Operational considerations to expedite genomic sequencing component of GISRS surveillance of SARS-CoV-2

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WHO continues to monitor the situation closely for any changes that may affect this document of operational considerations. Should any factors change, WHO will issue a further update. Otherwise, this document will expire 2 years after the date of publication.

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Introduction

This document provides practical guidance to Global Influenza Surveillance and Response System (GISRS) laboratories (1) and other relevant national laboratories to move beyond virus detection to genomic sequencing of SARS-CoV-2 PCR positive materials obtained from sentinel surveillance of influenza-like illness (ILI), acute respiratory infection (ARI) and severe acute respiratory infection (SARI). Operational aspects addressed include sample selection for sequencing, numbers of viruses to be sequenced, metadata and timeliness for sharing genetic sequence data (GSD) and opportunities for technical support.

The goal is for GISRS and other relevant national laboratories to contribute to the evidence base essential for an effective COVID-19 pandemic responses by achieving the following objectives:

- improve the geographic and demographic representativeness and timeliness of SARS-CoV-2 genetic sequence data in publicly accessible databases, such as the Global Initiative on Sharing All Influenza Data (GISAID) (2)
- monitor the trend and prevalence (proportions) of existing and emerging (co-) circulating genetic variants (clades) among samples from sentinel sites
- wherever possible, contribute to a better understanding of associations between genetic characteristics of SARS-CoV-2 and transmission scenarios and severity of COVID-19 disease.

In addition to sentinel surveillance, special studies (3) or convenience sampling should be considered for sourcing virus samples for sequencing (4) to achieve other important public health objectives of SARS-CoV-2 genomic sequencing, such as the early detection and outbreak investigations.

KEY POINTS

- Representative, quality, timely and continuous genetic surveillance of SARS-CoV-2 is critical to the COVID-19 outbreak response to monitor genetic variants.
- GISRS sentinel surveillance sites provide specimens for systematic and standardized sampling to conduct sequencing to monitor genetic variants of SARS-CoV-2.
- Countries are encouraged to expedite genomic sequencing of SARS-CoV-2 of a minimum of 15 samples per week from sentinel surveillance systems and share the genetic sequence data through a publicly accessible database.
Background

Genomic sequencing of SARS-CoV-2 viruses by laboratories in the GISRS network from samples obtained through systematic and standardized sampling of cases meeting ILI, ARI and SARI case definitions enables continuous monitoring of the trend and proportions of existing and emerging genetic variants and improved geographic and demographic representativeness. GISRS, currently comprising laboratories in 126 countries with more than 90 laboratories sharing SARS-CoV-2 genetic sequences, is uniquely placed to efficiently bridge the critical gap in systematic genomic surveillance.

Since March 2020 (5), GISRS has incorporated testing for SARS-CoV-2 into laboratory algorithms for testing of specimens from sentinel surveillance to monitor relative trends in co-circulation of influenza and SARS-CoV-2 viruses (6). On 15 January 2021, the 6th International Health Regulations (2005) (IHR) Emergency Committee for COVID-19 recommended increasing global genomic sequencing capacities and encouraged rapid sharing of sequence data and meta-data; and for WHO to actively support countries to strengthen systematic genomic surveillance by leveraging GISRS and other relevant networks (7). A week earlier, WHO had published interim guidance on SARS-CoV-2 genomic sequencing for public health goals (4).

This operational guidance, which was developed in response to recommendations by the Emergency Committee, builds on the abovementioned WHO interim guidance to leverage the existing GISRS influenza capacities and mechanisms for SARS-CoV-2 surveillance through ILI/ARI/SARI sentinel surveillance systems (6). The document was developed based on evidence generated from the WHO Consultation to Adapt Influenza Sentinel Surveillance Systems for Including COVID-19 in October 2020, the review of SARS-CoV-2 sentinel surveillance functions and data reporting to the WHO FluMart (8) by the NICs and other national officers. Sizes of sampling for sequencing are based on earlier guidance for SARS-CoV-2 sentinel surveillance through the GISRS; SARS-CoV-2 positivity rates among sentinel specimens; sequencing capacity in GISRS; experience from the field; and extensive consultations with national and international experts, WHO Regional Offices and partner organizations.
Operational considerations for GISRS laboratories with established sequencing capacity

Key considerations for GISRS laboratories are:

- **systematic nature** of sample collection
- **representativeness** of sampled patients (i.e., geographical origin, age and sex, disease severity, timepoint during the outbreak)
- **quality** of the genetic sequencing data (GSD)
- **timeliness** including time from sample collection to sequencing and GSD sharing in a publicly accessible database
- **continuity** and **sustainability** of the sequencing activity as part of ongoing national surveillance

For pandemic response, the above considerations are far more important than the absolute numbers of viruses sequenced from a country.

