, with a standardized questionnaire administered at enrolment and a chart abstraction at patient discharge (or death).

[1] See the protocol on the GIHSN website www.gihsn.org

- Enrolled patients would have respiratory specimen collected shortly after hospital admission and sent for testing at the local and/or reference laboratory or National Influenza Centre.

- PCR test for influenza as a priority. If multiplex PCR and/or wet assay for SARS-COV-2 (and RSV and other respiratory viruses) can be performed in addition, it would be a strong added value.

- Storage (-20C or -70C) of respiratory samples (swabs) from all enrolled patients for a minimum of one year. This will assure sample availability for additional retrospective investigations, pathogen discovery research, or evaluation of new diagnostic tool if necessary.

- Whole Genome Sequencing of a minimum of 50 to 100 influenza viruses will be expected. If number of influenza positive cases are low, site is encouraged to complete WGS of SARS-COV-2. WGS data will be uploaded to GISAID by site in a reasonable timeframe so that results are available for the WHO Vaccine Composition Meeting (VCM). A link to the WGS and the clinical data will be uploaded to GISAID to allow future analysis.

BENEFICIARIES' ELIGIBILITY CRITERIA

Applicants should be non-profit institutions and will be asked to provide substantiating documentation when submitting their application. *(See How to apply)*

All sites must show an excellent connection between a hospital surveillance platform and a virology laboratory in their country, allowing for influenza testing by RT-PCR and subsequent sequencing (subtype/lineage) of the positive specimens within 7 days from sample collection.

If a site has no capacity to generate WGS, the site should be able to ship its specimens to the GIHSN sequencing platform at the National Influenza Centre in Lyon, France, or to another GIHSN partner having sequencing capacity and located closer to the site, under the Terms of Reference for sharing materials in GISRS. Shipment expenses will be borne by the GIHSN.

All sites must have the capacity to submit WGS at a minimum consensus data of the HA and NA segments to the GISAID EpiFlu™ database[2]. Clinical information should be captured in the current questionnaire used by the GIHSN (possibly e-CRF) and will include the link with GISAID sequence.

SELECTION PROCESS

Applications from Institutions meeting the eligibility criteria will be reviewed and evaluated by the Independent Scientific Committee of the Foundation according to predefined quality criteria.

Main evaluation criteria are:

- **Description of study settings**: Clear description of the surveillance population and settings, number of facilities, infrastructure, whether data are shared with the National Influenza Centre or WHO reference centres.

- **Laboratory capacities**: Availability of RT-PCR testing for influenza viruses, including subtyping for influenza A and lineage for influenza B. The existing full genome sequencing capacities on site or proposed referral system to sequence influenza viruses (or SARS-COV-2) should be

[2] https://gisaid.org/

described. Sites should mention if they will test samples for other respiratory viruses and, if so, describe the strategy for testing (e.g., all samples tested for all viruses, including influenza and SARS-COV-2 or a random subset of samples tested for other respiratory viruses after influenza testing is done, or other options).

- **Surveillance period**: Sites are expected to run the surveillance year-round (from November 1st to October 31st the following year). If expected number of cases to be screened is too high, site should explain a strategy to systematically assess patients over the surveillance period. See suggested **Sampling Strategy** in Appendix 3.

- **Targeted sample size for WGS**: The estimated number of sequenced samples expected to be shared via the GISAID platform during the season is at a minimum 50-100 and will depend on the site's capacity and number of potential influenza or SARS-COV-2 cases identified.

- **Clinical information data collection capacities**: The proposal needs to include detailed description about the way the site will identify eligible patients, their local staff capacity to interview and collect information from charts (please indicate if electronical medical chart abstraction will be done), and whether they expect 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 disrupted seasons seen in 2020/21 and 2021/22. 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 Appendix 3.

- **Timelines of the data availability**: Sites should be able to upload data from the questionnaire using the e-CRF or through regular uploads using excel files to share data on enrolled patients (regardless of test results). The preferable approach should be clearly described in the proposal. Data would be expected to be uploaded every last Wednesday of each month. Sites with sequencing capacity should upload genome sequencing data in GISAID as soon as they have results available. Sites using the GIHSN sequencing platform or another GIHSN partner with sequencing capacity should be able to have their samples shipped in regular batches along the year-round surveillance and at least twice a year and 4 weeks before each WHO strain selection meeting (February and September each year). The proposal should describe the site's ability to manage data uploads and shipments and expected timelines for shipments. If the suggested timelines for data sharing or sample shipments cannot be met, site should explain the rationale.

- **Geographical representativeness**: sites in regions under-represented in the GIHSN will be given funding priority.

- **Cost-effectiveness**: the relevance of the cost in relation to expected sample size will be considered when reviewing applications. The Foundation is providing catalytic funding and is not expected to fund the full cost of the surveillance system (clinical and sequencing data collection). The Foundation encourages sites to seek for national or other sources of funding to guarantee the sustainability of their surveillance.

At the end of August/early September each year, the Executive Committee of the Foundation will select institutions and decide the amount of the grant provided during the season to support the implementation. For sites already participating in the GIHSN, the selection will be conditional to data transfer completion in the previous season.