1. **Sample Selection**

   **A. For countries performing sentinel surveillance of ILI/ARI/SARI**

   In general, specimens with a real-time reverse transcription polymerase chain reaction (rRT-PCR) cycle-threshold (Ct) value of ≤30 will likely allow for generating good quality genetic sequence of whole genomes.

   Unless laboratories conduct genomic sequencing of all SARS-CoV-2 PCR-positive sentinel specimens, selection should take the quality of the specimens and representativeness of the sampled patients into utmost consideration.

   **Selection of SARS-CoV-2 PCR-positive sentinel samples should reflect the representativeness of:**

   - different age groups (e.g. 0 to <2 years, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years, ≥65 years)
   - different geographic locations (sentinel sites) within the country
   - different time points
   - patients representing the spectrum of disease meeting case definitions in use for ILI, ARI or SARI
   - clinically significant cases from sentinel surveillance (e.g. fatal cases, vaccinated individuals, immunocompromised individuals, patients receiving treatment such as antivirals, plasma therapy or monoclonal antibodies), re-infected cases.
B. For countries not performing sentinel surveillance of ILI/ARI/SARI

Sampling strategy should follow Chapter 6.1 of the WHO technical document on Genomic sequencing of SARS-CoV-2: a guide to implementation for maximum impact on public health (9).

2. Number of viruses to be sequenced

For GISRS sentinel surveillance of SARS-CoV-2, WHO recommends at least 50 to 100 clinical specimens and ideally 150 specimens per week to be collected from sentinel systems and tested for SARS-CoV-2 (6).

- For countries collecting 150 or less specimens per week from ILI/ARI/SARI sentinel surveillance systems:
  - Wherever resources allow, laboratories should consider genomic sequencing of all SARS-CoV-2 PCR-positive sentinel specimens with a RT-PCR Ct value of ≤30.
  - Otherwise, try to maintain a minimum of 15 SARS-CoV-2 PCR-positive sentinel specimens per week for sequencing. If there are not enough good quality specimens from sentinel surveillance systems, random selection of samples from non-sentinel surveillance sources can be considered.

- For countries collecting more than 150 specimens per week from ILI/ARI/SARI sentinel surveillance systems:
  - Depending on resources available, consider sequencing all or a subset (ideally ≥10% as an indication), but at least a minimum of 15 SARS-CoV-2 PCR-positive sentinel specimens with a RT-PCR Ct value of ≤30 per week.

Operational considerations for countries without established sequencing capacity

Countries should consider referring some SARS-CoV-2 PCR-positive specimens with Ct value of ≤30 for genomic sequencing to WHO COVID-19 Reference Laboratories (10) following an agreement with them.

- For countries performing sentinel surveillance of ILI/ARI/SARI: consider referring all or a subset, but ideally, a minimum of 15 SARS-CoV-2 PCR-positive sentinel specimens per week with Ct value of ≤30 for genomic sequencing.

- For countries not performing sentinel surveillance of ILI/ARI/SARI, the genomic sequencing strategy should follow the guidance in the WHO technical document, Genomic sequencing of SARS-CoV-2: a guide to implementation for maximum impact on public health (9).
Shipments of positive samples to WHO COVID-19 Reference Laboratories can be expedited through a WHO shipment mechanism, with operational guidance provided (11).

For countries planning to establish national genomic sequencing capacity (9,12), it is recommended to consider building the capacity in their NICs, which can then address current needs for SARS-CoV-2, and other respiratory viruses of public health importance, e.g. influenza and Respiratory Syncytial Virus.

**SARS-CoV-2 genetic sequence data sharing**

1. **Metadata to accompany genome sequences**

   Metadata are essential to enabling the best use of SARS-CoV-2 GSD for the pandemic response. Whenever possible, laboratories should include metadata when sharing or publishing GSD, including date of collection, location, and source (sentinel/non-sentinel) of specimen collection; age, sex and clinical status of the patient; and other information concerning outbreak/clinical management/vaccination context.

2. **Timeliness for sharing GSD through existing sequence-sharing platforms**

   WHO encourages GISRS laboratories to sequence SARS-CoV-2-positive samples in a timely manner and share GSD with accompanying metadata through publicly accessible databases such as the GISAID EpiCoV database (2). Sharing of GSD should take place as quickly and regularly as possible (consider weekly or fortnightly batch uploading) and be consistent with relevant national guidance.

**Technical support and other practical information**

The WHO COVID-19 Reference Laboratories (10) provide technical support to countries on implementation of genomic sequencing of SARS-COV-2. The WHO Global Influenza Programme (13) coordinates the functioning of GISRS.

Other practical information can be found on the WHO COVID-19 website (14): https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
References