A formal letter from the Foundation describing grant modalities (in cash contribution) and payment milestones will be sent to the selected sites by September 2024. Kick off meeting with sites to review generic protocol and operational details will be organized in September. Sites are expected to implement the year-round surveillance starting November 1st for a one-year duration.

HOW TO APPLY AND HIGHLIGHTS

The call is posted on the www.gihsn.org website.
All applications must be submitted on-line on the GIHSN website via the application template. Applications could be submitted along the year. However, sites grant allocation by the Foundation occurs once a year (end of August-beginning of September) for implementation of the surveillance November 1st. Therefore, **application should be posted online, using the dedicated application form (see template below) for July 10st, 2024,** at the latest, to be considered for grant allocation early September. Please create your personal space on-line on the GIHSN website.

Recurrent sites (previous year(s) contribution to the GIHSN) should update their previous application form to account for change, if any, in study implementation and budget. Connect to your personal space on-line on the GIHSN website.

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.

The following documents should be provided along with the proposal to attest the above status:

- ☐ Last annual report (administrative document of the institution)
- ☐ Financial report (including earnings and balance sheet) of the previous year
- ☐ Bank account number (official bank document – with swift number)
- ☐ List of the members of the board of governors (i.e., group of people who jointly oversee the activities of the laboratory)
- ☐ Copy of the decree of creation (i.e., Statutory act returned by the president of the republic or the head of government)

The data sharing agreement *(See appendix 2)* will be requested to be signed by the selected sites at the start of the season.

Should you have any question, please do not hesitate to reach out to us: contact@gihsn.org

Abbreviations

GIHSN: Global Influenza Hospital Surveillance Network
GISAID: Global Initiative on Sharing All Influenza Data
GISRS: Global Influenza Surveillance and Response System
IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
WHO: World Health Organisation
IFPMA: International Federation of Pharmaceutical Manufacturers & Associations

Appendix 1: How the GIHSN operates?

The GIHSN is operated and supported by a dedicated fund, the Foundation for Influenza Epidemiology, under the auspices of Fondation de France (Fondation de France : fondation de toutes les causes - Fondation de France), a leading philanthropy network in France. As of January 2023, donors of the Foundation included Sanofi, Seqirus, Illumina, Abbott Diagnostics. Donors do not have access to the data and there is no commercial use of the data.

Scientific oversight of the GIHSN is ensured by an Independent Scientific Committee (The Foundation for Influenza Epidemiology (gihsn.org)) composed of world leading experts in epidemiology, virology, and public health, including representatives from WHO and field-based experts, investigators from GIHSN sites.

Coordination of the GIHSN, supervision of implementation and data management/data hosting are supported by Impact Healthcare, an independent organization based in Paris, France, specializing in the strategic and operational management of large innovative projects in Digital Health and the use of Health data, both in France and internationally. To comply with regulations on data access and privacy, the Foundation set up a data warehouse and a data access framework. Impact Healthcare is Data Controller for the GIHSN (jointly with Fondation de France). The GIHSN database is hosted in a secured environment (certified secured hosting for health personal data). Data are processed in full accordance with the European General Data Protection Regulation (GDPR) and French data protection regulations.

Data collected by sites receiving funding remains the proprietary of the site. A data sharing agreement is signed by each site with Impact HealthCare before surveillance implementation. All GIHSN analysis results are submitted for publication. Scientific publications and communications are mentioning contributing sites, with investigators names in the authorship. Sites are informed upfront for any planned data analysis beyond the routine annual pooled descriptive analysis, and they have the possibility to opt-out.

Appendix 2: Global Influenza Hospital Surveillance Network (GIHSN) data sharing agreement

Coordination of the GIHSN, supervision of implementation and data management/data hosting are supported by Impact Healthcare, an independent organization based in Paris, France, specializing in the strategic and operational management of large innovative projects in Digital Health and the use of Health data, both in France and internationally.

To comply with regulations on data access and privacy, the Foundation for Influenza Epidemiology set up a data access framework. Impact Healthcare is the Data Controller for the GIHSN (jointly with Fondation de France). Impact Healthcare is proposing an online data collection tool to ensure timely data sharing on the GIHSN platform.

The GIHSN database is hosted in a secured environment (certified secured hosting for health personal data). Data are processed in full accordance with the European General Data Protection Regulation (GDPR) and French data protection regulations.

Sites implementing the GIHSN protocol should be compliant with their ethical and national regulations for conducting the surveillance. Any obligation related to data protection and data transfer to Impact Healthcare platform should be anticipated.

With respect to existing WHO surveillance capacities, all data collected through the GIHSN Study questionnaires will be shared with corresponding National Influenza Centres and/or with WHO Collaborating Centres for Reference and Research on Influenza. Influenza strain genetic sequencing data will be shared via GISAID.

Data collected by sites receiving funding remains the proprietary of the site. There is no commercial use of the data. Donors of the Foundation for Influenza Epidemiology, who include, as of May 2024, Sanofi, Seqirus, Abbott Diagnostics, Pfizer, do not have access to the data. The data are transferred through a secured channel and the site has full access to the data through a secured platform managed by Impact Healthcare.

Impact Healthcare is given access to the GIHSN data for epidemiologic research fulfilling the three following conditions:

- Analyses can only be performed for research purposes in line with the mandate of the Foundation (i.e. surveillance and monitoring of influenza and other respiratory viruses).
- Analyses are exclusively performed with pseudonymised data.
- Any analyses plan will need to be approved **beforehand** by the Independent Scientific Committee of the Foundation.

Analysis results will be submitted for publication. Scientific publications and communications will mention contributing sites, with investigators names in the authorship, in line with the ICMJE rules.

Sites will be informed upfront for any planned data analysis beyond the routine annual pooled analysis, and **they have the possibility to opt-out.** Any research project leveraging on the GIHSN data must be approved beforehand by the Scientific Committee of the GIHSN and the Foundation for Influenza Epidemiology. Only anonymised data is shared.

Considering these rules, and in order to allow for continued analysis of both historical and current seasonal data, I hereby agree to share with Impact Healthcare the data collected at site level, according to the GIHSN protocol and questionnaire.

Main investigator First and Last Name	
Name and address of institution	
Country/region	

Date

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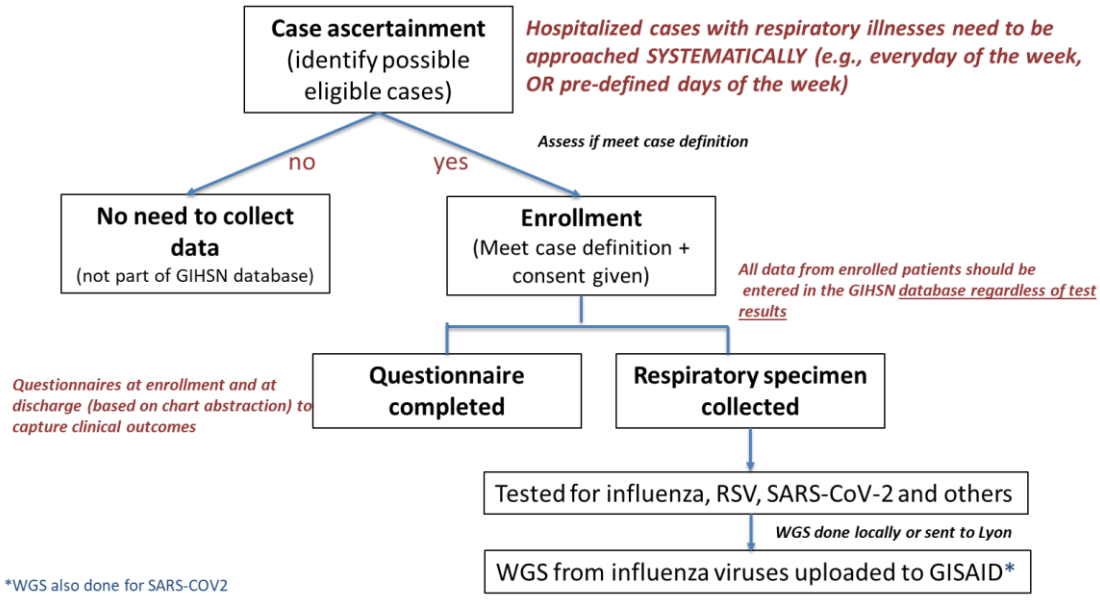
Signature

_____

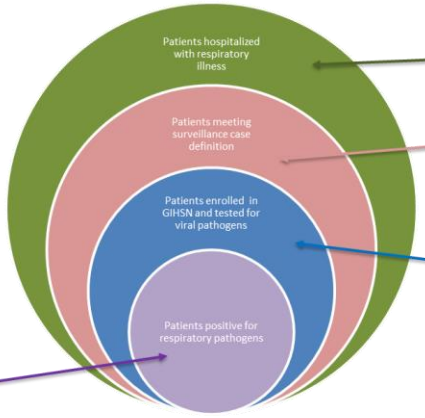
Appendix 3: Patient screening and enrollment

PROCESS FOR IDENTIFICATION OF CASES AND DATA COLLECTION - GIHSN



SAMPLING STRATEGY

Sampling strategy needs to be done systematically and done in a way to avoid potential biases



Full universe of cases hospitalized with respiratory illness Includes all the potentially eligible cases but not all cases will meet Case Definition for enrollment

It is challenging to approach every patient that meet Case Definition This is why we need to apply a sampling frame that could represent this pool of patients, minimizing selection bias (i.e., systematically applied)

Patients included in GIHSN database (with questionnaire and specimen collection – regardless of test results) They represent a sample of the cases hospitalized that met GIHSN surveillance case definition that were approached for enrollment and accepted inclusion

WHY DO WE NEED SYSTEMATIC SAMPLING?

If we only have virus-positive patients, we will not tell a complete story about these viruses…We need positive and negative patients (Blue + Purple)

Describe the percentage positivity for the various pathogens would also be important to understand/document virus circulation year-round

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 (from November 1st to October 31st the following year). 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 for 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